# Research Proposal

## Title: Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Sepsis Associated with Acute Necrotizing Soft Tissue Infections, The NASTI HAT Trial

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**SETTING:** Ascension Via Christi Hospital – St. Francis Campus, Wichita, Kansas

**DESIGN:** Single center, prospective, randomized, placebo controlled double-blind trial

**SAMPLE SIZE:** Will be 132 participants (66 participants per study group)

**INCLUSIONS:** All adult patients diagnosed with a necrotizing soft tissue infection and sepsis

### I. BACKGROUND AND PRELIMINARY STUDIES:

Necrotizing soft tissue infections (NSTIs) are a surgical emergency often presenting with concomitant sepsis. While the mortality associated with NSTIs has improved over time, it remains high at approximately 20%.[1-2] Furthermore, while early surgical excision remains the mainstay of treatment and improves survival, sepsis can still lead to organ failure and death.[3-5]

In 2017, Dr. Paul Marik published a retrospective before-after clinical study proposing early use of intravenous hydrocortisone, vitamin C (ascorbic acid), and thiamine (hereafter referred to as HAT) in critically ill patients with sepsis to prevent the progression of shock to multi-system organ dysfunction, and ultimately death. A significant decrease in mortality (8.5% vs 40%) in the treatment versus control group was reported, in addition to a significant decrease in the Sepsis-Related Organ Failure Assessment (SOFA) score, and all patients in the treatment group were able to be weaned off vasopressors.[6] Multiple rigorous randomized controlled trials have since followed and have not been able to replicate these beneficial findings.[7-12] Despite this, HAT appears to be safe. Furthermore, while these and other studies have looked at varying intensive care unit (ICU) populations, to our knowledge, none have focused specifically on NSTIs. Since HAT is felt to be a safe regimen and shock is common in this population, it is reasonable to explore the use of HAT among patients with NSTIs.

### II. STUDY OBJECTIVE:

Evaluate the impact of HAT therapy versus placebo in the treatment of patients with an acute NSTI and sepsis.

Primary outcome:

1. Hospital survival (including those who die within 24 hours of hospital admission)

Secondary outcomes:

1. Duration of vasopressor therapy
2. Requirement for renal replacement therapy in patients with Acute Kidney Injury (AKI)
3. ICU length of stay (LOS)
4. Change in serum procalcitonin (PCT) over first 72 hours
5. Change in SOFA score over first 72 hours (measured as SOFA score daily for four days, with day one being admission, then 3 days after, totaling 4 days of treatment with HAT)
6. Procalcitonin clearance (formula = initial PCT – 72 hour PCT divided by initial PCT x 100)
7. Number of wound related surgeries
8. Wound status at time of hospital discharge:
    a. Open
    b. Closed

## III. STUDY METHODOLOGY:

Study design:

Single center, prospective, randomized, placebo controlled double-blind trial.

Inclusion criteria:

1. Necrotizing soft tissue infection by clinical diagnosis and requiring surgical treatment.
2. Sepsis by clinical diagnosis and/or by Sepsis-3 criteria[15], with source attributed to the wound.
3. Anticipated or confirmed intensive care unit admission.

Exclusion criteria:

Adapted from VICTAS[12] protocol:

1. Age < 18 years of age
2. Weight < 40 kg
3. Prior enrollment in this study or current enrollment in another study of any kind
4. Surgical findings, pathology/histology findings, or other findings determined to be inconsistent with an infectious acute NSTI such that the clinical diagnosis is no longer that of a NSTI
5. Sepsis deemed unlikely
6. Limitations of care during enrollment [defined as refusal of cardiovascular and respiratory support modes described in inclusion criteria, including “do not intubate” (DNI) status and comfort care]
7. Known allergy or known contraindication to vitamin C, thiamine, or corticosteroids (including previous history or active diagnosis of primary hyperoxaluria and/or oxalate nephropathy, or known/suspected ethylene glycol ingestion, or known G6PD Deficiency)
8. Use of vitamin C at a dose of >1g/day (IV or oral) within the 24 hours preceding first episode of qualifying organ dysfunction during a given ED or ICU admission
9. Chronic disease/illness that, in the opinion of the site investigator, have an expected lifespan of < 30 days unrelated to current sepsis diagnosis (e.g., stage IV malignancy, neurodegenerative disease, etc.)

10. Kidney Stone(s) of any kind
11. History of Oxalate Kidney Stone(s)
12. Pregnancy or known active breastfeeding
13. Prisoner or Incarceration
14. Inability or unwillingness of subject or legal surrogate/representative to give written informed consent

Comparator:
Patients randomized to not receive HAT will comprise the control group and those randomized to receive HAT will comprise the treatment group.

Surgeons and surgical performance:
This study will not affect the surgical care of the patient. Patients with known/suspected NSTI will undergo surgery urgently/emergently as before. Patients who consent for and meet criteria for this study will be randomized, to either receive or not receive HAT. Care is otherwise identical for patients in each group. The only difference in the care of these patients will be in whether or not they receive HAT. The only surgeons who will be involved are those on the Burn service.

Study Site:
Ascension Via Christi Hospital – St. Francis Campus, Wichita, Kansas.

Duration of Treatment:
Patients will be enrolled within 24 hours of diagnosis of sepsis related to a NSTI. HAT will be initiated within 4 hours of enrollment (thus treatment with HAT can occur no later than 28 hours from diagnosis).

Per Dr. Marik's original study, HAT consists of:
1) 1.5 g vitamin C every 6 hours for 4 days or until ICU discharge
2) 50 mg hydrocortisone every 6 hours for 7 days or until ICU discharge (followed by a taper over 3 days)
3) 200 mg thiamine every 12 hours for 4 days or until ICU discharge

In our study, due to the prolonged ICU course typical of most patients with NSTIs, it is not felt feasible to continue indefinitely "until ICU discharge." Thus, treatment will be continued for 4 to 7 days plus a 3 day taper (respectively) as above, with no plan for a longer duration of treatment.

The control arm will receive the same standard ICU care for NSTI but will not receive HAT. They will receive a placebo consisting of normal saline, indistinguishable to the treatment team (blinded) but known to the pharmacy team (unblinded to treatment and placebo groups). This is so that if the treatment team elects to give stress dose steroids, they can be administered without breaking protocol (i.e. if the patient is getting HAT, it includes steroids, so if the treating team wanted to start hydrocortisone - because they didn't know if the patient was on HAT or placebo and felt steroids were indicated - the pharmacist could ensure the patient was on steroids one way or another without unblinding the providers).

Duration of Study:

The study enrollment period will continue for one year after its initiation, or until enrollment goal is met. Patients will be followed until hospital discharge.

Data Collection:
Data will be recorded prospectively by IRB approved study personnel and entered into a shared spreadsheet on the Ascension Google Drive. See the attached spreadsheet for the specific data to be collected.

**Variables collected will include:**

- Patient name
- Medical record number (FIN)
- Date of birth
- Date and time of diagnosis of NSTI
- Date and time of randomization
- Time from diagnosis of NSTI and sepsis to initiation of HAT: hours.
- Time on pressors prior to initiation of HAT: hours
- Patient demographics (age, gender)
- Location of NSTI infection
    - Perineum
    - Genitalia
    - Groin
    - Lower extremity
    - Upper extremity
    - Hand
    - Foot
    - Head/Neck
    - Back
    - Chest
    - Abdomen
    - Multiple/Other – free text
- Preexisting conditions – similar to Dr. Marik's study:
    - None
    - Diabetes mellitus
    - Hypertension
    - Heart failure
    - Malignancy
    - Chronic obstructive pulmonary disease
    - Cirrhosis
    - Cerebrovascular accident
    - Acute Kidney Injury (AKI)
    - Chronic kidney disease
    - Morbid obesity (weight and height)
    - Immunocompromised (HIV infection, neutropenia, post-transplantation, other)
    - Active medical systemic steroid use at baseline
    - Illicit drug use evident by patient history or drug screen
    - Active tobacco or nicotine product use
- Time from diagnosis of NSTI to surgery: hours

- Total number of visits to the operating room for NSTI-related surgical intervention
- Identification of NSTI derived from pressure-related injury
- Wound status at time of ICU discharge:
    - Open
    - Closed
- Duration of vasopressor therapy: hours cumulative from entire hospitalization
- Positive blood cultures (Y/N)
- Organism present on wound culture
- Time to antibiotic use
- Antibiotic used
- Requirement for renal replacement therapy in patients with AKI (Y/N)
- Procalcitonin level daily for 4 days (with day one being admission/enrollment, then 3 days after, totaling 4 days of treatment with HAT)
- Daily SOFA score for 4 days (with day one being admission/enrollment, then 3 days after, totaling 4 days of treatment with HAT)
- Total ventilator days
- ICU LOS: Days
- Hospital length of stay: Days
- Discharge disposition: alive or deceased
- If the patient withdrew: Y/N
- Reason for patient withdrawal: Free text

Population:
All adult patients presenting to Ascension Via Christi Hospital St Francis will be screened for inclusion and exclusion criteria. Once a potential study participant has been identified, a member of the study team will approach the patient or the patient's legal representative regarding inclusion into this study, and consent will be obtained. The length of the enrollment period of this study will be one year from the start of the study, or until the enrollment goal is met. Participants will be followed until hospital discharge.

Patient Enrollment and Random Assignment:
Patients who are admitted or diagnosed with sepsis secondary to an acute necrotizing soft tissue infection will be provided with the "Patient Informed Consent/HIPAA Authorization" document and will have the study explained to them during their initial evaluation by a member of the study team prior to enrollment. All qualifying patients who choose to participate in the study will sign the consent form, or have it signed by their legal representative. One copy of the consent form will be stored in the patient's chart and a second copy with the Research Scientist in the study files. A third copy of the consent will be provided to the patient for their reference. Randomization will be done via block randomization by the pharmacy department after a patient has consented to participate in the study.

The patient and/or his legal representative will have ample opportunity to decide whether they want to be included in this study and ask questions. The patient will be approached by a member of the study team prior to enrollment. This encounter will be within 24 hours of diagnosis, to provide ample time for consideration and to ask questions. Once consent is obtained, the HAT therapy should be started within 4 hours, such that the maximum possible time to initiation from diagnosis is 28 hours. If the patient meets inclusion criteria, then HAT or placebo (saline) will

be initiated per the randomization protocol, and only the pharmacy team will be unblinded. If the patient's legal representative signs the consent form on behalf of the patient, once the patient regains the ability to make medical decisions for themselves, they will be provided with the consent form and given the opportunity to continue in the study, signing a new consent themselves, or be given the option of discontinuing participation in the study. If the patient chooses to discontinue participation, all study data collected up to that point will be used in the study, although no new patient data will be collected, with the exception of any data needed to monitor the safety of the patient or adverse events in relation to the study treatments already administered.

Potential Risks to Subjects in the Study:
There exists the potential risk of a breach of subject confidentiality during the conduct of this research study. The following will be carried out to maintain patient confidentiality:

All medical information will be protected, and access will be limited to study investigators. Most of the data will be supplied from the electronic charting system at Ascension Via Christi Hospital – St. Francis Campus with patient identifiers (name, date of birth, medical record number [FIN]). The investigators will store data on an Ascension Google Drive. The research team is located in Room 3082 at Ascension Via Christi Hospitals on Saint Francis. The transfer will all occur within the @ascension.org email system, with no one able to view the Google Drive without an Ascension email. No information will transfer outside this system.

Patient identifiers will be kept with the participants PHI while the participant is hospitalized, and study data are actively being collected. Once the participant has been discharged, and all study data has been collected, subject identifiers (subject name, medical record number (FIN), date of birth, date of randomization, and date of procedures) will be maintained on a master list that links the subject to the specific study number. That list will be maintained under secure conditions at all times. Once all data has been deemed complete and analyzed and the work has been accepted for publication, the master list will be destroyed. This will effectively render the list de-identified as no other identifiers will be entered into the data set for analysis. The method in which this will be accomplished is that the master list will be shredded, and any computer file of the master list will be deleted from electronic media. The investigators and designated members of the research team will have access to the study data and will be responsible for data management.

Like any treatment there are potential risks with the administration of HAT, but these are overall low, as evidenced by numerous studies[6-8,12-14,]. The most recent large randomized control trial, VICTAS[12], which examined 501 patients, had no reported serious adverse events and only two adverse events (hemorrhagic shock and decreasing kidney function in the intervention group assessed as potentially related to study participation). In the 2017 Colliou et. al study, vitamin C-related oxalate nephropathy was seen in patients who received higher doses or received doses for a longer duration (1 month – 3 years) than Dr. Marik's HAT dose.[13] One trial found that hypernatremia was more common in the control group, which the study authors speculated might be due to increased sodium retention from glucocorticoids. GI bleed was another cited complication in this study with an incidence of 3:2 for treatment versus control groups.[8] Like vitamin C, thiamine is a commonly used vitamin and can rarely cause electrolyte abnormalities. Administration of hydrocortisone, a low strength mineralocorticoid, is a commonly used medication in the ICU setting and can rarely cause hypertension or arrhythmia. The risk to

omitting HAT has not been formally studied in this population. Finally, the treatment duration in our study will be limited (i.e. a maximum of 4 days for vitamin C and thiamine and 7 days plus a 3 day taper for hydrocortisone).

The potential risks due to septic shock from a NSTI itself are expected to be no different for patients whether they are enrolled in this study or not.

Evaluations During Treatment:
The evaluation period will begin at the time HAT or placebo is initiated after sepsis criteria is met and end at hospital discharge.

The investigators will collect data as outlined above under "Data Collection."

Subject Non-evaluability:
Subjects will be deemed non-evaluable and will be dropped from the study if they meet the exclusion criteria and/or elect to withdraw from the study.

Costs
Participants will never be charged for study-related drugs in this study, regardless of the group to which they are randomized. This means that participation in this study will not cost participants more or less than the cost of normal care. No charges for care other than those that would be normally received will be incurred during the study and the cost for participants' normal care will be the participants' and/or the participants' insurance provider's responsibility.

Participants will not be charged for the drugs used in this study. The pharmacy will be absorbing the costs of the drugs regardless of whether it's thiamine, vitamin C, hydrocortisone, or placebo.

## IV. STUDY TIME FRAME:

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| Proposal Development/Approval: | September 2020 - IRB Approval |
| Data Collection: | IRB Approval – June 2022 |
| Data Cleaning and Analysis: | June 2022 – June 2023 |
| Manuscript Preparation: | June 2023 – December 2023 |
| Abstract Submission: | February 2023 |

## V. PUBLICATION AND PRESENTATION OF DATA:

Data from this research study will be considered for submission to The Journal of Burn Care and Research, The Journal of the American Medical Association, the American Journal of Surgery, The American Surgeon, or other journal felt appropriate for publication. In addition, data from this research study may be submitted for presentation at the Annual Meeting of the American Burn Association, the Midwest Region Burn Conference, the Kansas Chapter of the American College of Surgeons, the Southwestern Surgical Congress Annual Meeting, and/or other meeting(s) as felt appropriate for the material.

## VI. STATISTICAL ANALYSIS:

The data that is collected will be compiled, evaluated and summarized by calculating means and standard deviations for continuous data, medians and quartiles for ordinal data, and proportions for discrete data. One-way analysis of variance will be utilized to compare continuous data. Where heterogeneity of variance is identified, data will be either transformed and analyses rerun, or data will be analyzed using the Mann-Whitney U-Test. Chi-square analysis will be utilized for comparison of categorical data. Ordinal data will be analyzed using the Mann Whitney U-Test. Logistic regression analyses will be utilized to identify independent predictors of the outcomes variables of interest. All analyses will be run as two-tailed tests and results of analyses will be considered significant if the resultant P-value is less than or equal to 0.05. Analyses will be run using SPSS 19.0.

## VII. POWER ANALYSIS AND DETERMINATION OF STUDY SIZE:

Based on published data in patients with necrotizing soft tissue infections, as well as our institutional data, we expect the mortality rate for our control patients to be approximately 20% when no NAT is used. If we anticipate a 78.8% decrease in mortality as observed in the trial by Marik,[6] we would expect to see a decrease in mortality to a rate of 4.24%. Assuming an $\alpha$ level of 0.05, and 80% power, analysis suggests that we would need a minimum of 66 patients in each of the two study groups for a sample size of 132 participants.

## VIII. PARTICPANT CONFIDENTIALITY, DATA SECURITY, AND RECORDING RETENTION:

Patients included in this study will be given a sequentially assigned number. This number will not be associated with any identifying information such as date of birth, social security number, or medical record number. Patient identifiers will be kept with the participants PHI while the participant is hospitalized, and study data are actively being collected. Once the participant has been discharged, and all study data has been collected, subject identifiers and their assigned study number will be kept as a separate list that will be maintained in a secure location. All collected data will be evaluated and analyzed as group data only and no specific individuals or cases will be used in presentation or publication from this study. Once the completed manuscript is accepted for publication, the master list will be destroyed and all computer files of the subject master will be erased.

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