International Journal of Infectious Diseases 36 (2015) 15–20

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Red Flags For Necrotizing Fasciitis: A Case Control Study

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ARTICLE INFO

Article history:
Received 25 February 2015
Received in revised form 27 April 2015
Accepted 30 April 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
necrotizing fasciitis
cellulitis
diagnosis
diagnostic accuracy
case control study

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.

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http://dx.doi.org/10.1016/j.ijid.2015.04.021

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

parsimonious risk score with a memorable acronym. All analyses were performed in Microsoft excel, and SAS version 9.3 (Cary, NC).

2.7. Sample Size Calculation

At an expected sample size of 100 patients with NF, we calculated that we would have 80% power to detect a 20% absolute difference between a given predictor variable among patients with and without NF (alpha 0.05).

3. Results

3.1. General Characteristics of NF and Cellulitis Patients

After screening all potential NF cases from our medical records department, operating room and microbiology database, we identified 40 patients who met our reference standard criteria for NF – 36 (90%) had gross evidence of NF on surgical inspection, 28 (70%) had documentation of NF on a pathology specimen, and 39 (98%) had a positive bacterial culture from a fascia biopsy specimen. We randomly selected two patients with cellulitis as controls from the same year of admission as each NF case, generating a total of 40 case patients with NF and 80 control patients with cellulitis. NF occurred more frequently in younger populations than cellulitis, but there was no difference in gender distribution (Table 1). Having had surgery at the site of infection within the last 90 days was significantly more common among NF cases than cellulitis controls (35% vs 5%, $p<0.001$). As expected, length of stay in hospital, mortality and need for ICU admission were all much higher in the NF group (Table 1).

3.2. Microbiology of NF and Cellulitis

Positive cultures were more common among NF cases than cellulitis controls (95% vs 24%, $p<0.001$). Among the patients with culture-positive NF, nearly two-thirds (60.5%) had type I (polymicrobial) NF. The most common microorganisms isolated from patients with necrotizing fasciitis included *Enterococcus spp.* (8 patients), *E. coli* (7), *Group A streptococcus* (6), coagulase negative staphylococci (5), *Staphylococcus aureus* (4), *Pseudomonas spp.* (3), *Enterobacter spp.* (3), *Candida spp.* (3), *Streptococcus viridians group* (3), *Group B Streptococcus* (2), other aerobes (5), other anaerobes (7). The majority of necrotizing fasciitis isolates were from sterile site cultures (45/58, 78%). The most common organisms isolated from patients with cellulitis were *Staphylococcus aureus* (10 patients), *Group A Streptococcus* (6), and Group B Streptococcus, *Moraxella spp.*, *Pasteurella* spp, *Actinomyces spp.*, and coagulase negative staphylococci (1 each). However, only a minority of cellulitis isolates were from sterile site cultures (2/18, 11%).

Table 1
Baseline Characteristics of Patients with Necrotizing Fasciitis versus Cellulitis

Patient Characteristics	*Necrotizing Fasciitis N(%)*	*Cellulitis N(%)*	P-value
Age ≥ 50 years	27(67.5)	68(85)	0.03
Female sex	21(52.5)	39(48.75)	0.70
Alcohol abuse	3(7.5)	5(6.25)	0.80
Coronary artery disease	7(17.5)	21(26.25)	0.29
Cirrhosis	1(2.5)	3(3.75)	0.72
Congestive heart failure	5(12.5)	14(17.5)	0.48
Chronic obstructive pulmonary disease	1(2.5)	10(12.5)	0.07
Chronic renal insufficiency	3(7.5)	11(13.75)	0.31
Diabetes mellitus	11(27.5)	22(27.5)	>0.99
Hepatitis B	0(0)	1(1.25)	0.48
Hepatitis C	1(2.5)	1(1.25)	0.61
Hypertension	21(52.5)	40(50)	0.80
Immunosuppression	2(5)	7(8.75)	0.46
Injection drug abuse	3(7.5)	2(2.5)	0.20
Malignancy	13(32.5)	23(28.75)	0.67
Obesity	5(12.5)	11(13.75)	0.85
Peripheral vascular disease	2(5)	4(5)	>0.99
Rheumatoid arthritis	0(0)	5(6.25)	0.11
Smoking	8(20)	14(17.5)	0.74
Cerebrovascular disease	4(10)	6(7.5)	0.64
Surgery at site of disease within 90 days	14(35)	4(5)	<0.001
Venous stasis	1(2.5)	12(15)	0.04
Length of stay in days [Median (IQR)]	13 (6.5-38.5)	5 (4-10)	<0.001
Survival to hospital discharge	27(67.5)	78(97.5)	<0.001
Required intensive care	18(45)	3(4.0)	<0.001

Data are shown as No. (%) unless otherwise indicated.
Human immunodeficiency virus infectious, systemic lupus erythematosis, corticosteroid use, and spinal cord injury were also evaluated, but were present in < 1 patient.

3.3. Accuracy of Historical Findings in Diagnosing Necrotizing Fasciitis

The most common presenting symptom was pain (sensitivity only 75%), and there were no items on history with a LR- below 0.5. The element in history that most increased the odds of having NF was surgery at the site of infection within the last 90 days (LR+ 7.0). We found that pain out of proportion also increased the odds of NF (LR+ 4.57) (Table 2).

3.4. Accuracy of Physical Examination Findings in Diagnosing Necrotizing Fasciitis

The most common physical exam finding was erythema (sensitivity only 85%), and there were no items on physical examination with a LR- below 0.5 (Table 2). Regarding the diagnostic accuracy of vital signs and other aspects of the physical examination, hypotension (systolic blood pressure < 90 mmHg), erythema progressive beyond margins drawn in the emergency department, hemorrhagic bullae and skin necrosis were associated with LR+ of 8.0, 3.09, 8.0 and 30.0, respectively (Table 2).

3.5. Accuracy of Basic Laboratory Findings in Diagnosing Necrotizing Fasciitis

The only laboratory result with a significant LR+ was the presence of severe leukocytosis (WBC >25 mm^3) (LR+ 3.0). Only 16 of the 120 patients enrolled in the study had their C-reactive protein level checked, which precluded validation of the LRINEC score in our study population (Table 3).

3.6. Use of Diagnostic Imaging to Detect Necrotizing Fasciitis

Overall, a high proportion of suspected and proven cases of NF had radiologic imaging prior to any surgical intervention. In the NF group, 26 (65%) patients underwent a computed tomography scan, 12 (30%) had an x-ray, four (10%) had an ultrasound and two (5%) underwent magnetic resonance imaging. The presence of gas and fluid collections increased the likelihood of having NF among the subset of patients that underwent imaging (LR+ 6.04 and 4.23, respectively), while the absence of gas across tissue planes only marginally decreased the likelihood of NF (LR- 0.46).

3.7. "PHONES For Surgical Doctor": A Risk Prediction Score for NF

In an exploratory analysis, we combined the individual findings with the strongest LR+ values for NF into an additive risk score, entitled "**PHONES F**or **S**urgical **D**octor". One point was awarded for each of the following findings, totaling to a maximum of nine points: **P**-pressure (systolic blood pressure <90 mmHg), **H**-hemorrhagic bullae, **O**-Out of proportion pain, **N**-Necrotic skin,

Table 2
Diagnostic Accuracy of History and Physical Examination Findings in Distinguishing Necrotizing Fasciitis from Cellulitis

History	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Subjective fever	0.45	0.68	0.41	0.71	1.38	0.81
Chills	0.33	0.66	0.33	0.66	0.96	1.01
Shortness of breath	0.3	0.85	0.5	0.708	2.0	0.82
Skin swelling	0.6	0.08	0.27	0.30	0.66	4.57
Pain	0.75	0.1	0.29	0.44	0.83	2.5
Pain out of proportion	0.4	0.91	0.7	0.75	4.57	0.66
Skin anesthesia	0.0	0.96	0.0	0.66	0.0	1.03
Surgery within 90 days	0.35	0.95	0.78	0.75	7.0	0.68
Nausea and vomiting	0.33	0.86	0.54	0.72	2.36	0.78
Diarrhea	0.075	0.98	0.75	0.68	6.0	0.93
Physical examination	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**LR+**	**LR-**
Erythema	0.85	0.05	0.31	0.4	0.89	3
Erythema progressive beyond margins	0.43	0.86	0.61	0.75	3.09	0.67
Tenderness	0.73	0.16	0.3	0.54	0.87	1.69
Swelling	0.7	0.05	0.27	0.25	0.74	6.0
Local warmth	0.35	0.28	0.19	0.46	0.48	2.36
Fluid-filled vesicles (ulcers, blisters, bullae)	0.3	0.75	0.38	0.68	1.2	0.93
Skin fluctuance	0.13	0.98	0.71	0.69	5.0	0.9
Skin induration	0.1	0.91	0.36	0.67	1.14	0.99
Hemorrhagic bullae	0.1	0.99	0.8	0.69	8.0	0.91
Skin anesthesia	0.0	0.98	0.0	0.66	0.0	1.01
Crepitus	0.13	1.0	1.0	0.7	N/A	0.88
Necrosis	0.38	0.99	0.94	0.76	30.0	0.63
Ischemia	0.0	1.0	N/A	0.66	N/A	1.0
Cyanosis	0.15	1.0	1.0	0.7	N/A	0.85
Purulence	0.4	0.85	0.57	0.74	2.67	0.71
Altered LOC	0.25	0.93	0.63	0.71	3.33	0.81

LOC = level of consciousness | LR+ = positive likelihood ratio | LR- = negative likelihood ratio | NPV = negative predictive value | PPV = positive predictive value

E-Erythema progressing beyond margins, **S**-Sensorium altered, **F**or-Fluctuance, and **S**urgical-surgical procedure within preceding 90 days, **D**octor - **D**iarrhea. A score of zero substantially lowered the probability of NF (sensitivity 97.5%, LR- 0.040), while a score of three or above substantially increased the probability of NF (specificity 100%, LR+ undefined). A receiver operating characteristics curve was generated based on the tradeoffs of sensitivity and specificity at increasing "**PHONES F**or **S**urgical **D**octor" scores (Figure 1).

4. Discussion

This study provides the first rigorous confirmation of the diagnostic accuracy of many of the clinical findings traditionally

Table 3
Diagnostic Accuracy of Vital Signs and Basic Laboratory Test Results in Distinguishing Necrotizing Fasciitis from Cellulitis

Vitals	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR
Blood pressure						
sBP<90 mmHg	0.2	0.98	0.8	0.71	8	0.82
dBP<60 mmHg	0.5	0.91	0.74	0.78	5.71	0.55
Heart rate						
>100 BPM	0.53	0.65	0.43	0.73	1.5	0.73
Respiratory rate	0.49	0.79	0.53	0.76	2.29	0.65
>20 RPM						
Oxygen saturation						
<95%	0.16	0.91	0.46	0.7	1.8	0.92
Temperature						
>38.0 °C	0.3	0.76	0.4	0.69	1.3	0.9
Laboratory findings	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Positive LR**	**Negative LR**
C-reactive protein*						
≥150 mg/L	0.5	0.75	0.4	0.82	2	0.67
Total WBC						
<4mm^3	0.13	0.98	0.71	0.69	5	0.89
>15mm^3	0.35	0.74	0.4	0.69	1.3	0.88
>25 mm^3	0.08	0.98	0.6	0.68	3	0.95
Hemoglobin						
<135 g/L	0.55	0.36	0.3	0.62	0.86	1.24
<110 g/L	0.3	0.85	0.5	0.71	2	0.82
Sodium						
<135 mmol/L	0.4	0.77	0.47	0.72	1.76	0.78
Creatinine						
>141 μmol/L	0.33	0.84	0.5	0.71	1.98	0.81
Glucose						
>10 mmol/L	0.26	0.91	0.59	0.71	2.78	0.81

BPM = beats per minute | LR = likelihood ratio | NPV = negative predictive value | PPV = positive predictive value | RPM = respirations per minute | WBC = white blood cell
* in contrast to the other laboratory tests which were collected in all patients as part of routine care, C-reactive protein measurements were only available for 16/120 patients

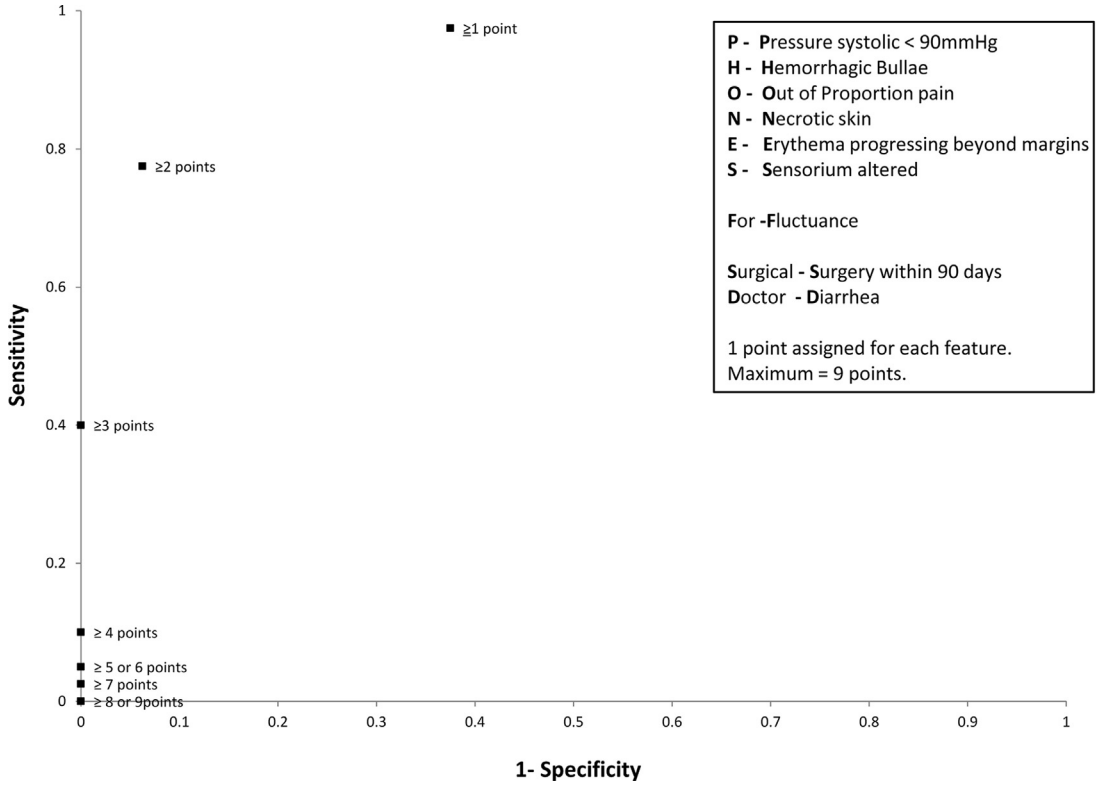

Figure 1. Receiver Operating Characteristic Curve for the "PHONES For Surgical Doctor" Risk Score for Necrotizing Fasciitis. In this risk score, 1 point was assigned for each of 9 clinical features (see box). A score of 0 substantially lowered the probability of necrotizing fasciitis (sensitivity 97.5%). A score of 3 or higher substantially increased the probability of necrotizing fasciitis (specificity 100%).

considered to be 'red flags' for NF. On history, the most important items are pain out of proportion, diarrhea, and surgery in the preceding 90 days; on physical examination, the most important signs are hypotension, altered mental status, erythema progressing beyond marked margins, skin fluctuance, hemorrhagic bullae and skin necrosis. The presence of three or more of these findings virtually ruled in NF (specificity 100%, LR+ undefined). Although, the absence of any individual finding was of little diagnostic utility, the absence of all of these findings virtually ruled out NF (sensitivity 97.5%, LR- 0.04).

The high LR+ associated with these clinical findings can be understood on the basis of the pathogenesis of NF, which involves rapid, uncontrolled bacterial proliferation and horizontal spread along the superficial fascial layer.[10] The high prevalence of preceding surgery in this population is not surprising, as deep surgical incisions offer a direct portal of entry to the fascia,[15] whereas most cellulitis cases result from more superficial, often imperceptible portals of entry.[16] The report of pain out of proportion can be understood on the basis of the initial spread of the infections in the fascial layer, with minimal initial involvement of the overlying skin and subcutaneous tissues. The greater severity of NF compared to cellulitis, and the potential association with Group A Streptococcal toxic shock syndrome, can explain the increased prevalence of hypotension and altered mental status as features of the systemic inflammatory response.[17] Although cellulitis, by definition, involves rapidly spreading inflammation of the skin and subcutaneous tissues,[16] the tempo of NF is faster; therefore, erythema is more likely to spread beyond initial marked margins. As NF progresses, the occlusion of perforating vessels is likely responsible for skin fluctuance, hemorrhagic bullae and skin necrosis.[10,18,19] The lack of sensitivity for any of these individual findings may relate to the origin of NF in the fascial layer, where hidden beneath the skin and subcutaneous tissues, substantial progression may take place before any particular symptom or sign becomes evident.

Previous literature assessing the diagnostic accuracy of NF tests has focused on laboratory and radiology results rather than history and physical examination findings. The most intriguing prior study involved the combination of C-reactive protein, total white blood cell count, hemoglobin, sodium, creatinine and glucose measurements into the LRINEC score.[12] A LRINEC score of 6 was associated with a PPV of 96% and a NPV of 96% for NF, and was thus considered helpful in both ruling in and ruling out NF. We were unable to validate the LRINEC score in our study, because CRP is not a routinely used biochemical test at our institution, and so was unavailable for most patients. Other smaller studies have evaluated the accuracy of magnetic resonance imaging in distinguishing NF from non-necrotizing soft tissue infections.[13]

However, clinicians are unlikely to make surgical decisions based on simple biochemistry and hematology laboratory results, and MRI scans are generally discouraged as part of the diagnostic evaluation process because they can delay definitive surgical intervention.[4] Therefore, we have sought to generate a simple clinical prediction rule, based on features of the clinical examination. This "**PHONES For Surgical Doctor**" scoring system (Figure 1), offers a potential means to rule in and/or rule out NF at the bedside, but requires further validation before being broadly implemented.

Our study has a number of important limitations inherent to its retrospective design. Under-detection of history and physical examination findings is possible due to incomplete chart documentation, and we had to assume the absence of documentation of a finding corresponded to absence of that finding. There may also have been a potential for ascertainment bias if more features were examined and documented in the chart once clinicians became concerned about the possibility of NF. Although a prospective cohort design would be preferable, it is difficult to

study NF prospectively because of low recruitment rates for this rare and severe condition.[20] Thus, most NF literature will inevitably be retrospective in design.[5] A spectrum bias may have been introduced by selecting any cellulitis patients as controls regardless of severity; however, any attempt to match on a clinical measure of severity would have precluded an assessment of the predictive utility of that clinical finding, and would have obscured the association of other predictors of NF on history and physical examination.[21] Lastly, some of our predictors of NF, such as necrosis, are reported to be late findings on examination.[19] Even though we recorded these signs on initial physical examination records, they may not be helpful findings to facilitate early diagnosis and improved outcomes. Lastly, a larger study with more NF cases, would enable subgroup analyses for type 1 versus type 2 NF, as well as multivariable modeling to determine the adjusted association of each history and physical examination characteristic.

5. Conclusions

In summary, we offer the first rigorous evaluation of the diagnostic accuracy of the clinical examination in distinguishing NF from cellulitis. We confirm the importance of a number of red flags including pain out of proportion, a report of surgery at the site of infection in the preceding 90 days, hypotension, diarrhea, altered mental status, erythema progressing beyond marked margins, skin fluctuance, hemorrhagic bullae and skin necrosis. Each of these features had a very strong LR+, and when considered together, the presence of at least three of these findings potentially ruled in NF, whereas the absence of all findings ruled out this devastating infection. Further prospective studies, with larger sample sizes, would be helpful to validate and refine this predictive rule, to aid in early diagnosis and improved outcomes for patients with NF.

Authors' Contributions: ND conceived the research question.

ND, KA, CT were all involved in study design, data acquisition, analysis and interpretation.

All authors were involved in drafting the manuscript, revising it for important intellectual content, gave approval for publication, and agree to be accountable for all aspects of the work.

Acknowledgments and Funding: ND is supported by a Clinician Scientist Award from the Canadian Institutes of Health Research. This funding source had no role in study design, collection, analysis, interpretation, writing, and decision to submit.

Conflict of Interest: The authors declare that they have no conflicts of interest.

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