University of South Florida

Protocol for Clinical Investigation

I. Summary

1. Title: Evaluation of a novel solution, IRRISEPT™, a new delivery system, containing a long-acting antimicrobial agent for irrigation of skin and soft tissue infections, in the form of an abscess, in the emergency department: a pilot study

2. Sponsor: IRRIMAX Corporation

3. Clinical phase: Phase III Pilot Study

4. Duration of the study: January 2010 – December 2011

5. Methodology: This is a prospective randomized controlled clinical trial.

6. Study site: Emergency Department, Tampa General Hospital

7. Number of subjects: 200 patients

8. Principal investigator: David Wein, M.D
   Director, Emergency Medicine Research Department
   Tampa General Hospital – University of South Florida
   One Davis Blvd, Suite 504
   Tampa, FL 33606
   (O) 813-627-5973

9. Co-investigators: Tamas Gaspar, MD, PhD
   Daryl D. DeNittis, RN, MS

10. Study coordinator: Erin Stirling, BPharm

II. List of abbreviations

ACEP	American College of Emergency Physicians
CHG	chlorhexidine gluconate
ED	Emergency Department
IRRISEPT	IRRISEPT™ Wound Debridement and Cleansing System
MRSA	Methicillin-Resistant Staphylococcus Aureus
SSTI	Skin and soft tissue infection
TGH	Tampa General Hospital
USP	United States Patent

III. Background

1. Significance of study

Skin and soft-tissue infections (SSTIs), including cutaneous abscesses, surgical site infections, and infected traumatic lesions, are commonly encountered among patients presenting for treatment in emergency departments (ED). While the available literature does not support the use of systemic antibiotic prophylaxis in emergency medicine practice [1-3], most experts recommend irrigation to decrease the rate and prevent the spread of infection, although the clinical significance of irrigation is not known [3,4].

The purpose of irrigation and cleansing is to remove debris, bacteria, and loose tissue. To be effective, the mechanical force used must exceed that of the adhesive forces of the contaminant. Low-pressure irrigation removes negligible small particles but cannot remove large particulate matter, such as devitalized tissue. However, when irrigating solutions are applied at high pressure, destruction of vital tissue may occur. The use of a self-contained irrigation device that can produce sufficient pressure may help standardize care and reduce the progression of infections.

Methicillin-resistant Staphylococcus aureus (MRSA) emerged in the 1960s as a cause of infection among patients exposed to the bacteria in health care settings. During the past decade, MRSA infections have been reported among persons without such exposure (community-associated MRSA) [5-7]. Community-associated outbreaks of MRSA infection have occurred among prisoners, intravenous-drug users, athletes, military trainees, low socioeconomic groups, children, and homosexual men [8-10]. MRSA has primarily been described as a cause of SSTI [10,11]. The number of ED visits for SSTIs has significantly increased in the past decade primarily due to a dramatic increase in the number of infections caused by community-associated MRSA [12]. Therefore, it is crucial to determine MRSA colonization in a population studied for SSTI rates.

Community-associated MRSA has changed the way physicians treat SSTIs. Based on clinical suspicion and on the prevalence of MRSA in certain populations, physicians now are treating these infections (e.g. cutaneous abscesses) with MRSA sensitive antibiotics. This has not been the standard of care and the use of oral antibiotics in treating MRSA associated abscesses has not been confirmed. Irrigation during abscess treatment has been used as an alternative and the self-contained irrigation device may obviate the need for systemic antibiotic coverage.

2. Device description

IRRISEPT™ Wound Debridement and Cleansing System (IRRISEPT) is a manual, self-contained irrigation device that is capable of producing 7-8 psi of pressure as recommended by American College of Emergency Physicians (ACEP) for effective wound cleansing/irrigation. This pressure is sufficient to agitate, loosen and remove debris from wounds. The device has an option for use with a standard irrigation tip or an abscess irrigation tip. The ingredients of the solution are 0.05% Chlorhexidine Gluconate (CHG) in Sterile Water for Irrigation, USP (99.95%). The mechanical action effectively loosens and removes debris. The CHG acts as a preservative to help inhibit microbial growth in the solution.

IV. Objectives

1. Primary objective
   The purpose of this pilot study is to provide estimates for sample size calculations for future determination whether IRRISEPT™ with the abscess irrigation tip, can effectively prevents the progression of SSTIs, in the form of an abscess, as compared to treatment by current standard of care utilized in the TGH ED.

2. Secondary objective
   The study also aims at determining overall prevalence of MRSA colonization in the studied population.

V. Design

Potential subjects will be recruited through the TGH Emergency Department. Patients presenting with SSTIs will be approached for screening purposes. Once deemed eligible, informed consent will be obtained and the patient will sign the appropriate paperwork for photography and participation in the study.

Randomization methodology will be controlled by a USF biostatistician, following which pertinent history data will be recorded on the study data collection instrument.. In addition to any samples taken by the treating ER physician, a nasal swab for determination of MRSA-colonization status, and a wound culture will be taken and sent to a central lab. A digital photo of the infected site will be obtained at the initial treatment and 48 hour follow-up.

Subjects will have their abscess treated either by **Usual Care** (according to treating physician instructions) or utilizing **IRRISEPT™,** abscess irrigation device as per manufacturing instructions (as below):
Step 1: Attach the Long Tip SplatterGuard (LTSG) to the IrriSept bottle. Insert the tip into the abscess through the incision. Squeeze firmly and empty bottle contents, ensuring that the abscess is thoroughly flushed.

Step 2: Wait 1 minute

Step 3: Attach the LTSG to the IrriRinse bottle. Insert the tip into the abscess through the incision. Squeeze firmly and empty bottle contents, ensuring that the abscess is thoroughly flushed.

Other aspects of care including the use of plain packing and oral antibiotics will be at the discretion of the treating physician in both arms.
Contact information will be obtained and subjects will be instructed to return for a wound check at a point approximately 48 hours after ED discharge; they will also be offered the opportunity to return at any time in event of problems or questions.

The primary end-point of the study is progression of signs and symptoms of infection 48 hours post initial treatment. On follow-up, a blinded investigator will examine the wound for clinical signs of infection (erythema, inflammation, itching, fluctuance, drainage, pain, and a second digital photograph of the site will be taken. The natural progression of the wound at hour 48 will be determined during data analysis as:

1.) Improved and healing well
2.) Required additional follow-up
3.) Required additional treatment

If signs of infection are present at the 48 hour follow-up visit, subjects will be referred to treatment from their primary physician or to the TGH ED.

In the event that subjects do not return for arranged follow-up at 48 hours, a telephone reminder will be made, and a telephone survey will be conducted to determine whether the subject might identify signs of infection. If subjects return subsequent to the phone reminder, their clinical condition will be recorded and used on follow-up visit. In the event that they do not return, the telephone survey result will be employed as the follow-up instrument. Subjects lost to all follow-up will be excluded from further analysis.

Secondary end-point of the study is MRSA colonization as determined by collecting nasal swab specimens obtained during initial patient contact (Baseline visit).

1. Source of research material
   Research material for this study includes clinical data (medical history and physical examination, results of laboratory and radiographic tests, consultant's clinical records), nasal cultures for MRSA, and possible wound cultures obtained on follow-up if wound infection identified.

2. Instrumentation
   Instruments include standard physician interview and examination, laboratory microbiology studies using existing credentialed clinical support facilities.

VI. Patient enrollment

1. Inclusion criteria

   i. Age 18 to 80
   ii. SSTIs, in the form of an abscess, which will require incision and drainage. Patient able to provide an informed consent
   iii. Patient volunteers to participate

2. Exclusion criteria

   i. Wound was caused by human or animal bite
   ii. Wound is a blunt crush injury or has tendon, bone, or joint involvement
   iii. Diabetic foot infection
   iv. Anticipated incision size less than 5mm
   v. Abscess extends to the muscle layer
   vi. Admission to hospital for any reason, including IV antibiotics
   vii. Clinical signs of systemic infection on initial patient encounter
   viii. Prior history of allergy or hypersensitivity to CHG
   ix. Neutropenic (known ANC<500/mm3), HIV (known CD4<50), or other severely immunocompromised state (e.g. receiving chemotherapy)
   x. Pt is diagnosed with systemic lupus erythematosus or other immunological disease
   xi. Currently in police custody
   xii. Patient withdraws from participation
   xiii. Patient unable or unwilling to give informed consent

3. Recruitment

   Any patient meeting inclusion criteria as defined above will be eligible for enrollment. Patients will be briefed on study, informed consent will be sought, and if conferred, subjects will be enrolled.

4. Number of subjects to enroll

Due to the descriptive nature of this pilot study, sample size calculations have not been conducted. We plan to enroll 200 patients total (100 in each study arm) in order to determine the overall prevalence of MRSA colonization in this population and to provide estimates for sample size calculations for future evaluation of non-complicated SSTI, in the form of an abscess, irrigation with IRRISEPT versus usual care. We will perform interim analysis when 100 subjects (or 50 subjects per arm) have been enrolled.

VII. Risks

Participants will receive appropriate and standard care for their presenting condition. Standard risks from participation would be the same as those for patients receiving emergency treatment for their presenting diagnosis: bleeding, infection, adverse reaction or side effect from wound irrigation, pain. There may be risk of a topical irrigation or allergic reaction to CHG. Investigators will be at risk for exposure to contaminated body fluids and tissues; this risk will be minimized by thorough observance of standard precautions. We are unaware of any additional risks imposed by participation in this study.

VIII. Data collection

All pertinent data on initial contact and follow-up will be recorded on the IRRISEPT™ ABSCESS STUDY – Data Collection Form. After completion, data sheets will be collected and data will be entered in a Microsoft Excel database for further evaluation. Only the principal investigator, the co-investigators and the study coordinators will have access to the database. No data with subject identifiers will be released.

IX. Statistical analysis

Descriptive statistics will be reported as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. No formal analytic statistics are planned for this pilot study.

X. Conflict of interest

This study is sponsored by IRRIMAX Corporation. We are unaware of any conflict of interest.

XI. Duration of study

Given the number of patients presenting with SSTI, in the form of an abscess, in the emergency room, we anticipate that we should be able to complete subject enrollment within twelve (12) months of initiation of the clinical protocol.

We anticipate a time requirement of two weeks to train all investigators, coordinators, and data managers on the protocol and data sheet. We will conduct a two-week "wash-out" period to familiarize the staff with the experimental protocol and employment of the device. After final enrollment, we plan for a two-month period for final data acquisition and a four-month period for data analysis. Thus, we predict a required period of 18 months to complete the study, once initiated.

XII. References

1. Ellis MW. Is antimicrobial therapy needed to manage uncomplicated skin and soft-tissue abscesses? Expert Rev Anti Infect Ther 2008; 6(1):9-13.
2. 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 2009; doi: 10.1016/j.annemergmed.2009.03.014
3. Fitch MT, Manthey DE, McGinnis HD, Nicks BA, Pariyadath M. Abscess incision and drainage. N Engl J Med 2007; 357(19): e20-23.
4. Abrahamian FM, Talan DA, Moran GJ. Management of skin and soft-tissue infections in the emergency department. Infect Dis Clin N Am 2008; 22:89-116.
5. Whitman TJ. Community-associated methicillin-resistant Staphylococcus aureus skin and soft tissue infections. Dis Mon 2008; 54(12):780-786.
6. Dryden M. Complicated skin and soft tissue infections caused by methicillin-resistant Staphylococcus aureus: epidemiology, risk factors, and presentation. Surg Infect (Larchmt) 2008; 9 Suppl 1:s3-10.
7. Boucher HW, Corey GR. Epidemiology of methicillin-resistant Staphylococcus aureus. Clin Infect Dis 2008; 46 Suppl 5:S344-349.
8. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant S. aureus infections among patients in the emergency department. N Engl J Med 2006; 355(7):666-674.
9. Gorwitz RJ. Community-associated methicillin-resistant Staphylococcus aureus: epidemiology and update. Pediatr Infect Dis J 2008; 27(10):925-926.
10. Johnson JK, Khoie T, Shurland S, Kreisel K, Stine OC, Roghmann MC. Skin and soft tissue infections caused by methicillin-resistant Staphylococcus aureus USA300 clone. Emerg Infect Dis 2007; 13(8):1195-1200.
11. Miller LG, Kaplan SL. Staphylococcus aureus: a community pathogen. Infect Dis Clin North Am 2009; 23(1):35-52.
12. Pallin DJ, Egan DJ, Pelletier AJ, Espinola JA, Hooper DC, Camargo CA. Increased US emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant Staphylococcus Aureus. Ann Emerg Med 2008; 51:291-298.