Protocol Title: Safety and Tolerability Study of Antimicrobial TheraGauze for Skin Abscess - Pilot Study

Phase of Study: I

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Background. Skin infections resulting in abscess, furunculosis, have become increasingly common in the past decade with the rapid emergence of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA). The increasing incidence of these skin infections has stressed the medical system at the primary care, urgent and emergent care levels at significant cost. Methicillin-resistant *S. aureus* (MRSA) killed 18,650 Americans in 2005, exceeding the number of deaths attributable to HIV/AIDS (Klevens, Morrison et al. 2007). MRSA infections were identified for 368,600 hospitals stays in the U.S. in 2005 for an estimated $5 billion in hospitalization costs (Healthcare Cost and Utilization Project, DHHS).

The primary endpoint of the study is to evaluate the safety of and identify side effects of TheraGauze/tobramycin wound packing compared with standard of care management for cutaneous abscesses requiring incision and drainage. Current standard of care in most emergency and urgent care settings for community-acquired skin abscess is incision and drainage followed by packing with cotton wick (± iodoform) and anti-MRSA systemic antibiotics given orally for 5 – 7 days (Mistry, Weisz et al. , LoVecchio, Perera et al. 2009). Commonly prescribed oral antibiotic regimens include trimethoprim-sufamethoxazol, doxycycline, and clindamycin. Common side effects from these systemic antibiotics include diarrhea (~20%), nausea, and rash (Powell and Wenzel 2008). Uncommon but severe side effects include *C. difficile* colitis, Stevens-Johnson Syndrome, toxic epidermal necrolysis, hepatitis, and aplastic anemia (Bell, Foster et al. , Mistry, Schwab et al. 2009).

The primary likely benefit of this novel therapeutic strategy is avoiding the side effects of systemic antibiotics that cause significant additional morbidity and medical expense. Other possible benefits of this novel strategy are improved wound healing time and less scar formation. This work will capitalize on the polymer structure of TheraGauze that provides a platform for fluid redistribution within the wound bed without causing skin maceration (Landsman 2008). We have developed an antimicrobial form of TheraGauze by loading TheraGauze with tobramycin (TheraGauze+tobramycin). Prior in vitro testing demonstrated potent and sustained antibacterial activity for TheraGauze+tobramycin against a wide range of bacterial pathogens, including all strains of community-associated MRSA tested (Echague, Hair et al. 2010). Lack of systemic absorption is a well-established property of tobramycin. Thus, high concentrations can be delivered locally in the wound greatly exceeding typical minimum inhibitory concentrations (MICs) without concern for systemic toxicity. Additionally, tobramycin is a highly bactericidal antimicrobial compound. Tobramycin is rarely used as a systemic antibiotic now having been largely replaced by fluoroquinolones. Therefore, selective pressure that could promote development of antibiotic resistance and compromise systemic antibiotic therapy is not a concern.

Tobramycin has been used for many years both as topical therapy applied to the eyes as well as in surgical wounds as tobramycin-containing polymethacrylate beads. Topical application of tobramycin to cutaneous wounds has also been reported without evidence of local or systemic toxicity. Andrew et al reported application of 3% (w/v) tobramycin with dexamethasone (i.e., Tobradex) ointment applied to post dermatological procedure surgical wounds twice-a-day for 2 weeks. Eighteen human subjects were enrolled and no local or systemic side effects were noted (Andrew, Luecke et al. 2012)

In 2003 Simplex P with tobramycin was the first FDA approved antibiotic impregnated bone cement (ww.stryker.com). Preparations of tobramycin-impregnated bone cement appear to generally range from 1g to 1.2g in 20 ml (50 – 60 mg/ml) (Sterling, Crawford et al. 2003, McLaren, McLaren et al. 2008). Tobramycin is reported to be the antibiotic of choice for bone cement for more than 75% of orthopedic surgeons (Fish, Hoffman et al. 1992) with excellent local tobramycin levels and minimal systemic tobramycin levels (Soto-Hall, Saenz et al. 1983, Eckman, Henry et al. 1988, Davies and Harris 1991, Pritchett and Bortel 1992, Brien, Salvati et al. 1993, Sterling, Crawford et al. 2003, McKee, Li-Bland et al. 2010). Despite the extensive literature on tobramycin bone cement there are no mentions of local toxicity. It is notable that so little toxicity has been reported given the significantly varying amounts of tobramycin cement are used for different types of orthopedic procedures and depending on the amount of bone being replaced. The wounds the tobramycin cement are in deep tissue spaces that are highly vascular. In contrast, TheraGauze/tobramycin will be placed into small (2 - 10ml) cutaneous abscesses where the bacterial infection has been walled off to protect the body from spread.

Tobramycin has also been used as a topical ophthalmic preparation for many years both as an ointment and drops (3 mg/ml) (e.g., Tobrex). Despite the very sensitive nature of topical application to the eye the package insert for Tobrex notes <1% hypersensitivity and eye or eyelid irritation is 3%, which is a typical rate for antibiotic eye drops. Additionally, Tobramycin eye drops (3 mg/ml) have been shown to have no adverse effects on reepithelialization and be well tolerated after penetrating keratoplasty (Blavin, Sauer et al. 2012)

Thus, there are several decades of human data demonstrating the safety of tobramycin when used topically for cutaneous and ocular wounds and in surgical wounds. The data suggests that local or systemic toxicity is extremely rare when tobramycin is used in these ways.

Primary Endpoint. The primary endpoint of the study is to evaluate the safety of and identify side effects of TheraGauze/tobramycin wound packing compared with standard of care management for cutaneous abscesses requiring incision and drainage.

Methods.

Design:

This is a proof-of-concept, prospective, randomized clinical trial for safety of TheraGauze-tobramycin in adult subjects who present to Emergency Department settings for care of skin abscess requiring incision and drainage. A control, standard of care, arm is included to provide some data with respect to the side effect profile of current furunculosis management for comparison.

Two arms are proposed for this study:

1. Incision + TheraGauze+tobramycin packing (no systemic antibiotics)
2. Incision + standard iodoform wick or plain cotton wick packing (± p.o. antibiotics)

Anti-microbial TheraGauze (saturated with tobramycin ophthalmic solution at 3 mg/ml) will be packed into the drained wounds of the subjects in the study arm. The control arm will receive current standard of care wound packing with a choice of iodoform wick or plain cotton wick, based on the preference of the ED physician. After packing, the wound excess TheraGauze or wick will be cut away. The ED physicians have the option to prescribe an oral antibiotic or not,

according to their preference. The following oral antibiotic choices are available for subjects in the control arm only:

- Bactrim (TMP/SMX)
- Vibramycin (doxycycline)
- Cleocin (clindamycin)

Antibiotics will be purchased by subjects from their local pharmacy.

TheraGauze-tobramycin.

We plan to use TheraGauze saturated with tobramycin ophthalmic solution (3 mg/ml). The decades of efficacy and safety with tobramycin eye drops justifies using the 3 mg/ml concentration. In vitro testing with TheraGauze/tobramycin (0.9 mg/ml), shows excellent broad-spectrum antibacterial activity against Gram-negative and Gram-positive bacterial pathogens including all clinical MRSA strains tested (Echague, Hair et al. 2010). We expect that >85% of the cutaneous abscesses (furuncles) will be infected with MRSA (Demos, McLeod et al. 2012). Additionally, tobramycin is a non-absorbable antibiotic and thus an excellent choice for achieving local antimicrobial activity with minimal risk of systemic side effects, which it is why it is the most common antibiotic bone cement.

Furunculosis skin abscesses typically have a volume of 1 – 5 ml up to a maximum of 10 ml (Mistry, Marin et al. 2013). Thus, a maximal volume of TheraGauze/tobramycin that can be packed in the wound will be 10 ml in the largest furuncles. If the entire length of the TheraGauze/tobramycin is used, which will rarely occur, the 17 cm length will hold only 21 grams of tobramycin, which will only be placed in the wound one time and not re-dosed. Standard intravenous dosing of tobramycin is 1 mg/kg/dose every 8 hours, thus ≥ 50 mg i.v. per dose for adults. The TheraGauze/tobramycin wound packing will be placed after the incision and drainage of the abscess and removed at the day 3 (- 1/+2) follow up visit in the Emergency Department. TheraGauze/tobramycin will only be placed in the wound a single time.

TheraGauze/Tobramycin creation

1. TheraGauze commercial preparation will be dehydrated in the factory and spiral dye to yield a 17 cm strip of TheraGauze of uniform width. After cutting the dry TheraGauze will be packaged and sterilized by gamma radiation. This follows all of the current steps of manufacturing only adding dehydration and cutting steps.
2. Dried TG packages will be provided to the Sentara Norfolk General Hospital (SNGH) Emergency Department (ED).
3. Commercial 10 ml vials of tobramycin ophthalmic solution (3 mg/ml) for human use will be provided by the SNGH pharmacy and stored in the temperature monitored med room in the SNGH ED. Each vial will be opened only once and then discarded.
4. After randomization has been determined, a new 10 ml vial of tobramycin ophthalmic solution will be opened and added to newly opened TG in a sterile dish by the study coordinator and allowed to rehydrate to saturation (5 minutes). Maximal saturation of the 17 cm TheraGauze strip is achieved with only 7 ml of solution.
5. The wound will be packed with the TheraGauze/tobramycin strip and any excess length will be cut off, measured and discarded.

Methods:

Study Population:
Subjects from the Hampton Roads region of southeastern Virginia will be recruited from the hospital emergency department site staffed by EVMS physicians at Sentara Norfolk General Hospital.

Study Size:
We anticipate screening 200 patients in order to enroll and randomize 100 subjects. Subjects will be randomized 2:1 to the TheraGauze+tobramycin or iodoform wick/ plain cotton wick, respectively. We anticipate 50 participants completing the study. The 50% retention rate is typical for emergency department populations.

Subject Eligibility:

Inclusion criteria:

- Ages ≥18 to ≤65 years at time of enrollment
- Subject has skin abscess (furuncle) requiring incision and drainage
- Erythema surrounding abscess
- Induration of ≥2cm in maximal diameter
- Fluctuance or purulent head evident
- Tenderness at abscess
- No or mild fever ≤38.5^{o}C
- Male or female
- Ability to read and understand the English language at a level sufficient to provide informed consent and comply with study requirements
- Subject is willing and able to comply with all study requirements

Exclusion criteria:

- Systemic illness or deep-seated infection requiring inpatient admission (i.e. hypotension, tachycardia, or tachypnea)
- Deep seated infection requiring referral to surgery
- Subject requires intravenous antibiotics for suspicion of systemic spread of infection (i.e. suspicion of bacteremia)
- Extensive cellulitis extending > 6cm beyond the area of induration
- Fever >38.5^{o}C
- Allergy to any aminoglycoside antibiotic, sulfamethoxazole-trimethoprim, doxycycline, clindamycin.
- An underlying medical condition that impairs normal immune function (e.g. AIDS, cancer, diabetes, lupus, rheumatoid arthritis, organ or marrow transplantation, ulcerative colitis, Crohn's disease)
- Subject is pregnant or breastfeeding and/or a woman of childbearing potential who is not surgically sterile, not at least 2 years postmenopausal, or does not practice contraception methods, unless sexually abstinent for the duration of the study.
- Subject has any medical or psychiatric condition, in the opinion of the investigator, could jeopardize the subject's health or compromise the subject's ability to participate in the study.
- Subject has prior treatment with antibiotics in the preceding 7 (seven) days.
- Currently taking or has taken oral or injection steroid medication (e.g. prednisone or Medrol Dosepak) in the past 30 (thirty) days

- Injection medications (Remicade, Humira, Cimzia, Simponi) other than vitamin (B6)
- Currently taking or has taken immune suppressing medications (e.g. methotrexate, Prograf, CellCept, Rapamune) in the past 30 (thirty) days
- Currently taking or has taken medications to treat cancer in the past 30 (thirty) days
- Subject is currently participating or has participated within the last two months in any study of an investigational drug or device.

Recruitment and Retention:
Subjects who present to Emergency Department setting for care of skin abscess requiring incision and drainage will be approached by on-site Study Coordinators for enrollment. The study coordinators and physician investigators are trained in obtaining informed consent. The potential subjects will be able to discuss participation with any family-member present, but due to the need for prompt treatment, the subject will need to make a decision regarding participate at the time of the Emergency Room visit. Upon meeting eligibility criteria and willingness to participate, subjects/LARs will provide informed consent. Complete demographic information to include residential and telephone contact information will be obtained. Prior relevant medical history and usual primary care contact information will also be collected. A medical information release will be obtained from the subject so that outcomes data can be collected related to additional unscheduled visits or adverse events cared for outside the emergency department setting.

Women and minority participation:
Adults up to 65 years of age will be enrolled regardless of gender and minority status as long as they are fluent in English.

Randomization:
A study subject identification number will be assigned. Subjects will then be sequentially randomized to one of two treatment arms upon enrollment in a 2:1 ratio, using a prepared list. Each subject's name will be recorded on the list next to his/her assigned subject number and randomization. For example, the first subject enrolled will be randomized to Treatment 1; the next enrolled subjects will be enrolled to Treatment 1; the third subject to Treatment 2. The fourth subject will be randomized to Treatment 1 and so on.

Study Treatments
Visit 1 - Day 1:

- Informed consent will be obtained from subject.
- Review of Eligibility Criteria (Inclusion/Exclusion)
- Randomization to Treatment Arm
- Contact Information to include phone number(s), address, and primary care provider information will be collected.
- Treatment and discharge with instructions to return to the ED for revaluation per routine care. The typical schedule is for the patients to return to the ED 2 days after initial wound care (Study Day 3 -1/+2).

The following information will be collected and recorded on a hard copy Case Report Form at this visit.

- Subject ID number
- Demographics

  - Date of visit
  - Age in years and months at time of enrollment
  - Race (white, non-white)
  - Ethnicity (Hispanic or non-Hispanic)
- Medical history
  - Chronic medical conditions:
    - ____
    - ____
    - ____
  - Concomitant Medications
    - ____
    - ____
    - ____
  - Allergies to medications
    - ____
    - ____
    - ____
- Characteristics of symptoms and history
  - Duration of symptoms (number of days)
  - Fever > 38.0°C duration? (y/n, record number of days febrile at home prior to ED visit)
  - Fever > 38.0°C in ED? (y/n, record temp)
  - Spontaneous drainage (y/n)
  - Prior skin abscess (y/n)
  - Immediate family history (parent, sibling, child) of skin abscess (y/n)
- Abscess characteristics
  - Erythema at widest diameter (mm)
  - Abscess induration at widest diameter (mm)
  - Abscess location (e.g. trunk, extremity, buttocks, perineal, axilla, head/neck)

- Procedure information
  - Diameter of wound after incision (mm)
  - Treatment Arm:
    1. Anti-microbial TheraGauze (TheraGauze/tobramycin)
    2. Iodoform wick/ plain cotton wick
  - Length of packing used (mm)
- Laboratory Assessments – Per standard clinical care the abscess contents will be sent for routine Gram stain, bacterial culture and susceptibility testing as dictated by the patient's insurance and ED policy.
  - Obtain results when available
- If patient is to receive iodoform wick/plain cotton wick then the care provider will have the option of prescribing a p.o. antibiotic, as is frequently done in these clinical settings. The following oral antibiotic choices are available for subjects in the <u>control</u> arm only:
  - Bactrim (TMP/SMX)
  - Vibramycin (doxycycline)
  - Cleocin (clindamycin)

Phone Follow up Contact Day 2 (+2)

Return visit reminder and wound status follow up performed by Sentara Study Coordinator.

- Questions
    - Fever since leaving ED? (y/n, record temp if taken)
    - If prescribed, was antibiotic prescription filled (y/n)
    - If prescribed, has antibiotic been taken (y/n, # doses)
    - If antibiotics taken, were any side-effects noted (y/n, list)
    - Increased or decreased pain (y/n, increased/decreased)
    - Increased or decreased size of redness (y/n, increased/decreased)
    - Any new symptoms? (y/n, list) Specific questions will include: presence of rash, loose stool, nausea, vomiting, abdominal discomfort, headache, dizziness, drowsiness, thrush, as well as any change in local signs or symptoms including pain and redness, new skin lesions, enlarged lymph nodes, and sore or white spots in the mouth.

Visit 2 - Day 3 -1/+2: (ED)

Subjects' wound status will be evaluated. The following information will be collected and recorded on a hard copy Case Report Form at this visit:

- Questions about infection
    - Infection overall (better/same/worse)
    - Fever > 38°C at home since incision? (y/n)
    - Persistent discharge (y/n)
    - Pain (increased/same/decreased/resolved)
    - Medical evaluation between day 1 and day 3 visit (y/n)
    - New lesions (y/n)
    - Was an p.o. antibiotic prescribed (y/n)
        - If yes, was the prescription filled (y/n)
        - How many doses have been taken so far? (##)
    - Any diarrhea? (y/n)
    - Any nausea or vomiting? (y/n)
    - Any abdominal discomfort? (y/n)
    - Any new rash? (y/n)
    - Any other new symptoms including headache, dizziness, drowsiness, thrush, as well as any change in local symptoms.
    -
- Bacterial burden in wound bed – Wound culture performed using quantitative methods for culturing wound base (Gardner, Frantz et al. 2006). Cultures taken to Cunnion lab for quantitation, swab may be stored at 4°C, if obtained after business hours.
    - Quantitation of bacteria present (colony counts performed in Cunnion lab)
    - Speciation of bacteria present (CHKD clinical microbiology laboratory using CLSI standards)
    - Antibiotic susceptibility testing of bacteria present (CHKD clinical microbiology laboratory using CLSI standards)
- Wound assessment
    - Fever > 38°C in ED? (y/n, record temp)
    - Packing present (y/n)
    - Erythema at widest diameter (mm)

  - Abscess induration at widest diameter (mm)
  - Tenderness around the wound? (y/n)
  - Removal of packing
  - Does wound require repacking? (y/n)
- Clinical Options
  - Return to ED for additional clinical evaluation and management (y/n)
    - Reason for reevaluation (infxn worsening/infxn non-improvement/other)
    - Another incision and drainage in the ED (y/n)
    - Addition of oral antibiotics (y/n)
    - Admission for i.v. Abx (y/n)
    - Admission for surgical intervention (y/n)
    - Return to ED in 2 more days (y/n)
- Schedule follow-up visit in Infectious Diseases Clinic at Children's Hospital of The King's Daughters (CHKD) in 5 ± 2 days

<u>Phone Follow up Contact Day Prior to CHKD visit:</u>
Return visit reminder performed by Study Coordinator.

  - Fever since leaving ED? (y/n, record temp if taken)
  - If prescribed, has antibiotic been taken (y/n, # doses)
  - If antibiotics taken, were any side-effects noted (y/n, list)
  - Increased or decreased pain (y/n, increased/decreased)
  - Increased or decreased size of redness (y/n, increased/decreased)
  - Any new symptoms? (y/n, list) Specific questions will include: presence of rash, loose stool, nausea, vomiting, abdominal discomfort, headache, dizziness, drowsiness, thrush, as well as any change in local signs or symptoms including pain and redness, new skin lesions, enlarged lymph nodes, and sore or white spots in the mouth.

<u>Visit 3 - Day 7 ± 2: (CHKD Infectious Diseases Clinic):</u>
Follow up on subjects' wound status. The following information will be collected and recorded on a hard copy Case Report Form at this contact.

- Questions about infection
  - Fever > 38°C at home since incision? (y/n)
  - Pain (increased/same/decreased/resolved)
  - Redness (increased/same/decreased/resolved)
  - Persistent discharge (y/n)
  - Wound size (increased/same/decreased/resolved)
    - If resolved, day of wound closure (day)
  - New lesions since day 3 visit (y/n)
  - Was an p.o. antibiotic prescribed (y/n)
    - If yes, was the prescription filled (y/n)
    - How many doses have been taken so far? (##)
  - Any diarrhea? (y/n)
  - Any nausea or vomiting? (y/n)
  - Any abdominal discomfort? (y/n)
  - Any new rash? (y/n)

  - Any other new symptoms including headache, dizziness, drowsiness, thrush, as well as any change in local symptoms.

- Wound assessment
  - Fever > 38°C in CRU? (y/n, record temp)
  - Packing present (y/n)
  - Diameter of erythema (mm) at widest diameter
  - Diameter of wound (mm) at widest diameter
  - Tenderness around the wound? (y/n)

- Clinical Assessment (decided by PI or sub-I)
  - Infection worsening, non-improvement, improvement
- Clinical Options (decided by PI or sub-I)
  - No follow-up needed unless infection worsens
  - Suggest follow-up
- Clinical Follow-up, if applicable (obtained from subject or medical record after follow-up)
  - Another incision and drainage in the ED (y/n)
  - Addition of oral antibiotics (y/n)
  - Admission for i.v. Abx (y/n)
  - Admission for surgical intervention (y/n)
  - Return to ED in 2 more days (y/n)

PROTECTION OF HUMAN SUBJECTS:

This research involves the recruitment, enrollment and management of human subjects participating in research. Adults up to age 65 years at enrollment are being studied because adults commonly suffer skin abscesses. Study oversight by the investigators will assure compliance with all regulatory requirements for Institutional Review Board approval prior to the initiation of the study, and will obtain annual re-approval for study activities.

Potential risks and benefits to subjects and procedures to mitigate risks:

- Physical/Medical
  - Serious Adverse Events will be reported to EVMS IRB
- Confidentiality/PHI
  - All PHI will be maintained in an encrypted and password protected electronic file.

RISKS AND SIDE EFFECTS

Risks and side effects related to the anti-microbial TheraGauze we are studying include:

- The skin abscess may re-accumulate and require a second drainage procedure and possibly evaluation for deeper infection.
- A new skin abscess may arise while on the study.
- A local allergic or irritation reaction to the wound packing.
- Inadvertent release of PHI

POTENTIAL BENEFITS.
There may or may not be direct benefit to subjects. Subjects will receive additional follow-up assessments.

SUBJECT COMPENSATION.
Subjects will receive a $40 gift card to a local merchant at each completed visit.

ASSESSMENT OF SAFETY
Subjects must be seen by a physician or an appropriately trained healthcare professional at every study visit, and the evaluation must be documented.

Adverse Events. An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not **c**onsidered related to the medicinal product.

Causality Assessment. For all AEs, the PI will provide an assessment of causal relationship to the study drug. Causal relationship must be assessed by answering the following question: Is there a reasonable possibility the study drug caused the event?

Yes: There is evidence to suggest a causal relationship between the study drug and AE, i.e.: there is a reasonable temporal relationship between the study drug and the event, and the event is unlikely to be attributed to underlying/concurrent disease, other drugs, or other factors.

No: There is no evidence to suggest a causal relationship between the study drug and AE, ie: there is no reasonable temporal relationship between the study drug and the event, or the subject did not take the study drug, or the event is likely to be attributed to underlying/concurrent disease, other drugs, or other factors, or the event is commonly occurring in the (study) population independent of drug exposure.

Adverse Reaction. An AE assessed as likely having a causal relationship with the intervention (i.e., TheraGauze/tobramycin). Specifically focusing on local-toxicity adverse reactions, we will evaluate for increasing redness, increasing pain or a new rash at the site of the packed wound. Increasing pain or redness could be due to progression of the infection (cellulitis/abscess) or local toxicity or reaction to the tobramycin in the TheraGauze/tobramycin packing. This will be assessed by an Investigator. Increasing purulent drainage or the identification of new areas of fluctuance requiring an additional incision and drainage procedure will be assessed as progression of the infection rather than evidence of local toxicity or reaction to the tobramycin.

Severity Assessment. The PI must provide an assessment of the severity of each AE by recording a severity rating, which will be assessed as described below. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a subject outcome or AE-required treatment measure associated with a threat to life or functionality.

Guidelines for Adverse Event Severity Assessments

Mild. Minor awareness of signs or symptoms that are easily tolerated without specific medical intervention.
Moderate. Discomfort that interferes with usual activities and may require minimal intervention.
Severe. Significant signs or symptoms that are incapacitating with an inability to work or perform routine activities and/or that require medical intervention.

Serious Adverse Events. An SAE is any untoward medical occurrence that at any dose: is life threatening**,** requires in-patient hospitalization or prolongation of existing hospitalization**,** results in persistent or significant disability/incapacity. Important medical events may be considered serious when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the drug and the event the event must be reported as a serious and unexpected suspected adverse reaction. SAE will be reported to the local IRB and the FDA within 5 calendar days.

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.
Stopping Rules. Adverse reactions, including local-toxicity adverse reactions, or SAEs will lead to immediate return to the SNGH ED for assessment and removal of the TheraGauze/tobramycin wound packing. The investigator will assess the need for treatment of the adverse reaction or SAE and, if necessary, either treat or refer for treatment, as appropriate. The subject will continue with their scheduled follow up: Day 3 visit in the ED, Day 6 phone follow up, and Day7 visit in the CHKD Infectious Diseases Clinic

STATISTICAL ANALYSIS PLAN

The research coordinators will collect data on a hard copy source document. Clinical and laboratory data will then be entered into an Access database by the coordinator and lab personnel.

The data will be analyzed using SAS 9.4 software. All statistical tests will be two-sided with a significance level of 0.05. Patients who withdraw while on treatment will be included in the data analysis for each time point before withdrawal. Baseline and follow-up measurements of safety, tolerability, numbers of pathogenic bacteria, wound infection persistence or worsening, and gross effects on the rate of wound healing will be summarized using descriptive statistics such as mean, median, standard deviation, interquartile range, frequency, and percentage where appropriate. Normality assessments for the continuous variables will be completed using Shapiro-Wilk tests and stem-and-leaf plots.

Tests of equivalence between the TheraGauze + tobramycin and standard iodoform wick packing treatment groups will establish statistical significance if the two-sided 90% confidence

interval for the difference falls within the limits (-δ, δ), where δ is the margin of clinically accepted difference. This analysis will determine whether the outcomes are equivalent between the TheraGauze+tobramycin and standard iodoform wick packing treatment groups.

CONFIDENTIALITY.
Subjects' research charts will be maintained in the locked coordinators offices until each subject completes the study. Electronic data will be in an encrypted password-protected database, accessible only to the study coordinators, biostatistician, and PI. Subjects' research charts and laboratory specimens will be stored until the completion of the study. Research charts will be maintained in a secured facility for the length of time mandated by federal law. Laboratory specimens (i.e. bacterial culture isolates) will be destroyed at the completion of the study.

AMENDMENTS.
Any changes in procedures will be approved by the IRB prior to implementation, except for those necessary for subject safety. Deviations that change the risk/benefit ratio will be reported to the IRB.

ROLES OF RESEARCH TEAM MEMBERS
Physician investigators and Emergency Room staff will identify potential subjects and will notify the coordinator. The coordinator will explain the study and she or the physician will obtain informed consent. The physician will collect medical history culture the wound, and care for the wound per standard of care, using TheraGauze with tobramycin or standard gauze per randomization. The coordinators will ensure that all data are collected and recorded in the study chart, collect lab results, schedule follow-up appointments and make telephone contacts. Routine cultures and sensitivities will be performed in the hospital laboratories. The research lab staff will perform quantitative analysis. Coordinators and lab staff will enter data into the database. The statistician, with the PI, will analyze the results. The PI will oversee all of the above activities as well as performing most of the Visit 3 clinical assessments. and report findings to the sponsor.

RESEARCH MONITOR.
All Serious Adverse Event (SAE) reports will be sent to the Research Monitor, Ursula Kelly, MD, within 24 hours. The Research Monitor will also review subject charts for safety on a 3 to 6 month basis, assessing for evidence of tolerability or superiority/inferiority between the arms, and will discuss her findings with the PI. The Research Monitor may discuss the protocol with the investigators, interview subjects, and consult with others outside the study about the research. She shall have the authority to stop the protocol, remove subjects from the protocol, and take any necessary steps to protect the safety and well-being of subjects until the IRB can assess the Monitor's report. The Research Monitor shall have the responsibility to promptly report her observations and findings to the IRB or other designated official. The Research Monitor is required to review all unanticipated problems involving risks to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the research monitor must comment on the outcomes of the event or problem and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The research monitor must also indicate whether he/she concurs with the details of the report provided by the principal

investigator. Reports for events determined by either the investigator or research monitor to be possibly or definitely related to participation and report of events resulting in death must be promptly forwarded to the USAMRMC ORP HRPO.

Study Visit Schedule:

PROCEDURE	VISIT 1	VISIT 2	VISIT 3
	Screening/Day 1	Day 3-1/+2 days	Day 7±2 days
Consent	X		
Inclusion/exclusion	X		
Demographics	X		
Medical history	X		
History and current symptoms	X	X	X
Temperature, wound assessment	X	X	X
Culture abscess	X	X	
Randomization	X		
Apply wick	X		
Provide prescription if applicable	X		
Remove packing (if applicable)			
Follow-up phone call Day 2 (+2)	X		
Follow-up phone call day prior to Day 7 visit		X	

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