Evaluation of Short versus Extended Duration Antibiotic Therapy on Outcomes in Necrotizing Soft Tissue Infection (DATa-NSTI Trial)

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SPECIFIC AIMS:

Necrotizing soft tissue infections (NSTI) are severe, rapidly spreading infections of the soft tissue and fascia with high morbidity and a historically high mortality. Recent studies have shown improvement in mortality with modern therapy[4-6, 8]. Although most would agree that initiation of broad-spectrum antibiotics and rapid surgical intervention are paramount, there is no consensus regarding duration of antibiotic therapy after source control. Current guidelines are based on small population, retrospective data and are varied in their recommendations. This has led to heterogenous clinical practice patterns with regards to antibiotic duration. It is well established that shorter course antibiotics reduce the risk of antimicrobial resistance and their associated complications. However, under-treatment may place the patient at risk for recurrent infection, increased length of stay, and mortality. Therefore, determining an ideal duration of antibiotic therapy inpatients with necrotizing soft tissue infections may help to mitigate these risks.

Aim 1: To determine if patients with NSTI who receive short course antibiotic therapy (<7 days after final source control procedure) have similar 30-day mortality compared to those patients who receive an extended duration of antibiotics (≥7 days after final source control procedure)

Aim 2: To determine the effect of short versus extended course antibiotics on postoperative outcomes including complications, length of stay, and readmissions.

Aim 3: To describe current practices regarding duration and appropriateness of antimicrobial therapy for patients undergoing surgical debridement for confirmed necrotizing soft tissue infection

STATEMENT ON IMPACT:

Duration of antibiotic therapy for Necrotizing Soft Tissue Infections is heterogenous amongst even high-volume centers. Current guidelines are based on retrospective, small population studies as well as expert consensus and derivations from similar infections. Because of this, clinical guidelines vary in their recommendations regarding this topic. This has led to our proposal for a multicenter prospective observational study regarding short (<7days) versus extended duration (>7 days) antibiotic therapy for Necrotizing Soft Tissue Infections. By reducing antimicrobial duration, this could potentially reduce antibiotic related complications which occur in up to 20% of hospitalized patients[1] and antimicrobial resistance, as well as decrease length of stay and cost. This benefits not only the patient and institution, but also the medical community, which is under crisis due to antimicrobial resistant pathogens which pose a serious threat to public health. This study is in line with mandates from the Joint commission, CDC, and CMS[.2,3]

**EAST MCT JUNIOR INVESTIGATOR AWARD FINALISTS*
During the EAST MCT Committee call on 8/28/18 it was voted and established that applicants that were selected as the finalists for the EAST MCT Junior Investigator Award, but not the recipients, would automatically roll over and be considered for the annual call for proposals. The 1st place proposal would automatically be accepted as an EAST Approved MCT.

A. SIGNIFICANCE:

This study is innovative in its prospective assessment of short duration antibiotics for the treatment of necrotizing soft tissue infection when compared to extended duration antibiotics. The findings of this study will provide new knowledge to understand the shortest effective duration of therapy for adjunct treatment of NSTI while mitigating unnecessary exposure to prolonged antibiotics. This research is significant as it will directly influence guidelines within organizations such as the Surgical Infectious Society as well the Eastern Association for the Surgery of Trauma.

A.1. The Incidence of Necrotizing Soft Tissue infection is increasing

Previous studies likely underestimated the true incidence of NSTI as they extrapolated data for Group A streptococcal infections or examined mortality rates alone. The incidence of necrotizing soft tissue infections is thought to be around 30,000 based on recent studies of the National Inpatient Sample.[4,5] May et al showed an increase in incidence from 22.3 in 2012 to 30.6 in 2016, with an estimated continued increase to 33.6 in 2018.[5] Greater awareness and recognition of this complex disease process may also be contributing to these more recent estimates of NSTI.

A.2. Mortality of NSTI is decreasing with modern therapy

Advances in recognition, time to intervention, and therapy have reduced the in-hospital mortality in more recent series. Mortality for NSTI has been reported as high as 34%.[6] but more recently has declined to 10-14%.[7] The mainstay of treatment is early and aggressive surgical debridement of infected and necrotic tissue. Early diagnosis and intervention are the only consistently proven predictors of outcome for NSTI. In a recent EAST Practice Management Guideline, the authors found an overall mortality rate of 14% in the early (<12 hours) intervention group versus 25.8% in the late ($\geq$ 12 hours) intervention group.[8] As mortality from NSTI declines, other quality measures, such as readmission rates, nosocomial infection and hospital length of stay, may assume more importance.

A.3. There is no consensus regarding duration of antibiotic therapy in NSTI

Current guidelines are based on retrospective, small population studies as well as expert consensus and derivations from similar infections. These guidelines suggest that broad-spectrum antibiotics including gram-negative, gram-positive and anaerobic coverage be initiated immediately after the diagnosis is suspected and continued until adequate source control is achieved.[9-11] The 2014 IDSA guidelines recommend that antimicrobial therapy should be administered until further debridement is no longer necessary, the patient has improved clinically, and fever has been absent for 48–72 hours, although they acknowledge a lack of clinical trials to support this recommendation.[11] The 2020 SIS updated guidelines state that a shorter course of antimicrobial therapy (<7 days) appears equivalent to longer therapy and should be considered.[12] A multi-center study in 2016 showed significant antibiotic variation between high-volume NSTI centers.[13] This further highlights how little is known about best care practices for patients with NSTI in terms of antibiotic duration.

The 2020 Surgical Infection Society (SIS) Updated Guidelines on the Management of Complicated Skin and Soft Tissue Infections states that shorter course antimicrobial therapy should be considered. However, this is a weak recommendation based on moderate quality evidence. The guideline also states that there is a need for further prospective evaluation into the duration of antimicrobial agents in necrotizing infections.[12] Furthermore, a recent survey of the SIS membership using a modified Delphi identified treatment duration for NSTI as one of the top three topics for further research.[14]

A.4. Shorter course antibiotic therapy is safe in the treatment of NSTI

While there have been no prospective trials specifically comparing short versus extended duration of antibiotics specifically for NSTI, several small retrospective studies have shown that a shorter course of antibiotics is not

associated with a higher mortality or worse outcomes. Lauerman et al performed a retrospective review of 168 patients with Fournier's gangrene in 2017 and found no difference in mortality with a shorter course of antibiotic therapy of 7 days or less, with a mean antibiotic duration of 4.8 days from final wound management.[15] In 2021, Valadez et al performed a retrospective review of 142 patients which showed no significant difference in in-hospital mortality or 30-day readmission with an antibiotic course of 7 days or less.[16]

A.5. Antibiotic Stewardship

Antibiotic resistance and the scarce antibiotic choices for multi-drug resistant organisms have become a public health problem. Consequently, antibiotic stewardship has become a critical responsibility for all healthcare institutions and antibiotic prescribers. Given the complexity of medical decision making surrounding antibiotic use and the variability in prescribing practices across various healthcare settings, the CDC has since recommended that guidelines with explicit recommendations for antibiotic stewardship be developed for treatment of specific infectious diseases, including skin and soft tissue infections. One of the goals of such antibiotic stewardship programs is to optimize the duration of antimicrobial therapy to avoid unnecessary antibiotic use and therefore reduce patient harm.[17]

B. INNOVATION:

B.1. Prospective evaluation of short duration antibiotics compared to extended duration antibiotics

No study has prospectively evaluated the primary outcome of mortality for patients with NSTI who receive short course antibiotic therapy (<7 days after final source control procedure) compared to those patients who receive an extended duration of antibiotics (≥7 days after final source control procedure). Therefore, it is critical to study this in a prospective manner in order determine appropriateness of this therapy.

B.2. Multicentered evaluation of short duration antibiotics compared to extended duration antibiotics

No study has evaluated the primary outcome of mortality for patients with NSTI who receive short course antibiotic therapy (<7 days after final source control procedure) compared to those patients who receive an extended duration of antibiotics (≥7 days after final source control procedure) in a large, multicenter trial. Therefore, it is critical to study this in a prospective manner in order determine appropriateness of this therapy.

C. APPROACH

The study will be a multicenter, prospective, observational cohort study to evaluate clinical outcomes of patients who received short-term versus long-term antibiotic therapy after source control. The study groups will be decided based on the duration of antimicrobial therapy, patients who received a short course of antibiotic therapy "ShortDur Group" (<7 days after final source control procedure) will be compared to patients receiving an extended course of antibiotic therapy "ExtDur Group" (≥7 days after final source control procedure).

C.1. Definitions

This study will define NSTI as skin and soft tissue infection requiring surgical debridement with evidence of necrotic skin, soft tissue, fascia, or muscle. Source control will be defined as any procedure that stops the ongoing contamination of the wound and removes the majority of the contaminated/necrotic tissue to the extent that no further acute interventions are felt to be necessary. Depending on the site and origin of the infection, multiple techniques can be utilized to obtain source control, including incision and debridement, wide local excision, as well as amputation. The adequacy of source control for any given patient will be determined by the operating surgeon.

C.2. Eligibility

Inclusion Criteria:
Patients > 18 years of age
Patient admitted to hospital with surgically confirmed necrotizing soft tissue infection (See definition above)
Patients receiving a minimum of 24 hours of antibiotics
Survival at least 7 days from source control procedure

Exclusion Criteria:
Patients <18 years of age
Patients with non-necrotizing soft tissue infection
Patients who did not undergo surgical debridement
Pregnant Patients
Incarcerated Patients
Patients who underwent surgical debridement at an outside facility

C.3. Data Collection

This study will prospectively collect patient information for two years from September 1, 2022 up to September 30, 2024 or until our sample size of 742 patients is reached. Patients will be enrolled from multiple centers throughout the United States and internationally. Demographic data, as well as laboratory values, radiographic findings, intra-operative management, pathology, microbiology results, antibiotic duration and type, complications and other clinical outcomes will be collected on all patients.

Data will be abstracted from the available electronic medical record and put directly into the Redcap database. A complete description of the data points is available (see Data Collection Sheet, Appendix). Data will include basic demographic information, documented co-morbidities, admission severity of illness, microbiology data, operative variables, primary and secondary endpoints, along with additional other clinical, confounding, or hospital course variables. Data collection will start at the coordinating site once IRB approval is obtained. Once the other sites obtain local IRB approval they may begin their own data collection. Sharing of de-identified data between other participating sites and the coordinating center will commence once their respective data use agreements have been fully executed.

C.4. Consent Procedures

This is a prospective observational study, designed to prospectively record data on patients who are managed according to institutional patient management protocols. Thus, waiver of informed consent is requested. Data will be recorded on a data sheet and transferred to a secured database that is devoid of patient identifiers.

C.5. Intervention

There will be no interventions solely for the purpose of this study. Care will be at the discretion of the local surgical team.

C.6. Risk/Benefit Analysis

This study involves no more than minimal risk to patients, as it is an observational study. A potential risk is a breach of confidentiality. There is a potential future benefit if we define optimal duration of antibiotic therapy in patients with necrotizing soft tissue infection. This would help to minimize the complications associated with unnecessary antibiotics including clostridium difficile colitis and antimicrobial resistance.

C.7. Sample Size required/Justification of sample size

We sought to determine equivalence between short duration and extended duration antibiotic groups on the outcome of mortality (per Aim 1), based on an estimated mortality rate of 14%. We assumed a 50/50 split of ShortDur Group and ExtDur Group. We calculated that a sample size of 311 patients per group would be required to give the study 80% power to exclude a difference in mortality rate of greater than 7% between the two groups, at an alpha level of 0.05. Recruitment will stop when 742 participants are enrolled to yield 622 evaluable subjects, assuming a 20% attrition or loss to follow-up.

C.8. Study Duration, Enrollment, Number of Sites

Given that this is an observational multicenter study, we anticipate enrolling 742 patients from 25-30 national and international sites over a two year period. This would equate to roughly 15 patients per year per center. This appears consistent with prior single-center annual NSTI capture data.[3,13,18-21]

C.9. Statistical Analysis Plan

Patients having a necrotizing soft tissue infection as defined below will be identified by the local study investigators. Within 72 hours of the initial intervention, the local investigator will review criteria for enrollment. Study data will be collected and managed using REDCap electronic data

capture tools hosted at the University of Alabama Birmingham. All participating sites will be instructed to record data elements onto the case report form (CRF) only as specifically documented in the medical record or examined by the clinician. If a data element is not recorded in the medical record, then it is left blank on the CRF and recorded as "missing". Missing items will be excluded from data analysis.

Continuous data will be reported as means +/- standard deviation or median (interquartile range) for nonparametric distributions and compared with T-test or Mann-Whitney U test as appropriate. Based on final diagnosis, subjects will be categorized into short term versus extended duration antibiotics. Comparisons between groups will be performed using analysis of variance, chi-squared test, and Kruskall-Wallace test. Counts will be reported as frequencies and compared with chi-squared test. A p-value of <0.05 will be considered statistically significant. Statistical analyses will be performed using Stata (StataCorp, 2021).[22]

C.10. Potential Limitations & Solutions

The Potential for uneven distribution of subjects into the study groups given that this is a non-interventional study. We will plan for interim analysis at 50% of targeted enrollment.

Lost-to-follow up bias is a potential for the outcome of 30-day mortality. To address this have adjusted our targeted enrollment assuming a 20% attrition or loss to follow-up

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