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Laboratory evaluation for pediatric patients with suspected necrotizing soft tissue infections: A case–control study

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ABSTRACT

Background/Purpose: Optimal outcomes for necrotizing soft tissue infections (NSTI) depend on rapid diagnosis and management. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is a validated diagnostic tool for adult NSTI, but its value for children remains unknown. We hypothesized that modification of the LRINEC score may increase its diagnostic accuracy for pediatric NSTI.

Methods: We performed a case–control study of pediatric patients (age <18) with NSTI (cases) and patients with severe soft tissue infections prompting surgical consultation (controls). The LRINEC score was calculated for cases and controls and compared to a modified, pediatric LRINEC (P-LRINEC) score. Diagnostic accuracy was analyzed through receiver operating characteristic (ROC) curves.

Results: From 2010 to 2014, 20 cases and 20 controls were identified at two children's hospitals. Median LRINEC score was 3.5 (1–8) for cases and 2 (1–7) for controls ($p = 0.03$). The P-LRINEC was comprised of serum CRP >20 (sensitivity = 95% (95%CI 79–100%)) and serum sodium <135 (specificity = 95% (95%CI 82–100%)). Area under ROC curves was 0.70 (95%CI 0.54–0.87) for the LRINEC score and 0.84 (95%CI 0.72–0.96) for the P-LRINEC score ($p = 0.06$).

Conclusion: The P-LRINEC is a simplified version of the LRINEC score utilizing only CRP and sodium and may provide superior accuracy in predicting pediatric NSTI.

Necrotizing soft tissue infections (NSTI) comprise a spectrum of rare but fulminant infections that lead to widespread necrosis of the subcutaneous tissue and fascia. Recent data suggest mortality rates among adults with NSTI range from 10% to 20% [1–3]. Prompt diagnosis and early, aggressive surgical intervention are the keys to reducing devastating outcomes such as amputation, severe functional limitations, and ultimately death [3–5]. The condition is so rare, with an estimated prevalence of 0.02%–0.03% of all hospitalization causes, that providers have minimal experience with NSTI leading to further delays in diagnosis [1,6]. Such infrequent exposure and limited expertise are magnified in pediatric NSTI [7].

A validated NSTI scoring system called the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was developed in 2004 with routine labs including hemoglobin, white blood cell count, glucose, sodium, creatinine, and C-reactive protein [8]. The scoring system was developed using a predominantly adult cohort of patients and has not been widely reported for use among children with suspected NSTI. Our objective was to determine the utility of the LRINEC scoring system in the pediatric population. We hypothesized that a subset of the laboratory components within the LRINEC scoring system would have stronger predictive value than others and that a modified version of the LRINEC score may increase the accuracy of pediatric NSTI diagnosis.

1. Materials and methods

1.1. Study design and setting

We performed a dual-center, case–control study examining the association between NSTI and the LRINEC score among patients <18 years old. Patient cohorts were selected from Children's Memorial Hermann Hospital, a quaternary, 278-bed children's hospital within the Texas Medical Center in Houston, Texas, and Seattle Children's Hospital, a quaternary, 250-bed children's hospital in Seattle, Washington. Pediatric surgeons, pediatric plastic surgeons, and/or pediatric orthopedic surgeons performed all operations during the study time-period. The STROBE Statement for case–control studies was utilized to guide data reporting [9]. The study was approved by the Institutional Review Boards of both institutions (SCH-15210, HSC-MS-14-0542).

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1.2. Case and control identification/definition

Cases of NSTI and controls with severe, soft tissue infections were initially identified using International Classification of Diseases (ICD) codes, 9th revision. The ICD-9 codes for necrotizing fasciitis (728.86), gas gangrene (040.0), and Fournier gangrene (608.83) were used to identify potential cases with NSTI from 2010 to 2014 within both institutions. Inclusion criteria for pediatric NSTI were 1) patients <18 years and 2) documented presence of NSTI in the operative note through keywords such as *necrotizing infection*, *dishwater-like fluid* or *tissue necrosis*, and/or a description of extensive debridement including subcutaneous tissue and muscle with attention to viable circumferential margins. Additionally, NSTI was independently confirmed by two surgeons at each institution. Controls with severe, soft tissue infections and/or abscesses requiring >72 hours of hospitalization were identified using ICD-9 codes 682.1 through 682.9 (cellulitis and abscess of various body areas) during the same 5-year period. Inclusion criteria for controls were 1) patients <18 years, 2) surgical consultation (with or without surgical intervention) during the same inpatient admission, 3) a complete panel of LRINEC laboratory values on admission, and 4) no evidence of NSTI in the consult, progress reports, or operative notes. Controls meeting all inclusion criteria were randomly selected by incidence density sampling.

1.3. Patient characteristics and hospital course details

Clinically important data such as patient demographics, mechanism of injury, presentation signs and symptoms, operative details, laboratory and radiographic findings, microbiology/pathology reports, hospital course, and outcomes were reviewed.

1.4. Statistical analysis

Patient demographics and other categorical data were compared using χ^2 tests, and continuous data were compared with Student's t-test or Mann–Whitney U tests. Continuous variables were converted to categorical variables using Youden's index to determine a cut point with maximum sensitivity and specificity. Univariate logistic regression analysis of each LRINEC lab value was performed, and any variable with a p-value ≤0.2 on univariate analysis was included in the multivariate logistic regression model in a backwards, stepwise fashion to determine variables independently associated with NSTI. Patient age was also included in the multivariate model given its clinical importance.

Based on methods similar to those previously described [8,10], we developed a pediatric LRINEC score (P-LRINEC) by maximizing the area under receiver operating characteristic curves (AUC). Sensitivity, specificity, negative predictive values (NPV), positive predictive values (PPV), and likelihood ratios are reported for the laboratory values included in the LRINEC and P-LRINEC. Stata 13.1 (StataCorp LP, College Station, TX) was used for all statistical analyses.

2. Results

2.1. Patient demographics and presentation

A total of 20 patients with NSTI were identified over the 5-year period, which were compared to 20 non-NSTI patients with severe, soft tissue infections. Median age (range) of NSTI and non-NSTI patients was 5 years (1 month – 17 years) and 6 years (2 months – 17 years, $p = 0.87$). Thirty percent of NSTI patients and 50% of non-NSTI patients were female ($p = 0.20$). Three (15%) NSTI patients and 4 (20%) non-NSTI patients were immunocompromised or were previously diagnosed with a systemic condition such as insulin-dependent diabetes, ulcerative colitis, biliary atresia, or cancer ($p = 0.68$).

The inciting events for both groups, including trauma, animal bites, or instrumentation, were similar overall, although there were more non-NSTI patients in whom no inciting event was identified (25% vs 65%, $p = 0.03$). The primary anatomic sites of infection were similar between groups with the extremities being the most common in both groups (both 60%) followed by the head and neck (20% NSTI, 15% non-NSTI). Median duration of symptoms at the time of presentation for NSTI and non-NSTI patients was 48 h (18–192) and 72 h (24–168), respectively ($p = 0.05$). Erythema was present for all patients; however, only three NSTI patients (15%) versus no non-NSTI patients demonstrated bullae ($p = 0.23$), and no patients in either group demonstrated crepitance.

2.2. Operative details and hospital course

NSTI patients underwent a median of 5 (2–10) operations versus 2 (0–3) operations for non-NSTI patients ($p < 0.01$). Intraoperatively, 8 (40%) patients with NSTI were found to have *dishwater-like fluid*, and necrotic tissue was confirmed in 19 (95%) pathologic specimens. Nine (45%) NSTI patients required at least limited skin excision though only 2 (10%) required skin-grafting. Positive microbiologic tissue cultures were confirmed in 18 (90%) NSTI patients: 8 (44%) Group A streptococcus, 7 (39%) other mono-microbial, and 3 (17%) poly-microbial. Median hospital length of stay was 12.5 days (3–36) and 4 days (3–15) for NSTI and non-NSTI patients, respectively ($p < 0.01$). One (5%) NSTI patient and 2 (10%) non-NSTI patients were readmitted, all because of wound complications. There were no deaths in either group.

2.3. Laboratory results

Median (range) laboratory values for NSTI and non-NSTI patients were similar except for CRP, which was significantly higher in the NSTI group (Table 1). Only CRP and WBC cutoff values were modified for the P-LRINEC based on Youden's index. Maximal cutoff values of 20 mg/L for CRP and 20/mm^3 for WBC were applied in the logistic regression models for P-LRINEC. On univariate logistic regression, serum sodium and CRP were the only two variables significantly associated with NSTI, so these laboratory parameters were included in the multivariate model along with patient age. Based on the multivariate model, the only laboratory value significantly associated with NSTI was CRP >20 (OR 43, 95%CI 4.2–435, $p = 0.002$).

To maximize the AUC, the P-LRINEC was comprised exclusively of serum sodium <135 mEq/L and CRP >20 mg/L. Application of the original LRINEC score model provided an AUC of 0.70 whereas the AUC for the P-LRINEC score model was 0.84 ($p = 0.06$, Fig. 1). CRP in the P-LRINEC model was the most sensitive laboratory value (sensitivity: 95%) with the highest NPV (93%) whereas sodium was the most specific (specificity: 95%, Table 2).

3. Discussion

Although rare, NSTI do occur among children and, when delays in diagnosis and intervention occur, increased morbidity and mortality result [4,5]. While the LRINEC score is a validated tool commonly used to heighten suspicion for NSTI in adults, the LRINEC laboratory parameters used for adults may be deceptively normal in children, further delaying diagnosis. We evaluated these commonly collected laboratory

Table 1
The median (range) values of LRINEC laboratory values were similar between the NSTI and non-NSTI groups except for CRP which was significantly higher in the NSTI group.

Laboratory test	NSTI	Non-NSTI	*p* value
CRP (mg/L)	102 (19–485)	12.5 (2.6–190)	<0.001
WBC (per mm^3)	15.8 (2.5–33)	14.6 (4.6–43)	0.80
Hemoglobin (g/dL)	11.7 (8.0–14.6)	11.7 (6.6–14.1)	0.90
Sodium (mEq/L)	137 (126–145)	138 (134–142)	0.63
Glucose (mg/dL)	104 (47–273)	99 (67–196)	0.44
Creatinine (mg/dL)	0.4 (0.2–0.8)	0.5 (0.2–0.8)	0.32

CRP C-reactive protein, WBC white blood cells.