Form "EAST Multicenter Study Proposal"
Details #69 (submitted 10/01/2018)

Study Title	Prospective Multicenter Derivation and Validation of a NECROtizing Soft tissue Infection Severity (NECROSIS) Score
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Are you a current member of EAST?	Yes
If you selected "No" above please identify a Sponsor that is an active EAST member:	
My Multicenter Study proposal is...	Prospective
Use this area to briefly (1-2 paragraphs only) outline the burden of the problem to be examined	Necrotizing soft tissue infections (NSTIs) are severe life-threatening infections that require prompt diagnosis and urgent surgical intervention in order to optimize patient outcomes. NSTIs are relatively rare with an incidence of 500 to 1,500 cases in the United States annually. Despite advances in our understanding of NSTIs, morbidity and mortality remain high, with up to 15% of patients experiencing limb loss and 20-30% of patients ultimately succumbing to multiple organ failure and death. Successful management of these lethal infections requires early recognition and a high index of suspicion based on patient history, physical exam, laboratory, and radiographic findings. Several risk indices and scoring systems have been developed to assist clinicians to identify NSTIs. However, many of these clinical decision instruments suffer from low sensitivity, varying levels of reproducibility, and failure to incorporate key clinical variables in model development.
Primary aim	The primary objective of this study is to develop and validate a clinical risk index score for identifying NSTIs in emergency general surgery patients being evaluated for a severe skin and soft tissue infection.

Secondary aims include:

Secondary aims

To describe the contemporary microbiology of NSTIs and explore the effects on outcomes.

To identify predictors of amputation and mortality.

Inclusion Criteria

All adult patients (age >=18 years old) referred for evaluation of a suspected NSTI

Exclusion Criteria

Patients <18 years old

Pregnancy

Prisoners or inmate status

Patients transferred from another hospital following an initial surgical debridement

Below ankle diabetic foot infections complicated by peripheral vascular disease

Burn wounds

Therapeutic Interventions

Prospective observational study only. Patients will be managed according to surgeon's discretion.

Primary Outcome

Intraoperative clinical confirmation of NSTI as evidenced by the presence of necrosis, "dishwater" fluid or deliquescent tissues, thrombosed vessels, or absence of bleeding.

Secondary Outcomes

Mortality (30-day)

Amputation

Discharge disposition

Center Characteristics: trauma center designation, type of hospital (academic, community, hybrid, other), annual EGS admissions, number of possible NSTI patients evaluated, number of ICU beds

Demographics: Age, gender, BMI (weight/height), comorbidities (diabetes, cirrhosis, renal failure [dialysis versus AKI], immunosuppression, HIV/AIDS, IVDU (recent or current), COPD, CV disease [MI, CHF, HTN, CVA, angina], CA [active malignancy; metastatic cancer; hematologic cancer], peripheral vascular disease, endocarditis, pre-existing conditions (history of NSTI, recent surgery at or adjacent to site of NSTI, recent blunt trauma, recent penetrating trauma, gastrointestinal perforation, gastrointestinal or urinary tract infections, use of immunosuppressants (same as immunosuppressed above), smoker, alcohol use, use of non-steroidal anti-inflammatory medications [NSAIDs])

Clinical Presentation/Characteristics Prior to Diagnosis: history (duration of symptoms), physical exam findings (bullae, pain out of proportion, violaceous hue or discoloration, skin necrosis, crepitus, foul smelling “dishwater” pus, skin anesthesia), admission vital signs (temperature, blood pressure, hear rate, respiratory rate, SIRS/sepsis, septic shock (Surviving Sepsis definition), primary location of infection (head/neck, chest, abdomen, perineum, upper extremity, lower extremity)

List specific variables to be collected & analyzed

Admission Laboratory Results: sodium, BUN, creatinine, glucose, white blood cell count, bands, hemoglobin, platelets, INR, PTT, PT

(Optional): c-RP, procalcitonin, lactate (arterial or venous), venous or arterial blood gas [pH, PaO2, PCO2, HCO3, BD], LFTs [albumin, bilirubin], ESR)

Scoring Systems: LRINEC score, SOFA score, qSOFA score, AAST EGS Grade for SSTI

Radiology Findings: gas on plain films; gas, fluid tracking or collections, muscle/fascial edema, inflammatory changes under fascia, absence/heterogeneity of tissue enhancement on CT scan; gas or fascial/tissue edema on MRI

Microbiological and pathological findings: results of wound and blood cultures (mono- or polymicrobial with or without beta-hemolytic streptococci), bacteremia, organisms detected, no bacteria detected, pathology reports (necrosis versus no evidence of necrosis)

2. Surgical Treatment: time from presentation to OR, time to first reoperation, indication for reoperation, total number of debridements, % surface area debrided (Lund and Browder burn area chart), time to amputation, indication for amputation, wound management following initial debridement (wet to dry, VAC, open, other), reconstructive surgery (timing and type)

Outcomes: presence of NSTI, mortality (30-day), amputation, length of stay (ICU, hospital), duration of organ support (mechanical ventilation, renal replacement therapy, vasopressor support), postoperative complications:

-superficial surgical site infection (Infection occurs within 30 days of the operation and involves only skin and subcutaneous tissue of the incision with at least one of the following:
1. Purulent drainage from the incision
2. Organisms isolated from an aseptically obtained fluid culture or tissue from the superficial incision
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture negative.)

-deep incisional surgical site infection (Infection occurs within 30 days of the operation if no implant is left in place or within 1 year if implant is in place and infection appears to be related to the operation. Infection involves deep soft tissues (fascial and muscle layers) of the incision with at least one of the following:
1. Purulent drainage from deep incision but not from the organ/space component of the surgical site
2. A deep incision spontaneously dehisces or is deliberately opened when the patient has at least one of the following signs or symptoms: fever (body temperature >38o C), localized pain or tenderness
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation or radiographic examination.)
-wound dehiscence (separation of the surgical wound, diagnoses clinically)
-pneumonia
-pulmonary embolism
-ventilator requirement >48 hours
-acute renal failure (postoperative elevation of serum creatinine >=2.0 mg/dL in a patient without antecedent renal dysfunction OR acute need for renal replacement therapy)
-urinary tract infection
-stroke/cerebrovascular accident
-cardiac arrest requiring cardiopulmonary resuscitation
-myocardial infarction
-bleeding requiring transfusion
-graft/prosthesis/flap failure
-deep vein thrombosis/thrombophlebitis
-sepsis (Confirmed infectious source AND ≥ 2 of the following:
1. Body temperature <36o Celsius or >38o C
2. Heart rate >100 bpm
3. Respiratory rate >20 breaths per minute or $PaCO_2$ <32 mmHg on arterial blood gas
4. WBC count <4,000 cells/mm3 or >12,000 cells/mm3 or >10% band forms.)
-septic shock (sepsis requiring vasopressor support)
-discharge disposition:
-home
-home with nursing services
-rehabilitation
-long-term acute care facility
-nursing home
-hospice

Data and outcomes will be observational and involve no prescribed therapeutic interventions or alterations from standard patient care. Data points to be collected are outlined under Variables (see above). Each institution will prospectively collect data points/elements on a standardized form. Patient follow-up will be through 12 months. Investigators at each institution will enter collected data into the Research Electronic Data Capture (REDCap) portal.

Outline the data collection plan and statistical analysis plan succinctly

During the derivation phase off the study, patients will be divided into groups according to the presence or absence of the main outcome measure. Continuous variables will be compared using Student's t-test and Mann Whitney U test. The Chi-squared test or Fisher's exact test will be used to compare categorical variables. Univariate exploratory analysis of patient demographics, clinical presentation, admission laboratory results, scoring systems, and radiologic findings will be performed to establish relationships with the presence of a NSTI. Significant independent variables will be included in a multivariate regression analysis which will be used to determine independent predictors of NSTI. Data will be reported as adjusted odds ratios (OR) with 95% confidence intervals. Statistical significance will be set at $p < 0.05$. Based on the relative impact of each identified predictor (i.e. odds ratio), using weighted averages, a novel score will be derived. Various measures for the assessment of risk prediction models will be calculated including accuracy, predictive values, and the area under the receiver operating characteristic (ROC) curve. Bootstrap analysis will be used to validate the model.

External validation of the score will be performed using a validation cohort. The score will be validated by calculating its C-statistic and evaluating its ability to predict the presence of a NSTI. The predictive value of NECROSIS will be compared to the LRINEC score.

Exploratory analyses using multiple logistic regression will also be performed to identify variables associated with mortality and extremity amputation.

Outline consent procedures here, if applicable

An institutional review board (IRB) application will be submitted with likely waiver of patient informed consent insofar as patients will be managed according to institutional patient management protocols. This is an observational data collection study only. Each participating site will be required to obtain study approval by their respective IRBs.

Succinctly outline a risk/benefit analysis

The study involves no more than minimal risk to patients. The risk involved in this prospective observational study is minimal as we are not aiming to change surgical management or examine any specific “therapeutic intervention”. A potential risk is a breach of confidentiality. However, no HIPAA-related data will be collected as part of this study.

A potential benefit to be derived from this study is the development of a clinical risk index tool which may be applied at the bedside to assist clinicians identify and diagnose patients with NSTIs earlier so that definitive care in the form of surgery may be provided. This may potentially minimize complications and improve outcomes among patients with this rare yet devastating disease process.

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Include a brief listing of key references

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