Necrotizing fasciitis

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Key points

Patients with necrotizing fasciitis (NF) have pain disproportionate to their physical findings.

During the early stages of NF, an apparently normal-looking skin is seen.

The LRINEC (Laboratory Risk Indicator for Necrotising Fasciitis) scoring system, surgical exploration, and tissue biopsy can detect necrotizing soft tissue infections.

Delays in diagnosis and surgical intervention increase tissue loss and risk of mortality.

Communication and teamwork between the intensivist, surgeon, anaesthetist, and microbiologist are essential.

Necrotizing fasciitis (NF) is a progressive, fulminant bacterial infection of subcutaneous tissue that spreads rapidly through the fascial planes causing extensive tissue destruction. NF can affect any part of the body and is the most serious presentation of necrotizing soft tissue infection (NSTI); it is a rare but potentially fatal condition. Prompt recognition and intervention is essential, as mortality is directly proportional to time to intervention.[1]

The UK incidence of reported NF is ~500 new cases each year,[2] although this is likely to be an underestimate. In Canada, it is estimated that 90–200 cases of NF occur each year in all age groups.[3] The USA reports an annual age-adjusted incidence of 4.3 invasive infections per 100 000 of the population.[4] In Australian studies, it is reported as a maximum yearly incidence of 3.8 cases per 100 000. Reported mortality in the literature varies widely with more recent studies reporting a mortality of around 25%.[2]

Classification

NSTIs vary from mild pyodermas to NF. NSTI can be classified in multiple ways (Table 1 and Fig. 1) but is most commonly classified by microbial source of infection (Table 2). Types I and II are responsible for the majority of cases of necrotizing fasciitis in the UK, whereas Types III and IV are extremely rare.

Type I

Type I infections are the most common form of the disease. They are polymicrobial and wound tissue isolates identify on average four different organisms. Causative microbes include a combination of Gram-positive cocci, Gram-negative rods, and anaerobes. Type I infections most frequently occur in the perineal and trunk areas in immunocompromised patients, particularly diabetics and patients with peripheral vascular disease. Fournier's gangrene refers to NF of the perineal, perianal, and genital regions and is a relatively common presentation in the UK. Other risk factors (Table 3) include obesity, chronic renal failure, HIV, alcohol abuse, abscess, i.v. drug use, blunt or penetrating trauma, insect bites, surgical incisions, indwelling catheters, chicken pox, vesicles, and (rarely) perforation of the gastrointestinal tract (e.g. carcinoma or diverticulitis).[5]

Type II

An infection caused by the group A streptococcus (*Streptococcus pyogenes*) either alone or in association with *Staphylococcus aureus*, classically located on the extremities of the body but truncal involvement has also been reported. Group A streptococci can survive and replicate in macrophages, thereby escaping antibiotic therapy even in those tissues that remain well perfused and considered amenable to antibiotic penetration.

Type II is the only NSTI associated with toxic shock syndrome. Type II is far less common than type I infection; however, this incidence is increasing, reflecting the rise in the incidence of community-acquired methicillin-resistant *S. aureus* (MRSA) in some parts of the world. MRSA soft tissue infection has been reported particularly in i.v. drug abusers, athletes, and institutionalized groups. Type II NSTIs often occur in healthy, young, immunocompetent hosts, although frequently there is a history of recent trauma or operation to the tissue involved.

Type III

Type III is a Gram-negative monomicrobial NF. The most common Gram-negative responsible are *Vibrio* spp., such as *V. damselae* and *V. vulnificus*. Type III is uncommon but carries a very high mortality of 30–40%, despite prompt diagnosis and aggressive therapy.

Type IV

Type IV describes fungal cases of *Candida* NF. These are very rare. Fungal invasion most commonly occurs in patients with traumatic wounds and burns and in those who are severely immunocompromised.

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Pathophysiology of NF

Microbial invasion of the subcutaneous tissues occurs either through external trauma or direct spread from a perforated viscus (particularly colon, rectum) or urogenital organ. Bacterial growth within the superficial fascia releases a mixture of enzymes and endo- and exotoxins causing the spread of infection through this fascia.[5] This process results in poor microcirculation, ischaemia in affected tissues, and ultimately, cell death and necrosis.

Thrombosis of small veins and arteries passing through the fascia causes profound skin ischaemia. This skin ischaemia is the fundamental process for the soft tissue presentation of NF as it progresses. Importantly, during the early pathological stages, an apparently normal-looking skin is seen, despite extensive infection of the underlying fascia. Haemorrhagic bullae, ulceration, and skin necrosis subsequently manifest with further involvement of the deeper structures.

The initial clinical skin findings underestimate the tissue infection present, although thrombosis of penetrating vessels to the skin is the key feature in the pathology of NSTI. Thrombosis of large numbers of dermal capillary beds must occur before skin changes suggestive of necrosis occur.[6]

Table 1 Classification of soft tissue necrotizing infections

Classification	Comments
Anatomic location	Cervical, thoracic, abdominal (Meleney's), pelvic, Fournier's gangrene
Depth of infection	Epidermis and dermis
	Erysipelas
	Impetigo
	Folliculitis
	Ecthyma
	Furunculosis
	Carbunculosis
	Cellulitis
	Superficial fascia, subcutaneous tissue, subcutaneous fat, nerves, arteries, veins, Deep fascia
	Necrotizing fasciitis
	Muscle
	Myonecrosis
Microbial cause	Types I, II, III, and IV

Risk factors and prognosis

Most patients with NF are immunocompromised with one or more chronic debilitating diseases. Table 3 lists known predisposing risk factors for NF. There may be a history of minor trauma such as gardening scratches or penetrating soft tissue injuries by insect, dog, or human bites and injections. A history of more major trauma should also be sought, for example, a recent operation, skin

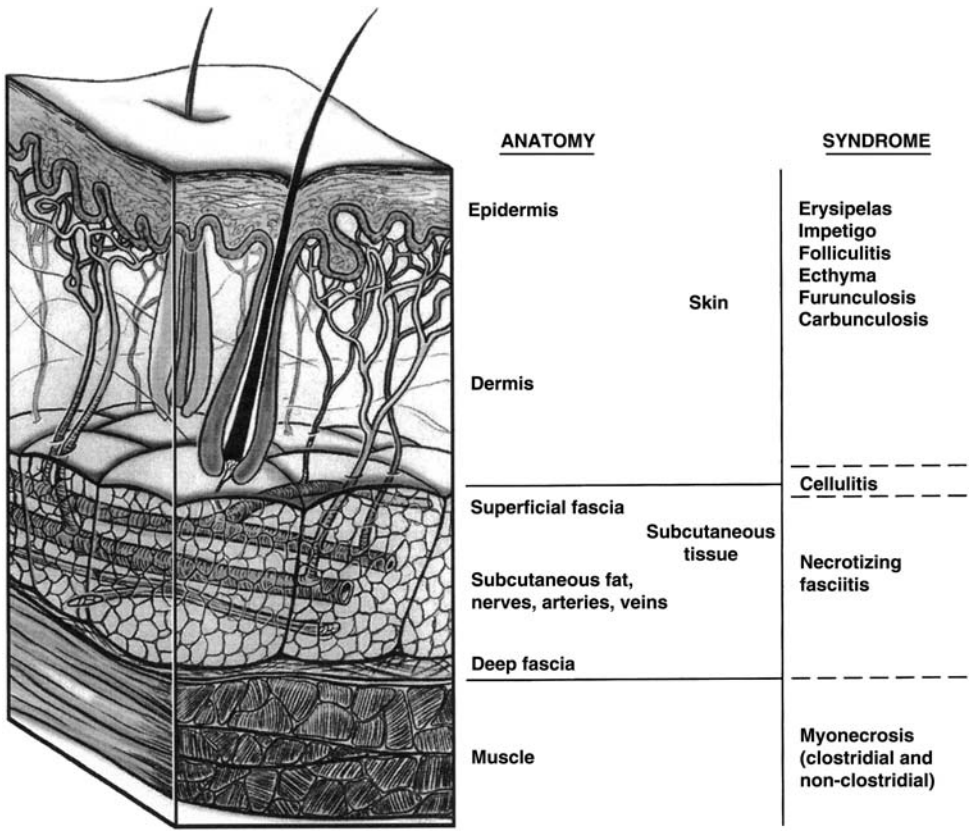

Fig 1 Depth of infection and clinical classification of soft tissue infections.[14] Reproduced with permission from the American College of Chest Physicians.

Table 2 Micro-organisms causing NF[8]

Types of NF	Aetiology	Organism(s)	Clinical progress	Mortality
Type I (70–80% cases)	Polymicrobial, synergistic, often bowel flora-derived	Mixed anaerobes and aerobes	More indolent, better prognosis, easier to recognize clinically	Variable; depends on underlying co-morbidities
Type II (20–30% cases)	Often monomicrobial, skin- or throat-derived	Usually group A β-haemolytic streptococcus (GAS), occasionally *S. aureus*	Aggressive, protean presentations, easily missed	>32%, depends if associated with myositis or toxic shock
Type III	Gram-negative, often marine-related organisms	*Vibrio* spp. mainly	Seafood ingestion or water contamination wounds	30–40%
Type IV (fungal)	Usually trauma associated, immunocompetent patients	*Candida* spp. immunocompromised patients. Zygomycetes immunocompetent patients	Aggressive with rapid extension especially if immunocompromised	>47% (higher if immunocompromised)

Table 3 Predisposing factors for NF[2]

Immunosuppression
Diabetes
Chronic disease
Drugs, for example, steroids
Malnutrition
Age >60
I.V. drug misuse
Peripheral vascular disease
Renal failure
Underlying malignancy
Obesity
Blunt or penetrating trauma
Soft tissue infections
Surgery
I.V. drug use
Childbirth
Burns
Muscle injuries

infection, or ulcer. Independent markers of mortality from NF in order of severity are: streptococcal toxic shock syndrome, immunocompromise, and advanced age.[7]

Clinical presentation and diagnosis

Many patients with NF are initially misdiagnosed with cellulitis, delaying appropriate management and increasing morbidity and mortality. Despite some similarities in the clinical presentation of cellulitis and NF, it is very important to correctly identify symptoms and signs allowing the correct diagnosis. The most critical early distinctive symptom of NF is a disproportionate level of pain compared with physical findings.

Unlike cellulitis where the infection begins at the junction between the dermis and superficial fascia, in NF, the infection starts at the level of subcutaneous fat and deep fascia. It is because of this sparing of the epidermal and dermal layers in the early stages of the disease that erythema and oedema of skin are not obvious,[6] and so the extent of infection clinically is not clear. Lymphangitis is rare in NF. Blister or bulla formation is an important but late feature of necrotizing fasciitis. Blisters result from ischaemia as the penetrating vessels that perfuse the skin are largely thrombosed due to the inflammatory process. In contrast, blistering and bullae are rare findings in cellulitis.

The rate of progression of NF can vary from several days from presentation to, in contrast, a rapid decline and death within hours from presentation. Patients with NF in the later stages of the disease often show symptoms and signs of septic shock, toxic shock syndrome, and multiorgan failure. Tachycardia, tachypnoea, fever or hypothermia, hypotension, cardiac arrhythmias, confusion, metabolic acidosis, abnormal renal and liver function, coagulopathy, and thrombocytopaenia may occur. These patients carry a high rate of mortality.

Clinical dermatological features of NF can be classified into three stages:

Stage 1: defined with signs such as erythema, tenderness beyond the erythema, swelling, and hot skin.

Stage 2: defined by the formation of skin bullae, blister, and skin fluctuation.

Stage 3: manifests with haemorrhagic bullae, crepitus, skin necrosis, and gangrene.

Investigations

Diagnosis of NF is essentially clinical. The gold standard is surgical exploration and tissue biopsy. The presence of fascial necrosis and myonecrosis or loss of fascial integrity along tissue planes and frank evidence of muscle involvement are diagnostic. There is a lack of resistance to blunt dissection of the normally adherent superficial fascia, accompanied by a lack of bleeding and the presence of foul-smelling 'dishwater' pus.[6]

These tests are all adjuncts to diagnosing NF. Many are non-specific, reflecting changes that occur in severe sepsis.

Haematology

Haematological changes in NF are consistent with any septic process. These changes include leucocytosis, leucopoenia, coagulopathy, and thrombocytopenia. Anaemia can be dilutional from fluid resuscitation or from haemolysis. Disseminated intravascular coagulation is not uncommon in any severe sepsis.

Biochemistry

Raised serum creatinine kinase indicates myositis or myonecrosis, and the effects of circulating toxins or ischaemia.[8] Hypocalcaemia

is a sign of fat necrosis and calcium deposit in necrotic tissues. Bacterial infection, inflammation, and necrosis cause raised C-reactive protein (CRP). As in severe sepsis, abnormal renal function, hypoalbuminaemia, hyponatraemia, abnormal liver function, metabolic acidosis, and high serum lactate concentrations may occur.

Microbiology

Blood cultures are positive in 11–60% of the patients with NF caused by group A streptococci. Percutaneous needle aspiration of the advancing edge is useful but a tissue biopsy is the investigation of choice. Tissues and aspirates should be Gram stained and cultured. Fungal culture is recommended in high-risk immunocompromised patients.[8]

Histology

Deep incisional biopsies and frozen sections with Gram staining of tissues are all diagnostic of NF. Samples should include the advancing edge and central necrotic areas. It reveals the underlying thrombi, necrosis, polymorphonuclear infiltrates, microorganisms, and vasculitis.

Laboratory scoring systems for the prediction of NF

The LRINEC (Laboratory Risk Indicator for Necrotising Fasciitis) scoring system was designed to distinguish NF from other soft tissue infections. A comparison of laboratory tests between these two groups of patients showed that the most reliable and significant indicators of the underlying NF rather than cellulitis were CRP, creatinine, haemoglobin, white cell count, sodium, and serum glucose. The score is calculated by adding up each of six predictive factors (Table 4). A score of >6 has a positive predictive value of 92% and a negative predictive value of 96%. A score of ≥8 is strongly predictive of NF, with a positive predictive value of 93.4%.[9]

Imaging

Computed tomography (CT) scan, ultrasound, and magnetic resonance imaging (MRI) have all been used to image NSTIs. It is important to emphasise that imaging is not a definitive procedure and should not delay surgery. However, with the increasing use of imaging, it may be possible to diagnose early NF, despite lack of clinical suspicion. CT scans demonstrate deep fascial thickening and enhancement, and the presence of fluid and gas within soft tissue planes in and around the superficial fascia. Ultrasound identifies features suggestive of thickening, distortion, and fluid collections along the deep fascia. MRI with gadolinium differentiates necrotic and inflamed or oedematous tissue. T2-weighted images on MRI are probably the best radiological adjunctive investigation for NF.

Table 4 Laboratory Risk Indicator for Necrotising Fasciitis score[9]

Variable	Score
C-reactive protein	
<150	0
≥150	4
WBC (cells mm^{-3})	
<15	0
15–25	1
>25	2
Haemoglobin (g dl^{-1})	
>13.5	0
11–13.5	1
<11	2
Sodium (mmol $litre^{-1}$)	
≥135	0
<135	2
Creatinine (μg $litre^{-1}$)	
≤141	0
>141	2
Glucose (mmol $litre^{-1}$)	
≤10	0
>10	1

Treatment

Early diagnosis, aggressive resuscitation, surgical debridement, antibiotic therapy, and supportive intensive care are necessary for managing patients with NF. Effective communication between the intensivist, surgeon, anaesthetist, and microbiologist is essential.

Resuscitation and supportive care

The aim of resuscitation is to establish an adequate tissue perfusion and oxygen delivery. Invasive arterial pressure monitoring and central venous access may be required; goal-directed therapy targets for haemodynamic resuscitation in patients with sepsis secondary to NF are as suggested by the Surviving Sepsis Campaign.[10] Adequate nutritional support and treatment of nosocomial infections are crucial. Critical care admission is strongly recommended in view of the aggressive clinical course, high risk of multiorgan failure, and significant mortality rate.

Surgical debridement

Several studies have shown that the most important factor affecting mortality is timing and adequacy of initial surgical debridement.[11] Delayed or inadequate debridement dramatically increases mortality. Radical debridement may necessitate limb amputation. Debridement removes the source of infection and toxins, and furthermore, removal of infarcted tissue improves the subsequent penetration of antibiotics. The infection is rarely eradicated after a single debridement and serial debridements are almost always needed. Optimally, three debridements spaced 12–36 h apart are required to obtain control of gross infection. Debridement may result in significant intraoperative blood loss and inability to close surgical wounds. Vacuum-assisted dressings and skin expansion

devices may have a role. Reconstructive surgery should be considered only when the patient has been stabilized and the infection fully eradicated.

Antibiotic therapy

Antibiotics are unable to penetrate infected necrotic tissue because of the thrombogenic nature of the process, so aggressive surgical debridement remains the first priority. Due to complex microbiology and fulminant nature of the infection, seeking advice from a senior microbiologist is crucial.

Empiric therapy requires an antibiotic combination that covers the variety of organisms that may cause NF. A broad-spectrum agent such as Tazocin, containing piperacillin (a penicillin which kills a wide variety of bacteria by interfering with the formation of bacterial cell walls) and tazobactam (a β-lactamase inhibitor which prevents bacteria from inactivating piperacillin leaving them susceptible to attack) or a carbapenem (such as meropenem), can be combined with clindamycin. If Group A streptococcus alone is responsible, antibiotics may be rationalized to a combination of penicillin and clindamycin. Clindamycin is included in antibiotic therapy as it is known to switch off toxin production. Likewise, when MRSA is suspected, Linezolid is preferred to vancomycin as it inhibits exotoxin production.

I.V. immunoglobulin therapy

The use of i.v. immunoglobulin (IVIG) is based on the theoretical mechanism that it can bind staphylococcal- and streptococcal-derived exotoxin, so limiting the systemic cytokine release associated with systemic inflammatory response syndrome.

There is very limited evidence which suggests a decreased mortality from using IVIG in group A streptococcal NF. IVIG use in other forms of NF has not been studied. Currently, IVIG should be restricted to consideration of use for critically ill patients with either staphylococcal or streptococcal NF.[5,12]

Hyperbaric oxygen

For synergistic infections, particularly involving *Clostridium* spp., hyperbaric oxygen (HBO) switches off toxin production. HBO is believed to increase the bactericidal action of neutrophils. However, the overall evidence of benefit in non-clostridial NF is weak. In addition, there are few hospitals with easy access to HBO units, appropriate staffing, and chambers large enough for patients receiving intensive care support.[8]

Anaesthetic implications

Anaesthesia for patients with NF is often challenging and should be undertaken by a senior anaesthetist. Patients with NF need multiple general anaesthetics for surgical debridement, reconstruction, and skin grafting. It frequently involves dealing with a severely septic patient. Surgical debridement is often more extensive than expected before operation, and this and coagulopathy can result in substantial blood loss.

Preoperative assessment should focus on the severity of sepsis, anatomical involvement, the presence of shock or multiorgan dysfunction, and the adequacy of haemodynamic resuscitation.[13]

The need for aggressive fluid resuscitation and the requirement for inotropic support should be pre-empted and often necessitate invasive blood pressure and central venous pressure monitoring. Cardiac output monitoring may be required to optimize cardiac output, inotropic state, and vasopressors response. It should be noted that cervicothoracic NF may limit the options for central venous access.

The postoperative care period is crucial and intensive care admission is recommended, with organ support as appropriate. Close observation of the debrided wound is necessary and multiple debridements are very common. Adequate analgesia must be provided; patient-controlled analgesia is often preferable in cases with extensive debridement.

The safety of health-care workers and close contacts of patients with NF must be considered. Currently, antimicrobial prophylaxis is not recommended for adults with close contact to patients with NF and group A streptococcus. However, the UK Health Protection Agency recommends increased vigilance and the seeking of early medical advice if signs and symptoms of infection develop in any such individual.

Summary

NF is a progressive, fulminant bacterial infection of subcutaneous tissue that spreads rapidly through the fascial planes causing extensive tissue destruction. NSTI is most commonly classified by microbial source of infection. Prompt recognition, diagnosis, and intervention are essential. Delays increase tissue loss, and mortality is directly proportional to time to intervention.

Clinically, pain precedes skin changes by 24–48 h and apparently normal-looking skin is seen during the early pathological stages, despite extensive infection of the underlying fascia. Common misdiagnoses are muscular pain and cellulitis. The LRINEC scoring system and the gold standard surgical exploration and tissue biopsy distinguish NF from other soft tissue infections.

Most patients with NF have one or more chronic debilitating diseases. Patients with NF may show symptoms and signs of sepsis, severe sepsis, septic shock, toxic shock syndrome, and multiorgan failure. Early diagnosis, aggressive resuscitation, surgical debridement, antibiotic therapy, and supportive intensive care are necessary for managing patients with NF. Preoperative assessment should focus on the severity of sepsis, anatomical involvement, the presence of shock or multiorgan dysfunction, and the adequacy of haemodynamic resuscitation. Anaesthesia is challenging, and haemodynamic instability of the septic patient, large blood loss, and fluid shifts should be anticipated. Invasive arterial and central venous pressure and cardiac output monitoring are often necessary. Effective communication between the intensivist, surgeon,

anaesthetist, and microbiologist is essential in the successful management of these patients.

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Declaration of interest

None declared.

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Please see multiple choice questions 13–16.

The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: A tool for distinguishing necrotizing fasciitis from other soft tissue infections*

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Objective: **Early operative debridement is a major determinant of outcome in necrotizing fasciitis. However, early recognition is difficult clinically. We aimed to develop a novel diagnostic scoring system for distinguishing necrotizing fasciitis from other soft tissue infections based on laboratory tests routinely performed for the evaluation of severe soft tissue infections: the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score.**

Design: **Retrospective observational study of patients divided into a developmental cohort (n = 314) and validation cohort (n = 140)**

Setting: **Two teaching tertiary care hospitals.**

Patients: **One hundred forty-five patients with necrotizing fasciitis and 309 patients with severe cellulitis or abscesses admitted to the participating hospitals.**

Interventions: **None.**

Measurements and Main Results: **The developmental cohort consisted of 89 consecutive patients admitted for necrotizing fasciitis. Control patients (n = 225) were randomly selected from patients admitted with severe cellulitis or abscesses during the same period. Hematologic and biochemical results done on admission were converted into categorical variables for analysis. Univariate and multivariate logistic regression was used to select significant predictors. Total white cell count, hemoglobin, sodium, glucose, serum creatinine, and C-reactive protein were selected. The LRINEC score was constructed by converting into integer the regression coefficients of independently predictive factors in the multiple logistic regression model for diagnosing necrotizing fasciitis. The cut-off value for the LRINEC score was 6 points with a positive predictive value of 92.0% and negative predictive value of 96.0%. Model performance was very good (Hosmer-Lemeshow statistic, $p = .910$); area under the receiver operating characteristic curve was 0.980 and 0.976 in the developmental and validation cohorts, respectively.**

Conclusions: **The LRINEC score is a robust score capable of detecting even clinically early cases of necrotizing fasciitis. The variables used are routinely measured to assess severe soft tissue infections. Patients with a LRINEC score of ≥6 should be carefully evaluated for the presence of necrotizing fasciitis. (Crit Care Med 2004; 32:1535–1541)**

KEY WORDS: early diagnosis; electrolytes changes; hematologic changes; necrotizing fasciitis; sepsis; systemic inflammatory response syndrome

Necrotizing fasciitis is a rare, rapidly progressive infection primarily involving the fascia and subcutaneous tissue. It is perhaps the most severe form of soft tissue infection and is potentially limb and life threatening. Early recognition and aggressive debridement of all necrotic fascia and subcutaneous tissue are major prognostic determinants, and delay in operative debridement has been shown to increase mortality rate (1–8). The differentiation of necrotizing fasciitis from other soft tissue infections is therefore critically important. However, early clinical recognition of necrotizing fasciitis is difficult, as the disease is often indistinguishable from cellulites or abscesses early in its evolution. Since Meleney's (8) time, the mortality rate of this condition has remained high with a reported cumulative mortality rate of 34% (range, 6–76%) (8, 9). Delayed recognition is one of the main reasons for the high mortality rate (1–7). Although modalities such computed tomography, magnetic resonance imaging (MRI), and frozen section biopsy have been shown to be useful in the early recognition of necrotizing fasciitis, routine application of theses modalities in the evaluation of soft tissue infections has been limited by cost and availability (10–14). We describe a novel, simple, and objective scoring system, the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score, based on routine laboratory investigations readily available at most centers, that can help distinguish necrotizing fasciitis from other soft tissue infections.

***See also p. 1618.**

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MATERIALS AND METHODS

Patients. The developmental cohort consisted of all patients treated at the Changi General Hospital for necrotizing fasciitis between January 1997 and August 2002. Patients were identified through a computer-generated search through the Medical Records Department for all patients diagnosed with necrotizing fasciitis (*International Classification of Diseases–9th Revision*). Data were extracted retrospectively from hospital records. The following characteristics at operative exploration were used for definitive diagnosis: the pres-

ence of grayish necrotic fascia, demonstration of a lack of resistance of normally adherent muscular fascia to blunt dissection, lack of bleeding of the fascia during dissection, and the presence of foul-smelling "dishwater" pus. Permanent histopathologic tissue examination was used to confirm the diagnosis when available (1, 6). Eighty-nine consecutive patients were identified and included in this cohort.

Two thousand five hundred fifty-five patients were admitted to our institution with the clinical diagnosis of cellulitis or abscesses during the same period. Control patients were randomly selected from this patient pool. Method of randomization is simple randomization using the SAS statistical software (SAS Institute, Cary, NC). Patient charts were reviewed to identify patients with severe soft tissue infection: The criteria we used for severe soft tissue infections were clinical impression of severe infection based on documentation in the patients' charts, the use of parenteral antibiotics for ≥48 hrs, and abscesses (when present) needing surgical debridement. Patients with a length of stay of <48 hrs and the use of oral antibiotics only were excluded as these patients were considered to have minor soft tissue infections. Three hundred twenty patients were randomly selected initially. Of these, 225 patients fulfilled our criteria for severe soft tissue infections and were used as controls for this study.

Demographic and clinical data and outcome of our cases and controls were collected (Table 1). The first biochemical and hematologic tests done on admission were analyzed. Variables analyzed were age, gender, total white cell count, hemoglobin, platelet count, serum sodium, potassium, chloride, glucose, urea, creatinine (Cr), C-reactive protein (CRP), and erythrocyte sedimentation rate.

Statistical Analysis and Development of Score. Thirteen variables were analyzed. Statistical analyses were performed using the SPSS statistical software (version 11.0, SPSS, Chicago, IL). To construct a diagnostic scoring system, factors were entered as categorical variables. For patients' age, an age of 50 was taken as a cutoff. For all the laboratory variables, the cutoff points were determined based on a combination of the means of our cases and controls, clinical experience, and review of previous reports (15–19). The methods of analyses used in this study were univariate and multivariate analyses by backward stepwise logistic regression procedure. We used $p < 0.1$ as a cutoff value for statistical significance for variable selection for the multivariate modeling in order not to miss any potentially important predictors. Statistical significance remained conventionally defined as $p < .05$ in the univariate and multivariate models. Intercept and regression coefficients were adjusted by the shrinkage factor of .89 to minimize the error estimates of these coefficients (20). Internal validation of the data set was done by bootstrap resampling technique. The LRINEC score was constructed by converting into integer the regression coefficients of independently predictive factors in the logistic model for diagnosing necrotizing fasciitis (21, 22, 23). The LRINEC score of each patient was calculated by totaling the scores of each independent variable (Table 2).

To evaluate model calibration, we performed Hosmer-Lemeshow goodness-of-fit test (24). The predictive accuracy of the LRINEC score was expressed as area under the receiver operating characteristic curve (Fig. 1) (25). The curve represents the relationship between corresponding values of sensitivity and specificity with all possible values of probabilities as a cutoff point to predict for the presence of necrotizing fasciitis.

Validation of Score. External validation of our diagnostic model was performed in a separate cohort of 56 consecutive patients with necrotizing fasciitis seen at a separate hospital (Singapore General Hospital) between June 1999 and December 2002. Eighty-four patients were randomly selected from patients admitted to that hospital for severe cellulitis or abscesses during the same period and used as controls. The criteria used for cases and controls selection were as described for the developmental cohort.

Table 1. Demographic and clinical variables and outcome of patients used in the developmental cohort

	Case (n = 89)	Control (n = 225)
Mean age[a]	56 (27–84)	47 (13–87)
Gender[b]		
Male	53 (59.6)	148 (65.8)
Female	36 (40.4)	77 (34.2)
Comorbidities[b]		
Diabetes mellitus	63 (70.8)	116 (51.6)
Peripheral vascular disease	20 (22.5)	86 (38.2)
No comorbidities	12 (13.5)	69 (28.9)
Variables on admission[b]		
Temperature >38.0°C	47 (52.8)	95 (42.2)
Hypotension	16 (18.0)	6 (2.7)
Multiple-organ failure at admission[b]	4 (4.5)	2 (0.9)
Mortality rate[b]	19 (21.3)	3 (1.3)

[a]The data are given as mean with range in parentheses; [b]data given as the number of patients, with the percentage in parentheses.

Table 2. Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score

Variable, Units	β	Score
C-Reactive Protein, mg/L		
<150	0	0
≥150	3.5	4
Total white cell count, per mm^3		
<15	0	0
15–25	0.5	1
>25	2.1	2
Hemoglobin, g/dL		
>13.5	0	0
11–13.5	0.6	1
<11	1.8	2
Sodium, mmol/L		
≥135	0	0
<135	1.8	2
Creatinine, μmol/L		
≤141	0	0
>141	1.8	2
Glucose, mmol/L		
≤10	0	0
>10	1.2	1

Final model constructed using factors found to be independently predictive of necrotizing fasciitis on multivariate analysis. β values are the regression coefficients of our model after adjusting for a shrinkage factor of .89. The maximum score is 13; a score of ≥6 should raise the suspicion of necrotizing fasciitis and a score of ≥8 is strongly predictive of this disease. To convert the values of glucose to mg/dL, multiply by 18.015. To convert the values of creatinine to mg/dL, multiply by 0.01131.

RESULTS

In the developmental cohort, 89 patients with necrotizing fasciitis and 225 control cases were included in the analysis. The clinical presentation of these 89 patients with necrotizing fasciitis in the developmental cohort has previously been described (1). A summary of the demographic and clinical characteristics and outcome of the cases and controls in the developmental cohort is shown in Table 1. Table 3 shows the means, SD, and ranges of the laboratory values of our cases and controls. Univariate and multivariate logistic regression analyses excluded seven of the candidate diagnostic variables. The final fitted model contains six variables: white cell count and CRP, hemoglobin, serum sodium, glucose, and serum Cr concentrations (Table 4). Of these six variables, complete data were available for five of these variables (total white cell count, hemoglobin, serum sodium, glucose, and Cr). CRP was available for 271 (86.3%) patients in the developmental cohort. Single imputation method was used to handle the missing values. The measures of association for the significant variables were expressed as odds ratio with 95% confidence intervals (CI) and p values. After adjusting the intercept and regression coefficients (by the shrinkage factor .89), we developed the final logistic model for probability of developing necrotizing fasciitis. The LRINEC score is derived from this formula by converting into integer the regression coefficients of independently predictive factors in the final logistic model (Table 2). The performance of the final model was very good (Hosmer-Lemeshow goodness-of-fit test, $p = .910$) (24) and discriminated well between patients with necrotizing fasciitis and those with other soft tissue infections. Area under the receiver operating characteristic curve for the developmental cohort was 0.980 (95% CI, 0.962–0.999) (25).

This model was validated externally using a cohort of 56 patients diagnosed with necrotizing fasciitis and 84 control patients with severe cellulitis or abscesses from a separate hospital. In the validation cohort of 140 patients, complete data were available on five variables (total white cell count, hemoglobin, serum sodium, glucose, and Cr). CRP was available for 123 (87.9%) patients. The model was found to be reliable on external validation with an area under the receiver operating characteristic curve of 0.976 (95% CI, 0.955–0.997) (Fig. 1).

A numerical score was derived from the regression coefficients of each independently significant variable in the manner as described earlier. The clinical application of the score chart is presented in Table 2. Using the LRINEC score, we

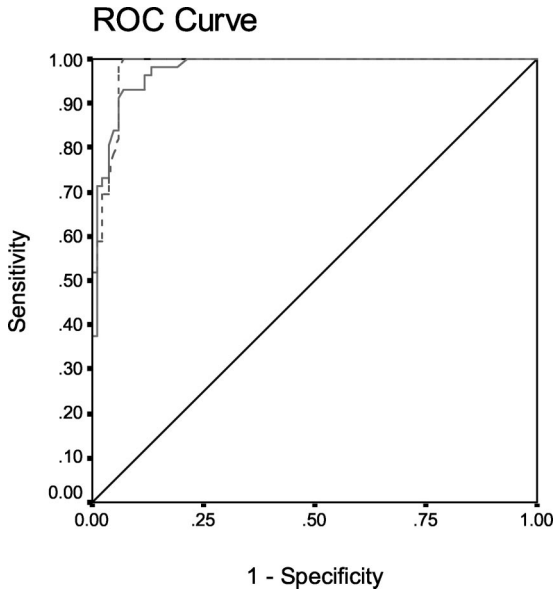

Figure 1. Receiver operating characteristic (*ROC*) curves for accuracy of the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score in predicting the presence necrotizing fasciitis. Area under curve for our model is 0.980 (95% confidence interval, 0.962–0.999) in the developmental cohort (*solid line*). The accuracy of this diagnostic model was validated in a separate cohort of patients with necrotizing fasciitis and control patients with severe cellulitis and abscesses (area under curve, 0.976; 95% confidence interval, 0.955–0.997, *dashed line*). A predictor that performs with perfect accuracy has an Az value of 1.

Table 3. Mean, SD, and ranges of the laboratory results of patients with necrotizing fasciitis (cases) and control patients with severe cellulitis and abscesses at admission

Variable (Normal Values)/ Units	TW (4–10) per mm^3	Hb (13.5–17.5) g/dL	Plt (140–440) per mm^3	Na (135–145) mmol/L	K (3.3–4.9) mmol/L	Cl (96–108) mmol/L	Glc (3.1–10) mmol/L	Urea (2.8–7.7) mmol/L	Cr (44–141) μmol/L	CRP (0–5) mg/L	ESR (1–10) mm/hr
Case											
Mean	20.72	12.1	326	129.3	4.2	98.1	15.6	11.1	137.9	254.3	81.1
SD	8.91	2.49	202	4.9	0.92	6.7	9.0	10.8	103.4	84.1	32.0
Min	5.7	5.8	9	114.0	2.6	82	2.2	2.5	10.8	44.5	5.0
Max	43.8	19.0	1266	139.0	8.0	115	47.1	67.8	846.0	476.0	145.0
Control											
Mean	11.48	14.1	275	137.0	4.0	104.3	7.9	5.1	90.5	63.1	33.2
SD	4.32	1.57	86	3.2	0.53	7.8	4.6	3.3	48.4	49.3	22.8
Min	4.60	8.6	35	124.0	2.5	90	3.1	1.7	22.0	0.1	2.0
Max	28.60	17.6	580	146.0	7.1	113	22.8	37.3	586.0	273.0	147.0

TW, total white cell count; Hb, hemoglobin; Plt, platelets; Na, serum sodium; K, potassium; Cl, chloride; Glc, glucose; Cr, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. To convert the values of glucose to mg/dL, multiply by 18.015. To convert the values of urea to mg/dL, multiply by 2.801. To convert the values of creatinine to mg/dL, multiply by 0.01131.

Table 4. Univariate analyses of the mean difference between cases and control

	Univariate Analysis			Multivariate Analysis		
Variable Name	OR (Unadjusted)	95% CI	*p* Value	OR (Adjusted)	95% CI	*p* Value
CRP, mg/L						
<150	1	—	—	1	—	—
≥150	95.34	42.3–214.7	<.001	50.33	14.9–169.7	<.001
Hb, g/dL						
>13.5	1	—	—	1	—	—
11.0–13.5	2.72	1.53–4.85	.01	1.22	0.36–4.13	.747
<11.0	17.8	7.36–43.06	<0.001	7.85	1.57–39.4	.01
Na, mmol/L						
≥135	1	—	—	1	—	—
<135	42.89	20.2–90.8	<.001	7.19	2.11–24.49	.002
TW, per mm^3						
<15.0	1	—	—	1	—	—
15.0–25.0	7.31	4.00–13.46	<.001	1.81	0.55–6.02	.333
>25.0	59.30	16.7–210.3	<.001	10.06	1.32–76.97	.026
Cr, μmol/L						
≤141	1	—	—	1	—	—
>141	11.60	5.2–25.8	<.001	7.43	1.57–35.04	.011
Glucose, mmol/L						
≤10.0	1	—	—	1	—	—
>10.0	7.28	4.2–12.5	<.001	3.97	1.26–12.49	.018
ESR, mm/hr						
≤50	1	—	—	1	—	—
>50	31.06	16.0–60.3	<.001	2.08	0.62–7.00	.24
Age						
<50	1	—	—	1	—	—
≥50	2.16	1.30–3.58	.03	0.61	0.19–2.00	.41
Cl, mmol/L						
≥96	1	—	—	1	—	—
<96	21.50	8.59–53.84	<.001	1.99	0.35–11.43	.44
K, mmol/L						
≤4.9	1	—	—	1	—	—
>4.9	5.15	1.84–14.39	.02	1.75	0.14–21.47	.66
Urea, mmol/L						
≤7.7	1	—	—	1	—	—
>7.7	10.32	5.64–18.92	<.001	1.26	0.31–5.05	.75
Gender						
Female	1	—	—	1	—	—
Male	0.624	0.38–1.04	.071	0.88	0.22–3.47	.85
Platelet, per mm^3						
≥144	1	—	—			
<144	2.05	0.74–5.68	.168			

OR, odds ratio; CI, confidence interval; CRP, C-reactive protein; Hb, hemoglobin; Na, serum sodium; TW, total white cell count; Cr, creatinine; ESR, erythrocyte sedimentation rate; Cl, chloride; K, potassium. To convert the values of glucose to mg/dL, multiply by 18.015. To convert the values of urea to mg/dL, multiply by 2.801. To convert the values of creatinine to mg/dL, multiply by 0.01131. Significant factors ($p < 0.1$) were entered into a multivariate model and analyzed with a multiple logistic regression approach by means of a backward stepwise selection procedure.

stratified the patients into three groups, low (LRINEC score ≤5), moderate (LRINEC score 6– 7), or high (LRINEC score ≥8) risk categories for necrotizing soft tissue infections. These risk groups corresponded to a probability of developing necrotizing soft tissue infections of <50%, 50–75%, and >75%, respectively (Fig. 2). At a cutoff of a LRINEC score of ≥6, the model has a positive predictive value 92.0% (95% CI, 84.3–96.0) and negative predictive value 96.0% (95% CI, 92.6–97.9). A score of ≥8 is strongly predictive of necrotizing fasciitis (positive predictive value, 93.4%; 95% CI, 85.5–97.2). The performance of the LRINEC score in the developmental and validation cohorts is as shown in Table 5. As shown in Table 5, 89.9% and 92.9% of patients with necrotizing fasciitis had a LRINEC score of ≥6 in the developmental and validation cohorts, respectively, whereas only 3.1% and 8.4% of control patients in the corresponding cohorts had a score of ≥6.

DISCUSSION

The LRINEC score is capable of detecting early cases of necrotizing fasciitis among patients with severe soft tissue infections. A LRINEC score of ≥6 should raise the suspicion of necrotizing fasciitis, and a score of ≥8 is strongly predictive of this disease. In the developmental cohort of 89 patients, only 13 (14.6%) patients had a diagnosis or suspicion of necrotizing fasciitis on admission. A majority were therefore initially missed, resulting in delayed operative debridement (1). In contrast, 80 (89.9%) of these patients had a LRINEC score of ≥6. The biochemical and hematologic changes in necrotizing fasciitis develop early in the evolution of the disease, and the LRINEC score can stratify patients into high- and moderate-risk categories even when the clinical picture is still equivocal. Used in the right context (patients with soft tissue infections with no other septic foci), the LRINEC score can significantly de-

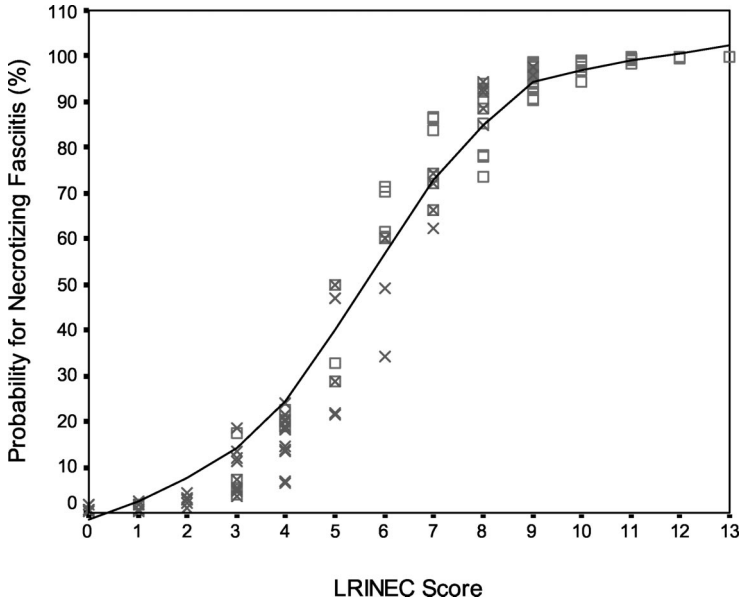

Figure 2. Plot of probability of necrotizing fasciitis against the ascending categories of Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score. Cases of necrotizing fasciitis (n = 145) are represented by boxes and control patients are represented by crosses (n = 309). From the graph, a probability of necrotizing infections of <50% corresponds to an LRINEC score of ≤5 and a probability of necrotizing infections of >75% corresponds to a score of ≥8.

Table 5. Performance of Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score for our cases and controls from the developmental and validation cohorts

	No. of Patients (%)		
	Low Risk (LRINEC Score ≤5)	Moderate Risk (LRINEC Score 6–7)	High Risk (LRINEC Score ≥8)
Developmental cohort (NF cases)	9 (10.1)	9 (10.1)	71 (79.8)
Validation cohort (NF cases)	4 (7.1)	9 (16.1)	43 (76.8)
Developmental cohort (Control)	218 (96.9)	5 (2.2)	2 (0.9)
Validation cohort (Control)	77 (91.6)	5 (6.0)	2 (2.4)

NF, necrotizing fasciitis.

crease the time to diagnosis by stratifying patients into risk categories for necrotizing soft tissue infections warranting immediate further evaluation.

Clinical variables alone are often nonspecific early in the course of the disease and can potentially lead to fatal delay in operative treatment (1, 6, 7). A diagnostic score that includes clinical as well as laboratory variables would inevitably favor advance cases of necrotizing fasciitis (where clinical recognition is usually not a problem) and risk missing early cases of necrotizing fasciitis (where early diagnosis would profoundly affect outcome). We therefore favor an objective diagnostic adjunct, based on laboratory variables alone to assess for the possibility of necrotizing soft tissue infections.

Necrotizing fasciitis is associated with severe sepsis (1–9). Sepsis and the associated systemic inflammatory response syndrome cause changes in the biochemical and hematologic variables in a predictable manner. These biochemical and hematologic disturbances that we observed in our patients with necrotizing fasciitis had also been previously reported by other authors (15–19). The LRINEC score is essentially a measure of these changes and predicts the probability of the presence of necrotizing fasciitis based on the severity of sepsis. Other soft tissue infections such as cellulites and abscesses rarely cause an inflammatory state severe enough to cause such disturbances in the laboratory variables. Although other laboratory variables such as prothrombin time, activated partial thromboplastin time, serum calcium, arterial blood gas assays, and liver function tests may be of diagnostic significance, they were not analyzed as these tests were not routinely performed for patients with soft tissue infections on admission. Furthermore, the inclusion of these tests in the evaluation of all soft tissue infections is difficult to justify and makes the scoring system inconvenient for routine clinical use.

Various modality and techniques have been proposed to aid in the early diagnosis of necrotizing fasciitis. Frozen section biopsies and MRI scans of the affected part have been shown to be capable of detecting early cases of necrotizing fasciitis (10–14). However, it is neither feasible nor logical to subject all patients with the suspicion of necrotizing fasciitis to frozen section biopsies, as the procedure is not without morbidity. Routine MRI scanning for all patients at the first suspicion of necrotizing fasciitis is financially prohibitive (7). Alternatively, the "finger test" should be considered. This is a bedside procedure where under local anesthesia a 2-cm incision is made down to the deep fascia and a gentle probing maneuver with the index finger is performed at the level of the deep fascia. The lack of bleeding, presence of characteristic "dishwater pus," and lack of tissue resistance to blunt finger dissection are features of a positive finger test and necrotizing fasciitis (26). The LRINEC score can be used for patient selection and for allocation of resources by stratifying patients with soft tissue infections into high-, moderate-, and low-risk categories. Depending on availability, frozen section biopsy, MRI scan, or a bedside finger test should be considered for patients with equivocal clinical findings but found to have moderate or high risks for necrotizing fasciitis based on the LRINEC score.

Figure 3 shows our suggested clinical pathway in the management of soft tissue infections. It should be emphasized that the diagnosis of necrotizing soft tissue infections is a clinical diagnosis, and this diagnosis or even suspicion of it warrants immediate operative debridement (1). The LRINEC score is, however, a very useful diagnostic adjunct in the management of soft tissue infections to stratify these patients into low-, moderate-, and high-risk categories for necrotizing fasciitis for further evaluation.

The potential applications and advantages of the LRINEC score are as follows:

1. It is based on routine laboratory investigations done on admission for evaluation of all severe soft tissue

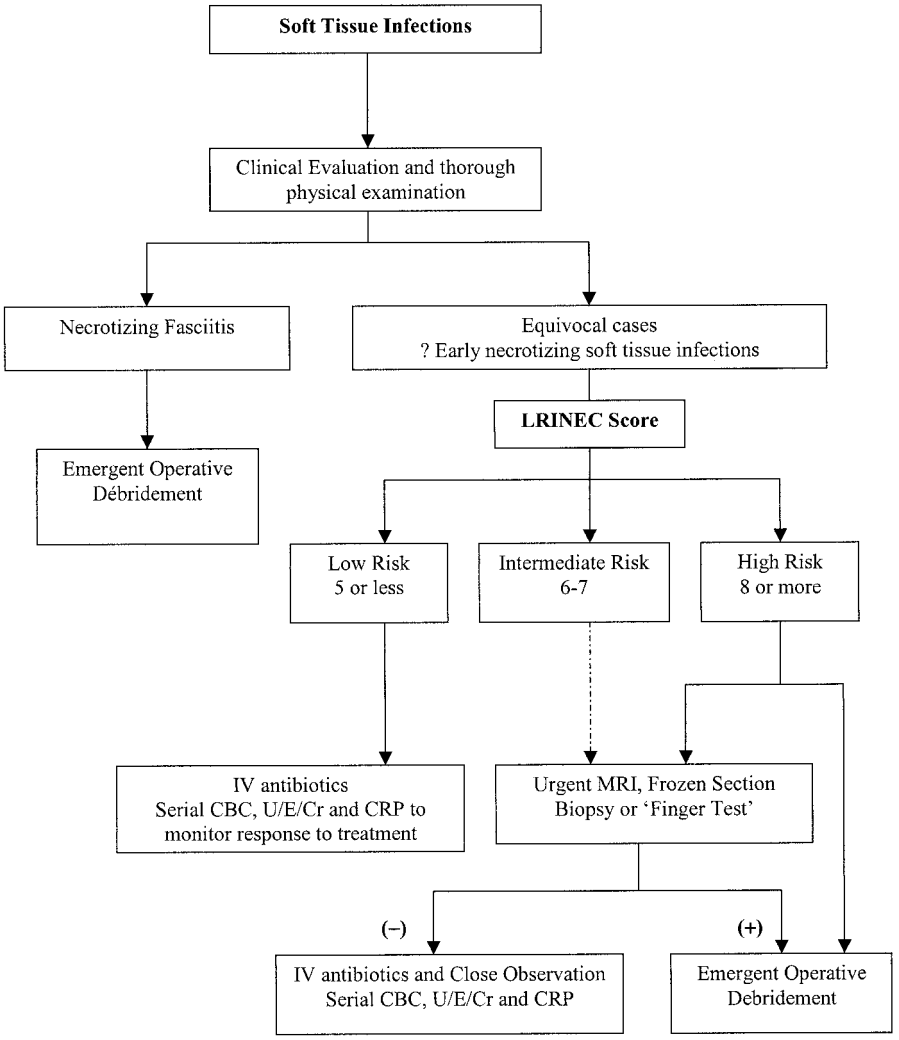

Figure 3. Suggested clinical pathway in the management of soft tissue infections. *LRINEC*, Laboratory Risk Indicator for Necrotizing Fasciitis; *IV*, intravenous; *CBC*, complete blood count; *CRP*, C-reactive protein; *MRI*, magnetic resonance imaging.

infections: complete blood count, serum electrolytes (U/E/Cr), and CRP. These investigations are cheap and readily available.

2. It can stratify patients into high-, moderate-, and low-risk categories for serious soft tissue infections warranting admission, intravenous antibiotics, and immediate further evaluation.
3. To achieve early diagnosis, operative debridement, and ultimately better survival in necrotizing fasciitis, patients in the moderate- and especially the high-risk categories should be evaluated urgently to exclude necrotizing fasciitis. MRI scan, frozen section biopsy, or the finger test are some diagnostic tests that should be considered in equivocal cases of soft tissue infections.

Some potential pitfalls and weaknesses of the LRINEC score should be borne in mind when using this scoring system. Serial LRINEC score monitoring is helpful, and in many cases an increasing score despite broad-spectrum antibiotics is a valuable diagnostic clue. However, in our experience, once in the hospital, interventions to correct laboratory disturbances described (intravenous normal saline, insulin infusions, and blood transfusions) tend to interfere with the accuracy of the score. In patients with multiple comorbidities, the inflammatory response may be blunted and the score should be interpreted with caution. Of note, neutropenia is a poor prognostics marker in sepsis and, in patients with a total white count of $<4 \times 10^3$ per mm^3, should alert the physician of the possibility of leukopenic sepsis (27). Finally, this is an adjunct in the management of soft tissue infections. Clinical acumen remains of paramount importance, and when the clinical suspicion is high, emergent debridement must be performed regardless of the LRINEC score.

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is a robust score capable of detecting even clinically early cases of necrotizing fasciitis.

CONCLUSIONS

The LRINEC score we have described is an indicator of the severity of sepsis. Although it measures nonspecific biochemical and inflammatory changes triggered by systemic inflammatory response syndrome and sepsis, we believe that when used in the right context, it can be helpful in stratifying patients into risk categories of possibility of necrotizing fasciitis, allocating resources (e.g., patient selection for MRI scan), and ultimately aiding in the early recognition of necrotizing fasciitis. The LRINEC score is a robust index that is capable of detecting early cases of necrotizing fasciitis and is simple enough for routine use. The score, however, needs to be prospectively validated before routine use in evaluation of soft tissue infections can be recommended.

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