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Review Article

Necrotizing Fasciitis- A Lethal Soft Tissue Infection: Review Article

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Abstract:

Background: Necrotizing Fasciitis is a rapidly progressive soft tissue infection that is almost fatal without prompt treatment. This review highlights about the basic approach to the diagnosis and treatment of NF.

Description: Various nomenclatures have been used to describe necrotizing soft tissue infections. These infections are classified on the basis of the microbes involved, depth of invasion and anatomical sites involved. Diabetes is the most common risk factor for NF. The masquerading cutaneous manifestations make the diagnosis of NF a challenge. Laboratory parameters, imaging techniques and scoring systems have been designed to aid in early diagnosis.

Conclusion: High index of clinical suspicion is needed to make prompt diagnosis of NF. Urgent aggressive surgical debridement with antimicrobial therapy limits the morbidity and mortality associated with NF.

keywords: necrotizing fasciitis; debridement; review article

Introduction:

Necrotizing Fasciitis (NF) is the most severe soft tissue infection primarily involving the fascia and subcutaneous tissue. It is rapidly progressive and potentially limb and life threatening [1]. The common sites involved are the lower extremities, perineum and genital area, abdominal wall and upper extremities [2,3]. Various recent studies show the incidence to be 0.04 cases per 1000 person-years in US and Canada [4-7]. Necrotizing Soft Tissue Infections (NSTIs) are emerging as the prime cause of infectious disease-related medical malpractice litigation in the U.S., usually related to allegations of delay in diagnosis and treatment [8]. The mortality rate from NF worldwide ranges from 8.3% to as high as 73% [9-14].

About 80% cases are Type I NSTIs which are polymicrobial, whereas Type II infections are monomicrobial, commonly caused by beta-hemolytic streptococcal species and seen in 10-15%. Rarely NSTIs may be caused by marine *Vibrio* and fungi [14, 15]. Although the etiology is unknown in about 20% cases, the commonly identified causes are trauma, surgery, bites or intravenous drug abuse that would allow bacterial entry [6, 10, 16, 17]. Risk factors include age > 50 years, peripheral vascular disease, atherosclerosis, chronic alcoholism and chronic debilitating co-morbidities (e.g., Diabetes Mellitus (DM), immunosuppression and obesity) [2,4,6,11,16,18,19].

NF patients present with swelling of the affected site, erythema, pain and tachycardia initially, and as the infection progresses, typical features such as tense edema outside the area of compromised skin, pain disproportionate to appearance, skin discoloration, blisters/bulla, necrosis, crepitus and/or subcutaneous gas are seen along with systemic findings of fever, tachycardia, hypotension and shock. Though these findings are typical, their sensitivity is low, and are seen in only 10-40% cases [6, 10, 11, 15].

Plain radiographs, Ultrasonography, CT and MRI have high sensitivity but low specificity and show no pathognomic imaging characteristics of NSTI. Also the issue of its availability, cost and time raises question on its application [6, 8, 20-22]. For early diagnosis, frozen-section biopsy has been recommended but is not practical due to need of experienced pathologists and is not readily available [1, 6, 23, 24]. Different scoring systems have been suggested to improve the diagnostic process and decrease the interval between presentation and definitive aggressive management.

Early diagnosis of NF is challenging and missed in 85-100% of patients because of the paucity of early pathognomic signs which make it indistinguishable from cellulitis or abscess formation. This delay of diagnosis leads to delayed surgical intervention, which is the most important factor for adverse outcome. Use of antimicrobials alone does not stop the infectious process and it is the urgent aggressive surgical debridement which remains the key for better outcome in patients with NF [6, 10, 11, 22, 25, 26].

Main text:

Necrotizing Fasciitis is a rare but highly lethal condition. It can be defined as rapidly progressive tissue infection characterized by extensive necrosis of the subcutaneous fat and fascia [1, 6, 27]. The earliest description of

this condition dates back to 5th century BC by Hippocrates who described it as a complication of erysipelas [28]. However, the first report of this dreaded disease in the United States was in 1871 by Joseph Jones. The term 'Fournier's gangrene' became popular for perineal NSTIs owning to description of necrosis of perineum in five men by Jean Alfred Fournier in 1883. Brewer and Meleney in 1924 introduced the term 'hemolytic streptococcal gangrene' after an outbreak of this condition in Beijing. Since then, multiple papers have been published describing NSTIs as a spectrum of disease involving various anatomical sites and depth of involvement. It was Wilson who coined the term 'necrotizing fasciitis' in 1952 and is the preferred terminology even today as it depicts the most consistent and key feature of this disease, that is, necrosis of fascia [6, 14, 16, 29].

The incidence of NF is about 0.4 cases per 1000 person-years in US and Canada [4-7]. About 500 new cases of NF are reported yearly in UK and a yearly incidence of 3.8 cases per 100000 is seen in Australia.[3] The actual incidence of NSTIs appears to be increasing due to better standardization of definition and reporting of cases [30,31]. NF, commonly known as 'Flesh eating disease', is predominantly seen in extremities, perineum and abdominal wall [2, 3]. However, it can affect any part of the body and NF of breast, head and neck has also been reported [27].

Pathology:

NF is a fulminant bacterial infection of the subcutaneous tissue that rapidly spreads through the tissue planes involving the skin, subcutaneous tissues, fascia and/or muscle causing vascular occlusion, ischemia, extensive tissue necrosis and lifethreatening sepsis [27]. Depending on the bacterial byproducts, necrosis can be mediated by toxins directly or result from vascular occlusion [14]. In NF, the primary site of pathology lies in the superficial fascia [22]. In most cases, the infection begins with the bacteria reaching the subcutaneous layer via a portal of entry such as preceding skin lesions or injury. However, hematogenous inoculums of bacteria from a distant site of infection (such as streptococcal pharyngitits) can also occur [32,33]. Then, proliferation of bacteria occurs in the superficial fascia and this is aided by host factors such as immunosuppression and hyperglycemia. Various toxins and enzymes, such as hyaluronidase, collagenase, streptokinase and lipase, are secreted by the bacteria to enable its spread through the fascia [2]. As a result of this uncontrolled proliferation of bacteria, angio-thrombotic microbial invasion and liquefactive necrosis of the superficial fascia occur. This constitutes the horizontal phase characterized by rapid spread of infection through the fascia and extensive undermining of the apparently normal looking skin. As the condition progresses, progressive skin ischemia and necrosis ensues due to the occlusion of perforating nutrient vessels to the skin, which manifests as blister or bulla formation, ulceration and skin necrosis [22, 34]. Myositis occurs when there is breach in fascia with involvement of muscle. Necrosis of the cutaneous nerves turns extreme pain to numbness. Venous thrombosis, lymphangitis and lymphadenitis are rarely seen [34].

Etiology and Risk Factors:

Although the etiology is unknown in about 20% cases, the commonly identified causes are trauma, surgery, animal bites, insect bites, intravenous drug abuse, visceral-cutaneous fistulas, percutaneous catheter insertion, acupuncture, skin infections and ulcers that would allow inoculation of pathogen into the subcutaneous tissue. [6,10,16,17,35] Hematogenous spread from distant sites such as in patients with streptococcal pharyngitits has also been suggested [35]. The most common risk factor for NF is diabetes mellitus with studies showing as high as 70.3% patients with NF having DM [36, 37]. Other known risk factors include age > 50 years, peripheral vascular disease, atherosclerosis, chronic alcoholism and chronic debilitating co-morbidities such as immunosuppression, obesity, malnutrition and hypoalbuminemia. In addition, burns, malignancy, neutropenia and high-dose corticosteroid therapy can increase the risk of NSTIs [2, 4, 6, 11, 16, 18, 19]. Some studies suggest that there is an association between Non-steroidal anti-inflammatory drug (NSAIDs) usage and severe necrotizing streptococcal infections as it may affect lymphocyte function but this may be due to delay in diagnosis as NSAIDs may suppress early clinical symptoms and signs of NF[14, 38, 39].

Classification

Various systems of classifications of NSTIs are in use on the basis of their microbiology, the depth of tissue involvement and their anatomical locations. Most commonly, NSTIs are classified on the basis of their microbiological prolife as knowing the involved microbe aids in clinical decision making such as selection of antibiotic. Originally, Giuliano et al in 1977 described two microbiological groups of NSTIs, however, with the isolation of additional pathogens, NSTIs are currently classified as one of the following four types on the basis of the involved microbes [14, 40, 41]:

Type I NSTI: This is the most common type and accounts for about 80% cases. Type I infections are typically polymicrobial and synergistic with the causative organisms being a mixture of anaerobes, aerobes and facultative anaerobes, often bowel flora derived. Gram-positive cocci such as Streptococcus, Staphylococcus along with gram-negative rods including E. coli and anaerobes such as Bacteroides are the pathogens commonly isolated from these infections. It is usually seen in older patients with co morbidities. Perineum and trunk are the common affected sites [14,15, 41, 42].

Type II NSTI: These are seen in 10-15% cases and are monomicrobial, skin or respiratory derived, commonly caused by beta-hemolytic streptococcal species, occurring either alone or along with *Staphylococcus aureus*, especially methicillin-resistant species. Type II infections are aggressive with potential for rapid local spread and systemic toxicity including TSS. The patients usually affected are younger and healthier with history of trauma, surgery or intravenous drug abuse. Commonly involved areas are the trunk and extremities [14, 35, 41].

Type III NSTI: It is a gram-negative monomicrobial infection, often caused by marine organisms, such as *Vibrio vulnificus* or *Aeromonas hydrophilia*. These infections are seen along warm-water coastal regions in the south eastern United States, Central and South America, and Asia. Infection can occur via wound contamination with seawater or ingestion of seafood, especially in patients with cirrhosis. Type III infections present with early evidence of systemic toxicity and cutaneous evidence of infection may be lacking [14, 35, 41, 43].

Type IV NSTI: This type of NF is rare and caused by fungi like Candida spp. in immunocompromised and Zygomycetes in immunocompetent patients. These are aggressive with rapid extension and are commonly seen in severe trauma, burn and immune compromised cases [14, 41, 44].

On the basis of depth of necrosis, NSTIs can be classified as [32, 41]:

1. Necrotizing cellulitis: involving dermis and subcutaneous tissue.
2. Necrotizing fasciitis involving the fascia.
3. Pyomyositis or myonecrosis: involving the muscle fascicle.

According to anatomical sites, it may be Fournier's gangrene (involving the perineum), Ludwig's angina (involving submandibular and sublingual spaces) or Meleney's gangrene (involvement of abdominal wall). However, no special name has been given to those involving the extremities [45-47].

Clinical Features

The clinical features of NF include evolving skin changes with systemic features. Initially, the patients present with pain, erythema, calor and swelling of the affected site which mimics uncomplicated skin infections such as cellulitis, impetigo and erysipelas. This is because NF begins in deep tissue planes and the epidermis may appear apparently normal until late in the course of infection. However, some cutaneous features should be noted that aid in diagnosis. Margins of tissue involvement are often indistinct, tenderness can be elicited over adjacent apparently normal skin

and lymphangitis is rarely seen in NF. An important diagnostic clue of NF is severe pain over the affected site, classically described as being out of proportion to the physical findings [6, 24, 36, 48].

As the infection progresses, more typical signs and symptoms appear such as tense edema outside the area of compromised skin, discoloration of skin and induration followed by formation of blisters and bulla draining a thin foul smelling discharge.[22,49] In later stages, the so called 'hard signs' of NF appear which include hemorrhagic bulla, skin anaesthesia, frank skin gangrene and crepitus.[11,36] The skin changes seen in NF are usually heterogenous and the clinical stage assigned is according to the skin area with the most advanced cutaneous changes [49].

Patients with NF can present with systemic features such as high grade fever, tachycardia, hypotension, shock, tachypnoea, mental obtundation and even multi-organ failure, with or without skin involvement. Therefore, patients with features of sepsis associated with nonspecific signs of soft tissue infection should be treated as NF until proven otherwise. The physical examination should include search for skin inflammation in all parts of the body, including the perineum and oral cavity. Careful serial assessment must be done because merely the absence of systemic features in patients with soft tissue infections does not rule out NF [24, 36, 50].

Diagnostic Aids:

Though laboratory findings are not specific, these reflect the septic process and aid in diagnosis of NF when analysed with the clinical features. Hematological changes such as leucocytosis with neutrophilia, leucopenia, coagulopathy, thrombocytopenia and anaemia can be seen. Inflammatory markers such as CRP are raised. Biochemical parameters can be altered and impaired renal function, hyponatremia, abnormal liver function test, hypoalbuminemia, metabolic acidosis and raised serum lactate levels may occur. Increased creatinine kinase reflects myositis or myonecrosis, and hypocalcemia is a sign of fat necrosis [4, 6, 22, 51].

In viewing the diagnostic challenges, various scoring systems, incorporating a combination of different laboratory parameters, have been suggested to improve the diagnostic process and decrease the interval between presentation and definitive management. Wall DB et al. in 2000 proposed that a WBC count greater than $15.4x10^9$/L combined with a serum sodium less than 135 mmol/L had a sensitivity of 90% and specificity of 76% in predicting NF. Though this combination had a NPV of 99%, it had a PPV of only 26% [25]. The most extensively used scoring system is the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) Score, devised by Wong et al. in 2004, which is based on the levels of C-reactive protein, WBC count, hemoglobin, serum sodium, creatinine, and glucose. In the initial article, the cut-off value for LRINEC score was 6 points with a PPV of 92% and a NPV of 96% which was quite encouraging, however, subsequent studies have shown poor results [1, 26,52, 53].

Harasawa et al. in 2019 proposed NSTI assessment score (NAS) based on Mean arterial pressure, CRP, Hemoglobin, Serum creatinine and glucose with promising sensitivity and specificity [54]. In 2019, Cribb et al. developed the SIARI score which is an acronym for Site of infection outside of lower limb, history of Immunosuppression, Age $\leq$ 60 years, Renal impairment (Serum creatinine > 141 µmol/L) and Inflammatory markers (White cell count >25 per mm^3, CRP $\geq$ 150mg/L) [53].

The gold standard modality for diagnosis of NF is surgical exploration and tissue biopsy. Presence of gray necrotic fascia, lack of bleeding, thrombosed vessels, foul smelling 'dishwater' pus, non-contracting muscle and lack of resistance of normally adherent superficial fascia to blunt dissection are the operative findings seen in NF. When the diagnosis is in doubt, frozen section biopsy and bedside finger test can be used as diagnostic adjunct. Histological criteria for diagnosing NF include necrosis of the superficial fascia, infiltration of the dermis and fascia by polymorphonuclear leucocytes, fibrin thrombi with fibrinoid necrosis of walls of arteries and veins coursing through the fascia and the presence of microorganisms within the destroyed fascia and dermis [4, 6, 22, 23, 48].

Stamenkovic and Lew published their retrospective study to recommend the use of frozen-section biopsy for early diagnosis of NF in 1984. Excision of about one cubic centimeter of tissue specimen from the suspected lesion under local anaesthesia was recommended for examination.[23] Frozen section biopsy was also suggested as a useful adjunct for diagnosis of NF by Majeski and Majeski.[55] Although this technique has beneficial results in early diagnosis of NF, it requires experienced pathologists and may result in high negative biopsy rate and some morbidity from the tissue sampling [22]. Bedside finger test was described by Andreasen et al. in which a 2 cm incision is made in the suspected area down to the deep fascia under local anaesthesia. Then, probing with index finger is done at the level of deep fascia gently. The test is considered to be positive if there is absence of bleeding, foul smelling dishwater fluid and minimal resistance to finger dissection. Tissue biopsy can be sent for frozen section analysis. If the finger test is positive, formal wound debridement is done [56]. However, the test is invasive and there are chances of negative results and associated morbidity.

Imaging Studies play a vital role as diagnostic adjunct and can confirm the diagnosis, define the extent of the disease, identify the source and complications of infection and also provide anatomical information for planning of surgery. In plain radiography, increased soft tissue thickness and opacity can be seen. Subcutaneous gas, which is a specific sign of NSTI, is appreciated in only 25-33% of NSTI patients [4, 6, 22, 57]. Ultrasound is often sought to rule out cellultis (cobblestone appearance seen) or deep vein thrombosis. Thrombosed small blood vessels or hyperemia can be seen in Doppler studies [58-60]. However, with current ultrasound technology, it is not sensitive enough to rule out NSTI.[59] Computed Tomography can be of great value in equivocal cases and has the additional advantage to identify other pathology like deep abscesses. It has a sensitivity of about 80% but is not very specific [61, 62]. MRI is the recommended modality of imaging as it offers excellent soft tissue definition in multiple planes. The cost, availability and time consumed in performing this test tend to limit its use [14].

Treatment:

The key aspects of management of NF include early diagnosis, aggressive resuscitation, supportive intensive care, radical surgical debridement, broad-spectrum antimicrobial therapy and finally wound coverage with reconstruction and rehabilitation. A multidisciplinary team comprising of general surgeon, plastic surgeon, intensive care physician, anesthesiologist and microbiologist is required [27, 35, 42]. The principle of management is to control the source of infection by aggressive surgical debridement, kill the organisms involved, neutralize the toxins and prevent necrosis of tissue by hemodynamic stabilization and support of failing organ systems of the patient [6,14].

Early and aggressive surgical debridement is the most important parameter for better outcome [6, 11, 22, 25, 26]. The retrospective study conducted by Wong et al revealed that a delay in surgery of more than 24 hours was significantly associated with increased mortality ($p<0.05$; relative risk = 9.4) [36]. Mok et al in their study found that inadequate debridement was associated with seven times greater likelihood of death from this dreaded condition [63]. During the operation, generous surgical incisions extending at least beyond the indurated area should be made initially, and all the dead necrotic tissues, including skin, subcutaneous tissue, fascia and muscle, must be excised. The extent of debridement is guided by the macroscopic extent of the disease and it should be kept in mind that the necrotic area extends beyond what is anticipated based on the external appearance of skin. Excision should extend to viable tissue at all margins as indicated by bleeding [6, 14, 35]. The debrided area is then covered with a saline soaked gauze and absorbent dressing such as burn pad is applied [14]. Amputation may be needed in 25-50% cases of NF involving the extremities, more in lower limb infections [11 ,64, 65]. If the NF involves the perineal area and the patient has stool incontinence, a diverting colostomy is required to prevent the contamination of the

perineal wound [11]. As it is rare for a single debridement to clear all the infected tissue, serial debridement at intervals of 6-48 hours are required until no further necrotic tissue is left. On an average, three to four such scheduled debridement are performed [6, 14, 27].

Antimicrobial therapy should be started promptly as an adjunct to source control and to counter or prevent the systemic features. However, antibiotics should not be considered a replacement for debridement. Empirical broad-spectrum antimicrobial therapy should be commenced initially to cover the organisms causing NF that includes gram-positive, gram-negative and anaerobic microbes. After receiving the tissue culture and sensitivity report, the selection of antimicrobial is modified accordingly [6, 14]. Superficial wound culture reports are not recommended because of likely colonization and therefore, the tissues obtained during debridement should be sent for culture.

Kaul et al in their study conducted between December 1994 and April 1995 noted that the 21 patients of streptococcal TSS treated with IVIG had higher 30-day survival than the 31 controls (67% vs. 34% respectively, p=0.02) and recommended the use of IVIG therapy in patients diagnosed with streptococcal TSS [66]. However, there is still limited evidence for using IVIG and its use in various forms of NF is still to be studied [6, 14].

Hyperbaric Oxygen Therapy has been investigated for treatment of NSTI with contrasting results [67, 68]. Soh et al in their retrospective study of 45,913 patients found that the 405 NF patients who received hyperbaric oxygen therapy had a lower mortality (4.5 vs. 9.4%, p = 0.001) though it resulted in longer hospital stay with higher costs [69].

After operative debridement, dressings need to be changed two to three times daily. To reduce bacterial contamination of the wound, adjuncts such as Mafenide (2.5-5%) cream, Dakin's solution (0.025% solution of sodium hypochlorite) soaks, forceful saline irrigation that is pulse lavage, and negative pressure wound therapy can be used. A vacuum-assisted closure system decreases time to wound closure by accelerating wound bed vascularization and assisting in wound contraction. This negative pressure wound therapy is favoured for deep recessed wounds such as in areas like perineum, groin, axilla and pannus of morbid individuals [14, 27,35].

Wound coverage should be done only after the sepsis has subsided, debridement is complete and, the wound has stabilized with adequate granulation tissue over the wound bed and no signs of infection. Various reconstructive options are available such as split-thickness skin grafts, full-thickness skin grafts, tissue expanders and free flaps. For larger defects, temporary skin substitutes such as allografts, xenografts, AlloDerm and Integra play a vital role in wound optimization for eventual skin grafting [14, 27, 35, 37].

Rehabilitation incorporates the physical, psychological and social aspects of care for the patients and is an essential component of recovery of NF patients to regain functional independence [27, 35].

Conclusion:

NF is a rare soft tissue infection but is potentially limb and life threatening. High index of clinical suspicion needs to be maintained in a patient with risk factor for early diagnosis of this condition. Radical surgical debridement needs to be done immediately to limit the morbidity and mortality related to NF.

List of Abbreviations:

NF : Necrotizing Fasciitis
NSTIs : Necrotizing Soft Tissue Infections
DM : Diabetes Mellitus
CT : Computed Tomography
MRI : Magnetic Resonance Imaging
PPV : Positive Predictive Value
NPV : Negative Predictive Value

Declarations

Ethics approval and consent to participate

Ethical approval has been taken from Institutional Review Board.

Consent to publish

Not applicable.

Availability of data and materials

The articles used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

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Authors' contributions

SA : conception and design of the study, drafting the manuscript.
KM : critically revised the manuscript and gave the final approval.
All authors read and approved the final manuscript.

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