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Red Flags For Necrotizing Fasciitis: A Case Control Study

Khalid Al Alayed [a], Charlie Tan [b], Nick Daneman [a,b,c,*]

[a] Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[b] Sunnybrook Research Institute, Toronto, Ontario, Canada
[c] Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

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ABSTRACT

Objective: to examine the diagnostic accuracy of traditional 'red flags' for necrotizing fasciitis (NF) on history and physical examination.
Methods: retrospective study of all cases of NF admitted to a large tertiary care hospital between January 1 2004 and December 31 2013, each matched to two control patients with cellulitis. We determined the diagnostic test characteristics of clinical features for distinguishing NF from cellulitis, with emphasis on positive (LR+) and negative (LR-) likelihood ratios.
Results: There were no individual findings with sufficient sensitivity to rule out NF (sensitivity $\leq$ 85% and LR- $\geq$ 0.5 for all findings). The clinical features that most significantly increased the odds of NF were recent surgery (LR+ 7.0) pain-out-of-proportion (LR+ 4.5), diarrhea (LR+ 6.0), hypotension (LR+ 8.0), altered mental status (LR+ 3.3), erythema progressing beyond margins (LR+3.1), fluctuance (LR+ 5.0), hemorrhagic bullae (LR+ 8.0) and skin necrosis (LR+ 30.0). Each individual finding conferred low sensitivity, but absence of all nine ruled out NF (LR- 0.04). The presence of >=3 findings ruled in NF (LR+ undefined).
Conclusions: When considered together, the traditional 'red flags' for NF may be sufficient to rule in or rule out the diagnosis. If future prospective studies validate these findings, there will be a potential opportunity to expedite NF diagnosis and improve patient outcomes.

1. Background

Cellulitis is among the most common bacterial infections,[1] and rates have increased over time to greater than 4 cases per 100 people/year in the United States.[2] Necrotizing fasciitis (NF) is a much more severe form of soft tissue infection, with mortality rates exceeding 30%; fortunately it is also much rarer than cellulitis, with an incidence of only 4 cases per 100,000 people/year in the United States.[3]

It is challenging to distinguish the once-in-awhile NF patients, from the every-day cellulitis patients presenting to the emergency department. Prompt recognition of NF is essential, though, because it requires different antimicrobial management (including polymicrobial coverage for Type I NF infections or clindamycin adjunctive treatment for Group A Streptococcal Type II NF infections), but more importantly because it requires emergent surgical debridement for cure.[4] The majority of cases of NF are initially misdiagnosed,[5] and delays in NF diagnosis are strongly associated with increased mortality.[6–9]

The definitive diagnostic test for NF is surgical exploration and biopsy; due to invasiveness, it should be reserved for patients with a meaningful probability of having this infection. Therefore, it would be helpful to have non-invasive clinical methods that aid in ruling in or ruling out NF. There are several symptoms and signs that are commonly considered to be 'red flags' for NF, such as pain out of proportion, hypotension and hemorrhagic bullae.[3,10] The Infectious Diseases Society of America (IDSA) guidelines for management of skin and soft tissue infection encourage assessment for these features on history and physical examination, but cite no references to support their diagnostic utility.[4] This is because prior studies of diagnostic accuracy in the evaluation of NF have focused only on the results of baseline blood work [11,12] or radiologic imaging.[13]

Abbreviations: LR+, positive likelihood ratio; LR-, negative likelihood ratio; NF, necrotizing fasciitis; NPV, negative predictive value; PPV, positive predictive value; SHSC, Sunnybrook Health Sciences Centre.

* Corresponding author. Division of Infectious Diseases, Sunnybrook Health Sciences Centre, University of Toronto 2075 Bayview Ave, Toronto, Ontario, Canada M4N 2M5 phone: 416-480-6100 x2791, Fax: +416-480-6737.
E-mail addresses: khalidmohammed.alayed@sunnybrook.ca (K.A. Alayed), charlie.tan@medportal.ca (C. Tan), nick.daneman@sunnybrook.ca (N. Daneman).

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The objective of this study was to evaluate the diagnostic test characteristics of common elements of the history and physical examination in identifying NF versus cellulitis.

2. Methods

2.1. General Study Design and Setting

We performed a retrospective case control study at Sunnybrook Health Science Centre (SHSC), to examine the diagnostic value of history, physical examination and laboratory findings among patients with NF or cellulitis admitted between January 1 2004 and December 31 2013. SHSC is a tertiary care, University-affiliated hospital with 824 acute care beds, located in Toronto, Ontario, Canada. Ethics approval was obtained from the SHSC Research Ethics Board.

2.2. Identifying Cases with Necrotizing Fasciitis

We screened for cases of NF using a computer-generated search through the medical records department for all patients diagnosed with NF (ICD-10-CM Diagnosis Codes M72.60-M72.69). Additional cases were detected by screening the SHSC microbiology laboratory database for patients with Group A Streptococcus isolated from a sterile site specimen, such as tissue biopsy or blood culture, as well as operating room databases for patients undergoing emergent wound debridement. The charts of all these patients with possible NF were screened to determine if they met our reference standard criteria for NF (see below). We also excluded patients transferred to SHSC from other health facilities, as the chart would not be expected to reliably contain full descriptions of initial history, physical examination and laboratory findings.

2.3. Identifying Control Patients with Cellulitis

We screened for candidate control group patients using a computer-generated search through the medical records department for all patients diagnosed with cellulitis (ICD-10-CM Diagnosis Codes: L03.00-L03.39, L03.8, L03.9). Since we expected the number of patients with cellulitis to far outnumber those with NF, we randomly selected two patients with cellulitis from the same year of admission as each NF case. The use of two rather than one control per case increased statistical power – but there are diminishing returns in statistical power with use of further numbers of controls per case.[14]

2.4. Reference Standard for Determining Necrotizing Fasciitis

To be included as a confirmed case of NF, the patient presentation had to meet at least one of the following criteria: (i) gross evidence of necrotic fascia during surgical exploration, (ii) positive bacterial culture from a fascia biopsy, and/or (iii) pathologic confirmation of necrosis on a fascia biopsy.

2.5. Potential Diagnostic Predictors of Necrotizing Fasciitis

After careful review of the literature, a data collection form was generated to capture demographic features, comorbidities and potential diagnostic predictors of NF on history, physical examination and laboratory testing. Demographic, history and physical examination features of interest were recorded as present if they were mentioned in any of the emergency room notes, initial nurses' notes, or initial doctors' consultation notes. If these features were not mentioned in any of these notes, they were recorded as absent. Given the retrospective study design, we did not require quantitative thresholds for comorbidity definitions (such as body mass-index for obesity, or recent time of malignancy diagnoses) because these may not be reliably recorded. Historical features of interest included subjective fever, chills, shortness of breath, skin swelling, pain, pain out of proportion, skin anesthesia, surgery within the preceding 90 days, nausea/vomiting and diarrhea. For vital signs, we used the first available measurements on presentation. We dichotomized all continuous variables based on routinely accepted thresholds, such as a lower limit of systolic blood pressure of 90 mmHg, such that test characteristics could be easily calculated based on the presence or absence of each abnormality. Other physical examination features of interest, included erythema, erythema progressing beyond marked margins, tenderness, swelling, local warmth, fluid-filled vesicles, hemorrhagic bullae, skin fluctuance, skin induration, skin anaesthesia, crepitus, necrosis, ischemia, cyanosis, purulence and altered level of consciousness. We collected data on all laboratory tests included in the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) scoring system for NF,[12] as well as a select number of other potentially important predictors including the international normalized ratio, lactate, creatine kinase and bicarbonate. We recorded the first laboratory values on arrival to hospital. Data on the use of radiologic tests (x-ray, computed tomography scan, magnetic resonance imaging) and the presence of abnormalities on these tests were also recorded.

2.6. Statistical Analysis

We compared baseline patient characteristics among NF cases and cellulitis controls using chi-square test for categorical variables, and Wilcoxon rank sum test for continuous variables.

As per standard definitions, sensitivity was calculated as the proportion of NF cases with a given finding, while specificity was calculated as the proportion of cellulitis controls without that given finding. Positive predictive value (PPV) was calculated as the proportion of patients with a given positive finding who had NF; negative predictive value (NPV) was calculated as the proportion without a given finding who had cellulitis. We also measured likelihood ratios. The positive likelihood ratio (LR+) is defined as sensitivity/(1-specificity) and expresses the increase in the odds of having NF when the finding is positive. The negative likelihood ratio (LR-) is defined as (1-sensitivity)/specificity and expresses the decrease in the odds of having NF when the finding is negative.

We put low emphasis on the results of PPV and NPV, since we arbitrarily set the prevalence of NF at 1/3 in our study design (because we included two controls for every one case) but in regular clinical practice the prevalence of NF would be much lower (with many more cellulitis cases for each NF case). In our study, the true NPV will be underestimated and PPV will be overestimated. Therefore, we emphasized the LR+ and LR- as the most important diagnostic test characteristics, because these are intrinsic characteristics of the diagnostic test and independent of population disease prevalence.

In our primary analysis, we separately determined the diagnostic test characteristics of each individual finding on history, physical examination and laboratory testing. In an exploratory secondary analysis, we developed an additive risk score combining the characteristics with the highest LR+ for NF. We generated a Receiver Operating Characteristics Curve, based on tradeoffs in sensitivity and specificity for each possible risk score in our index. The risk score was intended to be exploratory, because the available sample size of patients with NF was not anticipated to be sufficient to provide derivation and validation subsets, or to allow for multivariable modeling to enable weighted scoring. In the absence of multivariable modeling we weighted each predictive clinical characteristic equally (1 point each), in order to develop a