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Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Sepsis Associated with Acute Necrotizing Soft Tissue Infections: The NASTI-HAT Case Series

Morgan Gilmour M.D. [1], Erica N. Presnell Pharm.D., BCCP [2], Sarah Fischer M.S.N., R.N. [2], Jared Reyes Ph.D. [1] and Thomas Resch M.D. [1,*]

[1] Department of Surgery, University of Kansas School of Medicine-Wichita, 929 N. Saint Francis St., Room 3082, Wichita, KS 67214, USA

[2] Ascension Via Christi Hospitals Wichita, Inc., 929 N. Saint Francis St., Wichita, KS 67214, USA

* Corresponding author: tresch@wsspa.com

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Abstract: Necrotizing soft tissue infections (NSTIs) are surgical emergencies often presenting with concomitant sepsis. The use of intravenous hydrocortisone, vitamin C (ascorbic acid), and thiamine (HAT) has been proposed as beneficial in treating sepsis. To our knowledge, no study has focused exclusively on its use in NSTIs. This study aimed to evaluate use of HAT among patients with NSTIs and included patients from a single Midwestern regional burn center. Patients diagnosed with sepsis or septic shock secondary to an NSTI were randomized and received either intravenous HAT or placebo. The primary outcome was hospital survival. Secondary outcomes included vasopressor therapy duration, renal replacement therapy need, intensive care unit length of stay, serum procalcitonin and sequential organ failure assessment (SOFA) change in the first 72 h, number of wound-related surgeries, and wound classification at hospital discharge. While our study started as a randomized controlled trial, due to low enrollment it was transitioned to a case series. Of the 10 patients enrolled, half received HAT therapy. No significant difference was found between the treatment and placebo groups. Future larger, multicenter studies may help better elucidate the role of intravenous HAT therapy in patients with NSTIs.

Keywords: sepsis; shock; septic; soft tissue infections; fasciitis; necrotizing

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Introduction

Necrotizing soft tissue infections (NSTIs) are surgical emergencies that often present with concomitant sepsis. While early surgical excision is the mainstay of treatment, mortality remains high at approximately 20%, with sepsis being a contributing factor [1–5]. A 2017 retrospective before–after clinical study by Dr. Marik [6] reported that early use of intravenous hydrocortisone, vitamin C (ascorbic acid), and thiamine (HAT) in critically ill patients with sepsis led to a significant decrease in mortality (8.5% vs 40%) and sequential organ failure assessment (SOFA) scores [6]. All patients in the studys treatment group were able to be weaned off vasopressors [6].

The mechanism of action of intravenous HAT is thought to be a synergistic blunting of the dysregulated immune response seen in sepsis and septic shock. Hydrocortisone acts on multiple inflammatory cascade sites and is an adjunct treatment for suspected adrenal insufficiency in patients with septic shock [6,7]. Vitamin C is a well-known water-soluble vitamin and antioxidant. It may be depleted in critically ill patients who therefore may not have access to its multiple potential benefits: blocking reactive oxygen species released by neutrophils, preventing neutrophil-induced lipid oxidation, preventing depletion of other circulatory antioxidants, protecting the endothelial barrier, increasing the vasomotor response via increased endogenous norepinephrine and vasopressin synthesis, and potentially playing a role in wound healing in terms of improved macrophage and T-cell function and as a cofactor in collagen biosynthesis, among other effects [6,8,9]. Hydrocortisone facilitates uptake of vitamin C into cells by restoring cytokine-induced down-regulation of the vitamin C transporter [6]. Vitamin C can increase glucocorticoid receptor sensitivity to hydrocortisone, making cells more responsive to hydrocortisone administration [6]. Thiamine (vitamin B1) is thought to be deficient in many critically ill patients and acts as a coenzyme in the metabolism of vitamin C, facilitating the formation of CO_2 from glyoxylate (a metabolite of vitamin C) rather than the formation of renal oxalate stones [6,8,10].

While another case–control study showed a trend in lowering mortality and in duration of ventilation therapy [11], multiple rigorous randomized controlled trials have since followed Dr. Mariks landmark study [6] without having been able to replicate the beneficial findings of HAT therapy [12–21]. Still, HAT therapy appears to have few major adverse reactions [22]. Furthermore, while HAT treatment has been investigated in various intensive care unit (ICU) populations, to the authors knowledge, none have focused specifically on NSTIs.

The regional burn center in this study had previously utilized HAT therapy in some cases of septic shock associated with NSTIs and determined that it was beneficial. The goal of this research was to formally study HAT in the NSTI population to see if objective data supported this notion. Thus, this study began as a double-blind randomized controlled trial but ultimately, due to low enrollment, this investigation was transitioned to a case series.

Materials and Methods

Study Design, Setting, and Selection of Participants

Patients from a single Midwestern regional burn center were enrolled from September 2021 through May 2023. Inclusion and exclusion criteria for patient selection are listed in Appendix A. Inclusion criteria stipulated patients with an NSTI and sepsis requiring emergency surgery with anticipated admission to the burn ICU. While a general clinical diagnosis of sepsis was initially allowed, all patients ultimately had to meet the Sepsis-3 criteria [23] for sepsis or septic shock to qualify. Use of the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score [24] was allowed as part of the initial decision-making process, but was not required. Ultimately, the diagnosis of NSTI had to be confirmed intraoperatively and ongoing clinical course/findings had to remain clinically consistent with an NSTI. Patients were enrolled within 24 h of diagnosis of sepsis related to NSTI. Treatment (intravenous

HAT or placebo) was initiated within 4 h of enrollment; therefore, the maximum allowable time from diagnosis to treatment was 28 h.

The placebo group received normal saline; the treatment arm received HAT, consisting of intravenous 1.5 g vitamin C every 6 h for 4 days, 50 mg of hydrocortisone every 6 h for 7 days followed by a taper over 3 days, and 200 mg thiamine every 12 h for 4 days. All other treatment was in line with the standard of care therapy for an NSTI and sepsis or septic shock. The placebo was clinically indistinguishable from the HAT therapy and only pharmacy was unblinded due to necessity for drug preparation.

Data Collection and Analyses

Patient medical records were reviewed for demographic and outcome variables as listed in Appendix B. The primary outcome was hospital survival, including those who died within 24 h of hospital admission. Secondary outcomes included duration of vasopressor therapy, requirement for renal replacement therapy for acute kidney injury (AKI), ICU length of stay, change in serum procalcitonin (ProCal) over the first 72 h, change in SOFA score over the first 72 h, the number of wound-related surgeries, time to first antibiotic administration, and whether the wound was open or closed at the time of hospital discharge.

Data summaries were calculated using SPSS release 29.0. (IBM Corp, Summers, NY, USA). Summaries of group data are presented as medians with interquartile ranges for continuous data and percentages (counts) for categorical data. All tests were two-tailed with an alpha level of <0.05 considered statistically significant. All comparisons were completed prior to unblinding of the study treatment arms.

This study was conducted after approval for implementation by the Institutional Review Board of Ascension Via Christi Hospitals Wichita, Inc. and the Human Research Protection Program of the University of Kansas School of Medicine—Wichita (KUVC-1814). The trial was registered at clinicaltrials.gov (NCT05157360).

The sample size required was 132 participants, with 66 in each group based on a power analysis anticipating a 20% mortality rate in the control arm. However, due to low study enrollment, the study was concluded before 132 participants were enrolled and, instead, a retrospective chart review of enrolled participants was conducted.

Results

Enrollment

Twenty-three patients passed initial screening (NSTI requiring emergent surgery, sepsis/septic shock, and ICU admission) from September 2021 through May 2023 and were evaluated for enrollment. Ten patients were enrolled after informed consent was obtained. Of those who met criteria but were not enrolled, 3 declined to participate, 3 were admitted with poor prognosis and transitioned to comfort care shortly after admission, and 2 did not have a legally authorized representative. One patient was not approached for consent due to medication shortages at the time of admission, requiring a temporary pause on study enrollment. Of the 4 remaining individuals, one was a prisoner, one revealed a history of kidney stones not previously elicited by the admission history and physical, a diagnosis of sepsis was linked to multiple sources with overall poor prognosis for one patient, and one left against medical advice within the first 24 h of hospital admission.

Case Review

Case 1

A 67-year-old morbidly obese female with no other documented comorbidities presented with abdomen, pannus, and flank NSTI. She received intravenous HAT. From presentation to the hospital, the patient received antibiotics within 8 h and NSTI diagnosis within 25 h. She went to the operating room (OR) within 1 h of diagnosis, and ultimately had one additional wound-related surgery. She did not receive pressors during her stay. The patients wound cultures were positive for *Peptostreptococcus* species, *Prevotella* species, and *Actinomyces turicensis*. ProCal levels did decrease from admission, as did the patients SOFA score. She experienced sudden unexpected death when she arose to use the bedside commode. Without an autopsy available, the etiology of demise was suspected to be cardiac in nature and unrelated to HAT. Thus, this patient died on hospital day 7 despite treatment with HAT.

Case 2

A 66-year-old male with hypertension and tobacco use presented with an NSTI of the buttocks. He received the placebo. From presentation to the hospital, the patient received antibiotics within 1 h and NSTI diagnosis within 16 h. He went to the OR at 33 min from diagnosis and required 2 wound-related surgeries. He required pressors for 34 h and 36 min. Patient spent 4 days in the ICU and did not require a ventilator. The patients wound cultures were positive for *Peptostreptococcus* species, *Staphylococcus lugdunensis*, and *Corynebacterium jeikeium*. His ProCal levels increased and SOFA score decreased from admission. Patient was discharged with a closed wound after 8 days.

Case 3

A 47-year-old morbidly obese male with tobacco use presented with a perineal, genital, and buttock NSTI. He received the placebo. From presentation to the hospital, the patient received antibiotics within 7 h and NSTI diagnosis within 27 h. He went to the OR in one h and 8 min from diagnosis and required 2 wound-related surgeries. He spent 47 h and 8 min on pressors, required 3 days on a ventilator, and spent 4 days total in the ICU. The patients wound cultures were positive for *Escherichia coli* mucoid strain; *Enterococcus hirae*; and *Streptococcus constellatus*. ProCal levels and SOFA score for this patient both decreased from admission. He was discharged with a closed wound on hospital day 8.

Case 4

A 55-year-old morbidly obese male with hypertension, diabetes mellitus 2, heart failure, and tobacco use presented with a lower extremity NSTI. He received intravenous HAT. From presentation to the hospital, the patient received antibiotics within 5 h and NSTI diagnosis within 22 h. He went to the OR in 1 h and 4 min and required 4 wound-related surgeries. He spent 53 h and 48 min on pressors, required 5 days on the ventilator, and 11 days in the ICU. He was also treated for an AKI. The patients wound cultures were positive for *Fusobacterium* species, *Actinomyces* species, and *Prevotella* species. His ProCal levels increased and SOFA score decreased from admission. He was discharged with an open wound after 18 days in the hospital.

Case 5

An 80-year-old male with hypertension, tobacco use, and alcohol abuse presented with a lower extremity NSTI. He received the placebo. From presentation to the hospital, the patient received

antibiotics within 2 h and NSTI diagnosis within 10 h. He went to the OR in 15 min and ultimately required 3 wound-related surgeries total. He spent 128 h and 50 min on pressors and 7 days in the ICU. He did not require a ventilator. He was also treated for an AKI. The patients wound cultures were positive for *Streptococcus pyogenes* and methicillin-resistant *Staphylococcus aureus*. Patients ProCal levels and SOFA score decreased from admission. He was discharged with a closed wound on hospital day 17.

Case 6

A 66-year-old morbidly obese female with hypertension presented with a lower extremity NSTI. She received intravenous HAT. From presentation to the hospital, the patient received antibiotics within 5 h and NSTI diagnosis within 5 h. She went to the OR 22 h and 23 min after diagnosis and required 4 surgeries, including 2 wound-related surgeries and 2 exploratory laparotomies for emergent management of a duodenal perforation and necrotic bowel. She required pressors for 262 h and 29 min. She was also treated for an AKI. The patients wound cultures were positive for *Peptostreptococcus* species, *Proteus mirabilis*, β-hemolytic *streptococci*, group C *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*, and *Clostridium ramosum*. Her ProCal levels decreased and SOFA score increased from admission. Time to surgery was delayed due to the need for emergent hyperkalemia treatment. Bowel complications were suspected to be secondary to ongoing shock, among other comorbidities. Given the significant soft tissue loss and progressive organ failure, the family elected to proceed with comfort care. She spent 11 days on the ventilator and 13 days in the ICU before death.

Case 7

A 46-year-old female with diabetes mellitus II, hypertension, and malignancy presented with a buttock NSTI. She received intravenous HAT. From presentation to the hospital, the patient received antibiotics within 3 h and NSTI diagnosis within 12 h. She was diagnosed in the OR and required 3 wound-related surgeries. She spent 134 h and 53 min on pressors. She was also treated for an AKI. The patients wound cultures were positive for *Prevotella* species, *Bacteroides ovatus*, *Escherichia coli*, *Enterococcus avium*, *Staphylococcus simulans*, and *Corynebacterium species*. Her ProCal levels increased and SOFA score decreased from admission. Notably, patients ProCal was significantly higher than levels in the other 9 cases, with a peak of 66.24; for other patients, the next highest level was 7.81. Despite adequate debridement and maintenance of a clean wound environment, the patient was in profound shock refractory to treatment. Her family elected to withdraw care. Patient required 10 days on the ventilator and spent 10 days in the ICU before death.

Case 8

A 45-year-old morbidly obese female presented with an abdominal NSTI. She was suspected to have had undiagnosed diabetes mellitus II and hypertension. She received the placebo. From presentation to the hospital, the patient received antibiotics within 3 h and NSTI diagnosis within 24 h. The diagnosis of NSTI was made in the OR and she required only one surgery. She did not require pressors. The patients wound cultures were positive for *Streptococcus pyogenes*. Her ProCal levels and SOFA score decreased from admission. She spent 12 days in the ICU and was treated for an AKI. She was discharged with a closed wound on hospital day 15.

Case 9

A 69-year-old male with hypertension and diabetes mellitus II presented with a perineal NSTI. He received intravenous HAT. From presentation to the hospital, the patient received antibiotics within 2 h and NSTI diagnosis within 11 h. He went to the OR in 2 h and 43 min and required 4 wound-related surgeries. He spent 26 h and 41 min on pressors. He did not require a ventilator. He spent 8 days in the ICU. The patients cultures were positive for *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, *Escherichia coli*, and *Streptococcus anginosus*. His ProCal levels and SOFA score decreased from admission. He was discharged on hospital day 12 with a closed wound.

Case 10

A 54-year-old male with paraplegia, hypertension, and diabetes mellitus II presented with an NSTI of the genitalia. He received the placebo. From presentation to the hospital, the patient received antibiotics within 2 h and NSTI diagnosis within 8 h. He went to the OR in 1 h and 42 min and required 2 wound-related surgeries. He spent 29 h and 20 min on pressors. He did not require a ventilator. Patient spent 8 days in the ICU and was treated for an AKI. The patients wound cultures were positive for *Escherichia coli*, *Corynebacterium species*, and *Staphylococcus haemolyticus*. His ProCal levels and SOFA score decreased from admission. He was discharged with a closed wound on hospital day 10.

Patient Demographics

There were no statistically significant $P < .05$) differences between the control arm and treatment arm. The median age in the treatment arm was 66 years of age (interquartile range [IQR] 50.5–68) and that of the control arm was 54 years (IQR 46–73). The mean age was 59.5 years. The median body mass index in the treatment arm was 47.6 kg/m^2 (IQR 35.1–49.3) and 33.5 kg/m^2 (IQR 23.8–40.1) in the control arm. The median time to antibiotic administration was 2 h and 31 min. There were 6 males enrolled in the trial, of whom 2 received HAT. All enrolled patients had at least one preexisting condition. The most prevalent preexisting condition was hypertension, found in 7 patients. Concomitant AKI was present in 6 patients at time of admission. Of the 10 patients, 5 were morbidly obese. Four had diabetes mellitus type II, and 4 were active users of tobacco/nicotine. Table 1 displays the baseline characteristics of the HAT and placebo groups.

Discussion

General

Sepsis and septic shock were anticipated to be common among patients presenting with an NSTI. One recent small Dutch retrospective study reported septic shock in 55% of their 80 patients with NSTIs [25]. Our hospital includes the only regional burn center in a 180-mile radius, and patients with NSTIs are routinely referred to our facility, making it unlikely that they were referred elsewhere. While the option of a general clinical diagnosis of sepsis was allowed, ultimately, a more standardized diagnosis using the Sepsis-3 criteria was required in an effort to remain as objective as possible. Interestingly, not enough patients presenting with NSTI met the Sepsis-3 criteria to reach our enrollment goals. Although our enrollment appeared to be limited by the Sepsis-3 criteria, our original concern had been the opposite, ie, that the Sepsis-3- (qSOFA-) based identification of septic patients was simple and broad enough that we might over-enroll patients.

Table 1: Patient Demographics and Comorbidities

	HAT (n = 5)	Placebo (n = 5)	
	Mdn (IQR) or % (n)	**Mdn (IQR) or % (n)**	***P* value**
Age, y	66 (50.5–68)	54 (46–73)	.548
BMI, kg/m^2	47.6 (35.1–49.3)	33.5 (23.8–40.1)	.095
Gender, male	40.0% (2)	80.0% (4)	.524
Preexisting conditions	100% (5)	100% (5)	-
Diabetes mellitus	60.0% (3)	20.0% (1)	.524
Hypertension	80.0% (4)	60.0% (3)	>.999
Heart failure	20.0% (1)	0.0% (0)	>.999
Malignancy	20.0% (1)	0.0% (0)	>.999
Acute kidney injury	60.0% (3)	60.0% (3)	>.999
Requiring RRT	0.0% (0)	0.0% (0)	-
Morbid obesity	60.0% (3)	40.0% (2)	>.999
Tobacco/nicotine use	20.0% (1)	60.0% (3)	.524
Pressure-related	40.0% (2)	0.0% (0)	.444
Positive blood culture	0.0% (0)	20.0% (1)	>.999
COPD	0.0% (0)	0.0% (0)	-
Cirrhosis	0.0% (0)	0.0% (0)	-
CVA	0.0% (0)	0.0% (0)	-
CKD	0.0% (0)	0.0% (0)	-
Immunocompromised	0.0% (0)	0.0% (0)	-
Active steroid use	0.0% (0)	0.0% (0)	-
Illicit drug use	0.0% (0)	0.0% (0)	-

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; HAT, hydrocortisone, ascorbic acid, thiamine; IQR, interquartile range; RRT, renal replacement therapy.

Perhaps the Sepsis-3 definition was not the best choice for use in identifying sepsis or septic shock. It is no secret that the best way to clinically define sepsis and septic shock continues to be debated and revised over time. However, the Sepsis-3 criteria were used in the study referenced above to diagnose septic shock, wherein over half of the patients met the criteria [25]. Findings in the OR of obvious gangrenous tissue decomposition that one would assume would readily be associated with sepsis and septic shock were not always associated with Sepsis-3 criteria in our institution.

Perhaps some patients had occult immunosuppression and did not mount the typical inflammatory response. Fever, for example, may be blunted in this population [25]. Due to the study duration, it is also possible that there were just by chance fewer patients with NSTIs who met the Sepsis-3 criteria during the study time period. Ultimately, our results are observational only. Additional research is needed to reach any meaningful conclusions. Future studies can consider extending the study duration and/or involving multiple health care facilities to help reach goal enrollment. While disappointed that we were unable to reach our goal enrollment, it is the authors opinion that using the Sepsis-3 criteria is still a well-supported and objective way to enroll patients for such a study.

Clinical Markers and Patient Outcomes

ProCal levels and SOFA scores did not correlate well with severity of disease in our case review. Most SOFA scores (90%) trended down over 4 days. The only SOFA score that trended up was found in one of the 3 deceased patients. Similarly, 70% of ProCal levels trended down over 4 days. One patient with an increasing ProCal level ultimately died but the other 2 survived. It is interesting that all of the deceased patients received HAT. This indicates that in our case series, there is no correlation between a decrease in mortality and use of HAT. Additionally, HAT was not correlated with a decrease

in ventilator days, cumulative time on pressors, or hospital or ICU length of stay. As emphasized previously, these findings are observational only.

In the 3 deceased patients, there were no meaningful unifying characteristics noted. All were female; however, with such a small statistical sample, our opinion is that it is more likely that this observation was due to chance. The patient with the longest time to surgery after diagnosis of NSTI was one of the deceased patients; however, the other 2 deceased patients went to surgery very expeditiously with one being diagnosed in the OR, and the other going to surgery within one hour of diagnosis.

Antibiotics

All 10 patients met the Sepsis-3 criteria and received antibiotics in a median time of 2 hours and 31 minutes. The Surviving Sepsis Campaign suggests administration of antimicrobials immediately, ideally within one hour of definite or probable sepsis or septic shock, and within 3 hours if sepsis is possible with persistent concern and no shock is present [26]. In our patient population, sepsis was definite, meaning that the time to antibiotic administration was too long. However, it should be noted that we did not originally plan to collect these data, and, therefore, our best estimates regarding antibiotic timing are based upon the time the patient presented to the hospital, rather than the exact time the clinician suspected sepsis, and it is possible that antibiotics were administered in a timelier fashion. The authors assumed appropriate antibiotic selection and duration occurred. Future studies would likely benefit from better tracking of this variable.

Wound Characteristics

All wounds involved the lower body and/or abdomen. Of the 10 wounds, 6 ultimately closed; 2 of the open wounds were on deceased patients who might have been closed if they had lived. The total number of wound-related surgeries might be considered higher in those patients with open wounds on discharge. Of those with open wounds on discharge, all had 3 or more wound-related surgeries. One patient with 4 wound surgeries ultimately had a closed wound on discharge. All others whose wounds were closed on discharge had 2 or fewer wound surgeries. This is likely due to a positive correlation between wound severity and need for additional debridement. Wounds requiring additional and/or very extensive debridement are likely less amenable to closure prior to discharge and more likely to need delayed primary or other closure by future elective surgery, versus healing by secondary intention.

Limitations

Due to the small number of participants enrolled, the findings are observational only. Lacking an enrollment team or pharmacy research department at this facility, the study relied on the burn team and pharmacy department to carry out the enrollment, preparation and administration of medication, and data collection. Because spearheading a large multicenter study is not feasible at our institution, a case review was determined to be the most advantageous endeavor for relaying our observations to healthcare providers who care for patients with NSTIs.

Future Research

With more resources, an adequately powered randomized control trial could be undertaken to discover whether statistically significant differences in the outcome measures might be present. A multicenter approach would likely be most beneficial. Additionally, the timing of intravenous HAT administration may play a role in outcomes, with some suggesting earlier administration may be beneficial [27,28]. Therefore, future studies may want a much shorter window to administration than used in our study

and may want to monitor this aspect of treatment more closely. It is the authors opinion that using the Sepsis-3 criteria is a well-supported and objective way to enroll patients for such a study. Finally, standardizing or monitoring antibiotic timing may be of benefit to reducing confounding variables.

Conclusions

This was an attempt at a single-center, prospective, placebo-controlled, double-blinded randomized controlled trial that failed to enroll an adequate number of participants. Thus, study was transitioned to a case series report. No benefit from intravenous hydrocortisone, ascorbic acid, and thiamine treatment in patients with NSTIs was observed. Future studies may help better elucidate the role of intravenous HAT therapy in patients with NSTIs.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Ascension Via Christi Hospitals Wichita, Inc. and the Human Research Protection Program of the University of Kansas School of Medicine--Wichita (KUVC-1814 on 9 July 2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A. Inclusion and Exclusion Criteria

Inclusion criteria

1. NSTI by clinical diagnosis and requiring surgical treatment.
2. Sepsis by clinical diagnosis and/or by Sepsis-3 criteria [23], with source attributed to the wound.
3. Anticipated or confirmed burn intensive care unit admission.

Exclusion criteria (adapted from VICTAS [19] protocol)

1. Age < 18 years.
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 an NSTI.
5. Sepsis deemed unlikely.
6. Limitations of care during enrollment [defined as refusal of cardiovascular and respiratory support modes, do not intubate (DNI) and comfort care/palliative care status].

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 (intravenous or oral) within the 24 h preceding first episode of qualifying organ dysfunction during a given emergency department or intensive care unit admission.
9. Chronic disease/illness that, in the opinion of the site investigator, has an expected lifespan of <30 days unrelated to current sepsis diagnosis (eg, 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.

Appendix B. Patient Demographic and Outcome Variables

1. Patient name
2. Medical record number
3. Date of birth
4. Patient age
5. Patient gender
6. Date and time of diagnosis of necrotizing soft tissue infection (NSTI)
7. Date and time of randomization
8. Time from diagnosis of NSTI and sepsis to initiation of hydrocortisone, vitamin C (ascorbic acid), thiamine (HAT) therapy: hours
9. Time on pressors: hours and minutes
10. Location of NSTI infection:
    - Perineum
    - Genitalia
    - Groin
    - Lower extremity
    - Upper extremity
    - Hand
    - Foot
    - Head/Neck
    - Back
    - Chest
    - Abdomen
    - Multiple/Other (using free text)
11. Preexisting conditions—selected based on Dr. Mariks study [6]:
    - None
    - Diabetes mellitus
    - Hypertension
    - Heart failure
    - Malignancy
    - Chronic obstructive pulmonary disease
    - Cirrhosis

- Cerebrovascular accident
- Acute kidney injury
- 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

12. Time from diagnosis of NSTI to surgery: hours
13. Total number of visits to the operating room for NSTI-related surgical intervention
14. Identification of NSTI derived from pressure-related injury
15. Wound status at time of ICU discharge:

    - Open
    - Closed

16. Duration of vasopressor therapy: hours cumulative over entire hospitalization
17. Positive blood cultures (Y/N)
18. Requirement for renal replacement therapy in patients with acute kidney injury (Y/N)
19. Procalcitonin level daily for 4 days (with day one being admission/enrollment, then 3 days after, totaling 4 days of treatment with HAT)
20. Daily SOFA score for 4 days (with day one being admission/enrollment, then 3 days after, totaling 4 days of treatment with HAT)
21. Total ventilator days
22. Intensive care unit length of stay, days
23. Hospital length of stay, days
24. Discharge disposition: alive or deceased
25. Did the patient withdraw? (Y/N)
26. Reason for patient withdrawal (free text)

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