Necrotizing fasciitis—a review

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ABSTRACT: Necrotizing fasciitis is an uncommon, rapidly progressive, often aggressive bacterial infection that causes extensive necrosis of the subcutaneous tissue and fascia, relatively sparing the muscle and skin tissues. Rapid diagnosis of the disease is mandatory because the delay in initiation of aggressive treatment negatively influences the outcome. Specific clinical signs may not be always present, which makes an accurate and timely diagnosis difficult. Based on the literature, this article presents a review of the historical background, etiology, pathophysiology, clinical findings, diagnostic strategies, treatment and prognosis of the disease.

KEYWORDS: antibiotics, idiopathic, laboratory risk indicator, necrotizing fasciitis, superficial fascia, surgical debridement

ABBREVIATIONS

AIDS – acquired immunodeficiency syndrome
BC – Before Christ
CT – computed tomography
HIV – human immunodeficiency virus
LRINEC – Laboratory Risk Indicator for Necrotizing Fasciitis
m-LRINEC – modified Laboratory Risk Indicator for Necrotizing Fasciitis
MRI – magnetic resonance imaging
NF – necrotizing fasciitis
NSAID – non-steroidal anti-inflammatory drug
US – United States

INTRODUCTION

Necrotizing fasciitis (NF) is a rapidly progressing bacterial soft tissue infection that can lead to sepsis, systemic toxicity, multiorgan failure and a potentially fatal outcome [1, 2]. The term literally means “decaying infection of the fascia”. The estimated incidence in the western world is about 0.24–0.4/100 000 people per year and it is ranked among most difficult emergencies encountered by healthcare providers. However, in some areas of the world, NF is more common and more than one case in every 100 000 people is reported [3–6].

NF has multiple causes, risk factors, anatomical locations, and pathogenic mechanisms, and results in widespread tissue destruction, which may extend from the epidermis to the deep musculature. Mortality is high and even the survivors have a long clinical course. An early clinical suspicion and diagnosis are vital to the outcome, but an accurate diagnosis is reached in only 15% to 34% of patients at the time of presentation [7]. Hence this review is aimed to increase the awareness about various aspects related to NF.

METHODS

The original articles, meta-analyses, reviews, case series and case reports dealing with the NF were searched in PubMed and ResearchGate after search on following terms: “necrotising fasciitis” AND (“physiopathology” OR “etiopathogenesis” OR “etiology” OR “management”). Only the articles published in English were included and time limits were set between the years 2000–2021. Reference lists in all the selected articles examined and used to identify additional articles for inclusion. Older references were included only, if they shed light on the historical background.

HISTORICAL BACKGROUND

NF has been recognized and reported for centuries, the earliest dating back to Hippocrates in the 5th century BC [8]. However, Confederate military surgeon Joseph Jones was the first to describe the disease on modern lines based on his experiences during the US Civil War (1961–1965). He described it as an infection with flesh-eating bacteria and reported a mortality of about 50% [9]. Before his report, the disease was generally known as hospital gangrene.

In 1883, Jean Alfred Fournier, a French dermatologist reported a series of five cases of necrotizing fasciitis affecting the perineal and genital region [10]. Frank L. Meleney later reported twenty cases from China, where the disease had been caused by hemolytic streptococcus [11]. McCafferty and Lyons characterized supplicative fasciitis as the essential feature of hemolytic streptococcus gangrene and reported the utility of fasciotomy and early wound closure [12]. The term ‘necrotising fasciitis’ was coined by Wilson who explained the disease as necrosis of the fascia and subcutaneous tissue with relative sparing of the underlying muscle, without assigning any specific pathologic bacterium as the causative agent [13].

ETIOLOGY

NF is typically an acute process that evolves very rapidly over a few days. In approximately 80% of all cases, it is a direct consequence of a disruption of skin’s integrity followed by bacterial infection.

The disease occurs when the right set of conditions are present; in approximately 80% of all cases, these include a disruption of skin’s integrity that allows bacterial infection, such as surgical wounds, animal bites, lacerations, scratches, burns, minor invasive procedures (joint aspiration, acupuncture), intramuscular injection, and folliculitis [14].

NF is observed particularly in cases with comorbidities and risk factors, which can include: systemic diseases, diabetes, alcoholism, immunosuppression, and a history of prior infectious disease. It is more common in the pediatric age group and among the elderly. It can also be seen in persons with a history of alcohol abuse, diabetes mellitus, sickle cell disease, malignancy, and immunosuppressive medication usage [15].

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The disease is often associated with a high mortality rate, with the highest mortality occurring in patients with necrotizing fasciitis involving the perineum, genitalia, and retroperitoneum. The mortality rate is also higher in patients with underlying medical conditions such as diabetes, alcoholism, and immunosuppression [16].

REFERENCES

Staphylococcus aureus, Streptococcus pyogenes, and enterococci, Gram-negative aerobes such as Escherichia Coli and Pseudomonas species, and anaerobic organisms, such as Bacteroides or Clostridium species. Monomicrobial infections are less common and Gram-positive cocci (Staphylococcus aureus and Streptococci) are responsible for the majority [19].

PATHOPHYSIOLOGY

Infection rapidly spreads along the fascial planes and causes microvascular occlusion which leads to liquefactive necrosis at all tissue levels (Fig. 1.). The overlying skin initially appears unaffected, but

factors include diabetes, chronic disease, immunosuppression, malnutrition, advanced age, non-steroidal anti-inflammatory drug (NSAID) use, morbid obesity, liver cirrhosis, intravenous drug misuse, alcoholism, peripheral vascular disease, chronic renal failure, immunological disorders, HIV–AIDS, paraplegia, underlying malignancy and varicella infection [15–17]. Bingol-Kologlu et al. has reported NF even after application of a cream containing menthol to the cervical region [18].

Microbiologically, NF may be either type I (polymicrobial) or type II (monomicrobial). Polymicrobial infections are more common, with cultures yielding a combination of aerobic and anaerobic organisms, including Gram-positive organisms such as
after several days, it becomes warm, erythematous, tender and warm. Skin breakdown usually begins in 3 to 5 days and is accompanied by bullae, subcutaneous emphysema, skin sloughing, and cutaneous gangrene. With the onset of cutaneous gangrene, pain becomes reduced secondary to destruction of superficial cutaneous nerves. Advanced stages of NF are characterized by systemic symptoms, such as pyrexia, tachycardia, and sepsis [20].

**HISTOPATHOLOGY**

Sections from NF tissue show extensive superficial fascial necrosis with small and medium-sized blood vessels occluded by thrombi. Dense aggregates of neutrophils may be observed in the fascia and deeper parts of the subcutaneous tissue. Extensive subcutaneous fat necrosis and vasculitis are also evident. Eccrine glands and ducts may also display necrotic changes. Gram staining shows clusters of various types of microorganisms. Alcian blue or periodic acid-Schiff staining with diastase may show clusters of bacteria and fungi. Without adequate treatment, deeper muscle layers may get secondarily involved, resulting in myositis or myonecrosis. Normally, however, the muscles remain healthy under the yellowish green fascia. Bakleh et al. conducted a retrospective study to determine what correlations, if any, exist between histopathologic features of debrided tissue in patients with NF and the clinical outcome. The study suggested that histopathologic findings may correlate with the clinical outcome and since the histopathologic scheme is based on results of commonly available stains, it could be easily adopted for use as a prognostic tool [21].

**CLINICAL FEATURES**

Diagnosis of NF can be difficult and a high level of suspicion should be maintained by the clinician. Studies have shown that an accurate diagnosis is reached in only 15% to 34% of patients at the time of presentation [7, 22, 23]. In a series of 39 pediatric cases of NF reported by Fustes-Morales et al., diagnosis at admission was made in only 28% [22]. Antecedent trauma or surgical intervention can be identified in many cases of NF, but the initial lesion may be trivial, such as an insect bite, minor abrasion, boil, or an injection site. Besides, idiopathic cases with no additional predisposing factors, are also commonly reported in literature [14, 22, 24, 25]. In the series by Fustes-Morales et al. about half of the cases did not have any predisposing factors [22].

Excruciating pain over the involved skin and underlying muscle is the hallmark symptom (Fig. 2.). The intensity of pain may cause suspicion of a sprain/torn or ruptured muscle [26]. Uncommonly, pain may begin at a site distant from the initial trauma. Pain may be out of proportion to physical findings in the initial hours. However, a minority of patients may report with minimal pain due to factors like diabetic neuropathy. Over the next several hours to days, the local pain may diminish due to nerve damage and the patient may adopt a laissez-faire attitude toward their illness [14].

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<tr>
<th>VARIABLE</th>
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<tr>
<td>C-reactive protein (mg/l)</td>
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<td>Serum creatinine (mmol/L)</td>
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<td>Blood glucose level (mg/dl)</td>
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**Interpretation**

Score < 6: Low Risk; Score 6−7: Intermediate; Score ≥ 8: High Risk

**Tab. I. LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score.**

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Fig. 3. Necrotizing fascitis of right lower limb: (A) – Day 4 of symptoms with erythema, edema and blisters. (B) – Day 5 of symptoms with skin peeling off. (Image courtesy: Dr John P Livingstone, Orthopedic Surgery, Queen’s Medical Center, Honolulu, USA.)
At initial assessment (day 0), almost all patients had erythema, tenderness, warmth, and edema. Blistering occurred in 41% of patients at presentation whereas late signs such as skin crepitus, necrosis, and anesthesia were infrequently seen (0–5%). With elapsed time, more patients formed blisters (77% at day 4) and eventually, late signs of necrotizing fasciitis characterized by skin crepitus, necrosis, and anesthesia (36%) were apparent. A clinical staging system was developed based on these observations and stage migration from early to late-stage NF was evident, with majority of patients in stage 1 at day 0 (59%), whereas majority had progressed into stage 3 (68%) by day 4. This study demonstrated the continuum of cutaneous manifestations as NF evolves, the recognition of which would translate into early intervention [27].

In a recent prospective study by Huang et al., it was concluded that the difference in features of the bullae in NF can potentially predict the different outcomes. According to the presence of different bulla types, the cases were categorized into no bullae group (Group N), serous-filled bullae group (Group S), and hemorrhagic bullae group (Group H). Group H had the worst outcome with highest incidence of amputation or need of intensive care. In Group N, more patients were infected with *Staphylococcus* spp., in Group S, more patients were infected with β-hemolytic *Streptococcus* and in Group H, most patients were infected with *Vibrio* species [28].

Physical findings may not be commensurate with the intensity of pain that the patient reports. In the early course, patient may look deceptively well, and this pitfall is reported to interfere with the early disease detection, which is otherwise a key to a favorable outcome. Soon, however, the patient will display systemic septic signs, like pyrexia and tachycardia, and tend to appear moderately to severely toxic [22, 23].

On local examination, the initial sign is erythema and warmth that quickly spreads. There is tenderness and edema that extends beyond the erythematous border. The edema often has a tense quality, making the skin feel hardened or “wooden” and rendering it difficult to detect the fascial planes and muscle groups cannot be detected by palpation. As infection progresses, skin vesicles, bullae, ecchymosis, and dysesthesia/paresthesia/anesthesia appear over the affected area (Fig. 3.). Subcutaneous emphysema and crepitus are only present in the gas-producing type of necrotizing fasciitis, and their absence does not rule out the disease [22, 23].

Wang et al. [27] conducted a retrospective study on patients with necrotizing fasciitis at Singapore Central Hospital with an aim to study the manifestations of the cutaneous signs of NF as the disease evolves. The daily cutaneous changes from the time of presentation (day 0) through the day 4, were documented after a review of the records/charts. At initial assessment (day 0), almost all patients had erythema, tenderness, warmth, and edema. Blistering occurred in 41% of patients at presentation whereas late signs such as skin crepitus, necrosis, and anesthesia were infrequently seen (0–5%). With elapsed time, more patients formed blisters (77% at day 4) and eventually, late signs of necrotizing fasciitis characterized by skin crepitus, necrosis, and anesthesia (36%) were apparent. A clinical staging system was developed based on these observations and stage migration from early to late-stage NF was evident, with majority of patients in stage 1 at day 0 (59%), whereas majority had progressed into stage 3 (68%) by day 4. This study demonstrated the continuum of cutaneous manifestations as NF evolves, the recognition of which would translate into early intervention [27].

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In certain cases, cutaneous changes may be subtle and Iwata et al., based on an analysis of their case series, suggested a possibility that the paucity of skin inflammatory signs, such as erythema and warmth in NF may be a clinical clue to predict the fulminant type and poor prognosis [29].

**IMAGING STUDIES**

Imaging modalities including plain radiography, ultrasound, CT-scan and MRI help the diagnosis and management by helping exclude diseases imitating NF and demarcating debridement margins [30].

Plain radiographs are often obtained to detect soft-tissue gas. Presence of gas is specific but not sensitive, as it presents in only a quarter of Type 1 NF cases after the disease has advanced, causing soft tissue emphysema along the fascial planes. Furthermore, plain radiographs may demonstrate certain non-specific findings of soft tissue edema, which mimic cellulitis and myositis. So, plain radiographs do not have adequate value in the diagnosis of necrotizing fasciitis. In fact, studies have found that such non-diagnostic plain radiographs may even lead to diagnostic errors and delay in operative intervention with consequent increased morbidity and mortality [31].
Ultrasonography is a useful tool in NF, as it can determine subcutaneous emphysea along the fascial planes, edema, dense echogenicity of fatty tissue with interlacing fluid collections and abscess formation, thereby allowing prompt surgical intervention [30–32].

CT scan is about 100 percent sensitive and 80–98 percent specific in detection of NF. It displays dilution of soft-tissue, fat stranding and fluid or air in fascial planes. However, CT findings in early NF are only minimal. A negative intravenous contrast-enhanced CT scan can reliably rule out the need for surgical intervention in patients with initial suspicion of NF [33, 34].

MRI has evolved as modality of choice for detailed evaluation of soft tissue infection. Various studies have demonstrated its usefulness in differentiating non-necrotizing cellulitis that can be treated medically from severe NF, which requires aggressive debridement. When MRI is combined with clinical assessment, it could aid in determining the requirement and extent of debridement [35].

LABORATORY TESTS AND LRINEC SCORE

In 2004, Wong et al. introduced the concept of the LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score as a robust tool for distinguishing necrotizing fasciitis from other soft tissue infections [36]. The score is based on six blood tests that are otherwise very commonly performed in patients of soft tissue infections (Tab. I.).

Recently, in June 2021, a modified Laboratory Risk Indicator for Necrotizing Fasciitis (m-LRINEC) scoring system was developed by Wu et al. based on a retrospective nested case-control study [37]. They added coexisting diabetes and kidney disease to the original LRINEC scoring system, used high-sensitivity C-reactive protein (HCRP) to replace the CRP and redefined the cut-off values for the other four variables, to develop the m-LRINEC system. The authors suggested that m-LRINEC scoring system shows high sensitivity and specificity in discriminating NF from other severe soft-tissue infections and that in patients with an m-LRINEC score of > 17 points, a high index of suspicion be maintained for the presence of NF. However, the validity of the m-LRINEC needs to be confirmed in studies with larger samples and better design.

THE FINGER TEST FOR DIAGNOSIS OF NECROTIZING FASCIITIS

If there is a strong suspicion of NF, and imaging results are negative or else the facilities are not available, then a ‘Finger Test’ may be considered for diagnostic confirmation. After proper infiltration with local anesthesia, a 2- to 3-cm incision is made in the skin (large enough to insert the index finger) down to the deep fascia. Absence of bleeding and/or discharge of “dishwater-colored pus” (gray-colored fluid) in the wound are very suggestive of necrotizing fasciitis. Tissues are gently probed with the finger and if the deep tissues dissect easily with minimal resistance, the finger test is deemed as positive for NF [38].

MANAGEMENT

Once the diagnosis of NF is confirmed, treatment should be initiated without delay (Fig. 4.). Key concepts for treatment include:

1. Resuscitation and early administration of appropriate wide-spectrum antibacterial coverage empirically;
2. Adequate control of infection sources, such as surgical intervention for abscess drainage and aggressive debridement of necrotizing tissue;
3. Specimen analysis and identification of causative pathogen followed by applicable adjustment of antimicrobial coverage.

SURGICAL DEBRIDEMENT

Early and aggressive surgical debridement of necrotic tissue is the cornerstone of management. It reduces the infection burden, minimizes ultimate tissue loss, reduces the need for amputation and thereby, decreases mortality [5]. Debridement should be extensive and all the necrotic and poorly perfused tissues that can be easily elevated off the fascia with gentle pressure should be excised (Fig. 5.).

Some difference of opinion exists in the literature regarding the extent of tissue that should be initially excised as the skin may often appear normal. Andreasen et al. performed microscopic analysis of normal-appearing tissues in NF and reported that the tissues had extensive early vascular thrombosis as well as vasculitis, indicating thereby that the tissues with apparent normal appearance have a high potential for deterioration and full-thickness loss [39].

After the initial debridement, patient may require further surgical debridement as the general hemodynamic instability of the patient with peripheral vasoconstriction can cause progressive skin necrosis. Once all the affected tissues have been debridged, meticulous wound care with various dressing material (including Negative Pressure Wound therapy) prepares the wound bed for soft tissue (Fig. 6., 7.) reconstruction.

PROGNOSIS AND OUTCOMES

Necrotizing fasciitis is a serious surgical emergency with mortality as high as 32–50% [40, 41]. Mortality in NF is usually caused by pronounced sepsis with secondary multiorgan failure. Poor prognosis has been linked to advanced age, type of organism, uncontrolled diabetes, state of immunosuppression and delay in aggressive surgical intervention. Even people who survive may require prolonged recovery due to significant functional deficits as a result of amputations and scarring. Outcomes are best for patients who undergo immediate radical debridement, resuscitation, broad-spectrum antibiotics and intensive care. Certain studies have found that even with optimal treatment, survivors of NF tend to have a shorter lifespan than age-matched controls [42, 43]. Some recent studies have pointed towards potential benefits of the use of intravenous immunoglobulin in hemodynamically unstable, critically ill patients [41].

CONCLUSION

Although necrotizing fasciitis is rare, its lethal potential must be appreciated, and early diagnostic features should be recognized. Clinical suspicion remains the key to the diagnosis of necrotizing fasciitis. Once diagnosed, early and adequate surgical debridement must be undertaken. Similarly, in uncertain cases, early surgical exploration is the best approach. Mortality and morbidity associated...
with NF can be minimized with increased clinical awareness, early diagnosis, and urgent surgical debridement followed by intensive supportive care and early wound resurfacing.

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