Review Article

Necrotizing fasciitis: The importance of early diagnosis, prompt surgical debridement and adjuvant therapy

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Abstract

Background: Necrotizing Fasciitis (NF) is a necrotizing soft tissue infection involving the fascia and subcutaneous tissue that can cause rapid local tissue necrosis and life-threatening severe sepsis. **Aim**: This article aims to review the aetiopathogenesis, investigations and management based on a literature review. **Methods and Materials:** The Medline literature search of relevant articles restricted to English language on necrotizing fasciitis was conducted and reviewed. **Results**: Necrotizing fasciitis is rare with an incidence ranging from 0.15 to 0.55 cases per 100,000 of the population. Accurate assessment and timely intervention are critical in the treatment of patients affected with NF. Understanding the history and unique characteristics of this disease is crucial to achieve early recognition, effective treatment and a favorable outcome. Classic symptoms include severe pain out of proportion to local findings, erythema, mottling, crepitus, skin anesthesia, warmth, tenderness, hemorrhagic bullous formation, edema in the affected area and fever. Predisposing conditions of NF are classified into 2 main categories (type I and II) based on causative microorganisms. Radical surgical debridement, broad spectrum antibiotics, negative pressure wound dressings, and hyperbaric oxygen therapy are considered to be the cornerstone of treatment. The mortality rate ranges widely from 10% to 75% and is related to delay in initial debridement, patient age of more than 60 years, associated hypotension, acidosis, bacteremia, renal failure, hyponatremia, peripheral vascular disease, myonecrosis and myositis. **Conclusion**: Necrotizing fasciitis is a devastating infection of the fascia and subcutaneous tissue. The presentation of the disease is nonspecific and variable. Delay in recognition and effective treatment increases the mortality. Prompt radical surgical debridement, appropriate antibiotics and adjuvant therapy contribute to an improved outcome.

Keywords: Necrotizing Fasciitis, streptococcal toxic shock syndrome, debridement, hyperbaric oxygen, myonecrosis.

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Introduction

Necrotizing Fasciitis (NF) is essentially a severe inflammation of the muscle sheath that leads to necrosis of the subcutaneous tissue and adjacent fascia. The condition is difficult to diagnose early and even more difficult to manage effectively [1-3]. Early clinical suspicion, appropriate antimicrobials and surgery are key to improving survival. Mortality rate has been reported to vary from 4.2% to 75% [1-5]. The significant difference is closely linked to early recognition and expeditious initial excision and debridement of the infected tissues along with appropriate antimicrobials. Understanding the history and unique characteristics of the disease is crucial to achieve early recognition, effective management and a favorable outcome.

History and Terminology

The description of NF by Hippocrates in the fifth century and that of confederate physicians in the American Civil War are no different from the presentation today [5, 6]. The initial appearance of a purple or blue spot on the skin in the affected spot which clears in 24 hours and then a deep blue and purple, almost black, areola surrounding the dead mass appears and spreads rapidly in increasing circles are true even today [6]. Meleney's gangrene, which is commonly used to refer to abdominal wall fasciitis, is

streptococcal dermal gangrene that can be present anywhere in the body [7]. Several terms in the older literature refer to similar entities with different terms: necrotizing ersypilias, acute non-clostridial crepitant cellulitis, synergistic necrotizing cellulitis, hemolytic streptococcal gangrene, phagedena (literally eating away) and putrid ulcer [8, 9]. Fournier's gangrene refers to necrotizing infection of the perineum and may be due to a variety of organisms, including group A *Streptococcus* (GAS) [8] (Figure1). In 1952, Wilson was the first to coin the term "necrotizing fasciitis," as he described the dominant feature of the disease, namely inflammation and necrosis of the subcutaneous fat and the deep fascia with sparing of muscle [10].

Fig. 1 Fournier's Gangrene - Necrotizing fasciitis involving scrotum exposing the testis

Epidemiology and Risk Factors

The incidence of NF is rare. Population-based surveillance for group A streptococcal necrotic infection in Canada showed an incidence range from 0.15 to 0.55 cases per 100,000 in those younger than 45 to those older than 65 years [11]. Increasing age is a consistent risk factor across several case series, although the conditions can affect any age group [1-5]. An accurate predictor of the disease has not been consistently demonstrated. The inoculation of the bacteria into the subcutaneous space can occur with any damage to the overlying skin or via hematogenous spread from a distant site. Reported mechanism of injury has included cuts, burns, blunt and penetrating trauma, chronic skin conditions, animal and insect bites, child birth, intravenous injections and illegal drugs, postoperative infection, perirectal abscesses, incarcerated hernias and

even secondary to acute pharyngitis [12-14]. In up to 36% of cases, however, no preceding skin lesions or antecedent injury can be found [14]. Subcutaneous tissue damage and systemic toxicity are related to the production and release of bacteria toxins and endogenous cytokines. NF pathogenesis could be due to a triggering mechanism that can be caused by bacteria. This includes activation of interleukins, tumor necrosis factor, alpha and gamma interferon--the principal molecular agents responsible for a capillary thrombosis, which lead to necrotic events that involve the fascia, skin and subcutaneous tissues [1-4].

The majority of adults that acquire NF have at least one of the underlying diseases that will increase their susceptibility to infection [1, 2]. Nonsteroidal anti-inflammatory drugs (NSAID) have always been implicated as a risk factor, but the strength of the association is still to be established [14, 15]. It is most likely that these drugs may lead to delay in diagnosis and definitive treatment. It is not clear if the role of NSAIDs is related to their direct inhibition of neutrophil granulocyte function or indirectly to their anti-inflammatory, antipyretic or analgesic effect, which may mask NF symptoms in the earliest stages. This consequently delays appropriate diagnosis and treatment [14, 15].

Microbiology

Based on the microbiology and culture, clinical progress and mortality, NF has been classified into 4 groups, with the first 2 being predominant. (Table 1).

Type I. This synergistic NF is seen in 80% in practice [15-17]. This affects patients who are immunocompromised or those with underlying abdominal pathology and usually results due to synergistic mixture of anaerobic, aerobic and facultative anaerobic bacteria (e.g. *Escherichia Coli, Psuedomonas spp*, and *Bacteroids spp*) [15]. Synergistic NF in children usually affects those who are immunocompromised [18].

Type II. These contribute to 20% of the NF and is usually caused by monomicrobial gram positive organisms, the most common of which is group A *Streptococcus* (GAS) alone or occasionally with *Staphylococcus aureus*[15]. A significant increase in the incidence has been reported since 1990 with a reported mortality of 43 to 58% [19]. An increase from 0.085 to 0.4 per 100,000 of the population has been noted in Ontario between 1991 and 1995 [21]; 18 % of invasive GAS infection was associated with NF in Florida between 1996 and 2000 [21].

Type III. This is caused by gram negative monomicrobial NF, including marine-related organisms. The most common gram negative organism is *Vibrio spp* such as *V damselae* and *V vulnificus*, which are responsible for 0.53 cases per 100,000 in Hong Kong in the late 1990s [22-24]. Wound contamination with sea water accounts for 25% of cases [23]. Virulence factors and digestive enzymes contribute to high mortality of 30-40% despite prompt diagnosis and aggressive therapy [23]. Monomicrobial

gram negative non vibrio NF is uncommon, but does occur with *Pasturrela Multocida*, *Haemophillus influenza*, *Klebsiella spp* and *Aeromonas spp* [22-24].

Type IV. This is caused by fungal infection and most commonly follow traumatic wound and burns and isolation of *Aspergillus* or *zygomycetes* may be seen [25, 26]. Candida NF is very rare, mainly affecting patients who are immunocompromised. In contrast, zygomatic necrotizing infection (*Mucor* and *Rhizopus spp*) affect immunocompetent patients after severe trauma and are responsible for nearly 32% of NF type IV cases [26].

Table 1 Characteristic features of necrotizing fasciitis

Types of NF incidence	Aetiology	Organism	Clinical progress	Outcome/mortality
Type I (70-80% of cases)	Immunocompromised patients/complicated abdominal surgery/perianal abscess Polymicrobial synergistic, often bowel flora derived	Mixed aerobes and anaerobes (*E. coli, Psuedomonas spp, Bacteroides*	More indolent better prognosis, easier to recognize clinically	variable: depends on underlying comorbidities
Type II (20-30% of cases)	skin or throat derived direct inoculation from trauma/intramuscular injection pharyngitis/vaginitis/proctitis often monomicrobial	Usually group A – β hemolytic streptococcus(GAS) Occasionally ± *S aureus*	Aggressive protean presentation easily missed. Rapidly progresses to myonecrosis	Depends if associated with myositis or toxic shock syndrome(STSS) STSS negative- <32% STSS positive >67%
Type III (commoner in Asia)	Gram negative, often marine related organisms	*Vibrio spp mainly Aeromonas hydrophilia Enterobacteriaceae*	seafood ingestion or water contamination of wounds	30-40% despite prompt diagnosis and aggressive therapy
Type IV (fungal)	Usually trauma/burns associated immunocompetent patients	*Candidia spp*. Immunocompromised patients. Zygomycetes in immunocompetent patients	Aggressive with rapid extension especially if immunocompromised	>47%(higher if immunocompromised)

Pathophysiology

The speed of development of NF and associated clinical features differ markedly depending on the causative organism(s) [2, 11-13, 18, 20, 23]. Although the underlying pathophysiology is common to all types of NF, synergistic NF is a comparatively slow process that evolves over days. Synergistic NF develops particularly when gut flora breaches the mucosa that enters tissue planes often following complicated abdominal surgery or ischiorectal and perineal abscesses [1, 2]. A slow, evolving bruise on the abdominal wall or perineal infection may reflect underlying malignancy [26]. Culture of *Clostridium septicum* or *C tertium* points to an intra-abdominal focus, whereas *C sordellii* is more associated with gynecological pathology [26, 27].

Gas-forming organisms and anerobic infection may produce crepitus. Exploration of the underlying fascia may reveal classical dishwater fluid due to lysis of polymorphs. Serous discharge, together with macroscopic fascial necrosis, myositis or myonecrosis, may be demonstrable [1-4, 11] (Figures 2 & 3). Crescendo pain necessitating progressive strong analgesia is typical as occlusion of perforating nutrient vessels and infarction of nerves produces progressive skin ischemia and pain [28]. Muscle hypoxia and swelling alter oxygen tension, increasing intracompartmental pressure, at times resulting in compartmental syndrome [29]. GAS NF may arise spontaneously with no obvious focus and is initially more insidious than type I but progresses far more rapidly [1-3]. In such cases, hematogenous infection from many foci include the throat, ascending vaginitis, primary peritonitis or necrotizing proctitis that reaches the fascial layer [30-36]. Direct inoculation of GAS through wounds or associated with surgery is less common. An example of this includes injection sites, cesarean section, plastic surgery and even minor cosmetic procedures [37-43]. Where nosocomial GAS NF is suspected or if there is a cluster of cases, the source may prove to be a member of the hospital staff [44-46].

The M protein of GAS confers resistance to phagocytosis with mucoid strain being more pathogenic[47]. Exotoxins acting as superantigens produce massive T-cell proliferation and a concomitant release of inflammatory

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North American Journal of Medical Sciences 2011 March, Volume 3. No. 3.

agents and cytokines, culminating in the systemic inflammatory response syndrome and multiple organ dysfunction [48]. Massive amounts of enzymes, hemolysins, DNAase, protease and collagenase are produced by streptococci embedded in tissues, which allow spreading of the streptococci to undermine normal skin with progressive coagulation necrosis. In addition, streptokinase produces clotting abnormalities [46-49].

The consequence of the above pathological changes is agonizing pain, which is out of proportion to any external signs and is the earliest clinical feature that is common to all types of NF [47-49]. Diabetic neuropathy or strong analgesia, however, may significantly influence the degree of pain [50]. As nerves supplying the necrotizing area of skin die, the central areas become anesthetic, while laterally the tissues overlying the deep spreading fascial infection remain tender [2,47]. Infection in the deep layer finally ascends, producing edema of the epidermal and dermal layer (peau d orange) and a woody firmness of tissues. Hemorrhagic bullae progress to cutaneous gangrene with sensory and motor deficits, resulting from fascial and nerve destruction [1-4, 17] (Figure 2).

GAS NF and Septic Toxic Shock Syndrome (STSS)
STSS is an exotoxin-driven disease that is noted in 50% of type II NF cases and significantly increases the mortality of streptococcal NF alone from <40% to 67%. Up to half of these patients require amputation [50, 51].

The subtype of GAS with M protein type 1,3,12 and 28 is responsible for most STSS, including those associated with GAS NF [49,52]. GAS superantigens bypass normal stimulating mechanism causing massive activation of T cells, cytokine release tissue damage and toxic shock-like syndrome. The capillary leak syndrome, causing hypotension and disseminated intravascular coagulation due to superantigen production, are predominantly responsible for the associated shock [53]. Hypoalbuminemia ensues with edema and respiratory distress syndrome [53]. Production of the prototypic Th1 cytokine results in production of tumor necrosis factor alpha, which mediates TSS symptom by affecting the myocardium and striated muscle causing myonecrosis. Increased mortality is in part due to delay in identifying and excising the primary sites of infection [53, 54].

Fig. 2 Findings on re-exploration of the wound in the right thigh

24 hours after initial exploration shows further necrotic tissue to be debrided. Also noticed are the hemorrhagic bullae on the overlying skin. This Type II NF followed administration of intramuscular analgesic for pharyngitis.

Fig. 3 Dish water fluid revealed following incision to explore the underlying fascia in an otherwise nonspecific skin finding in type I NF.

Fig. 4 Necrotizing fasciitis involving the dorsum of the foot of a three-year-old child following a recent Herpes Zoster infection.

Clinical Diagnosis
Symptomatology
NF is difficult to diagnose in the early stage due to nonspecific signs such as tenderness, swelling, erythema and pain at the affected site that mimic non-severe soft tissue infection such as cellulitis and erysipelas. It is often misdiagnosed as muscle strain or viral illness [1-4]. Among these, the cardinal manifestation in NF is severe pain at the onset out of proportion to physical findings. Since severe pain precedes skin changes by 24-48 h and is present in >97.8% of patients, the use of a simple arbitrary 'pain score' (such as how severe is the pain on a scale of 1-10 or use of a pain visual analogue) is advisable as it is important in early detection during the evolution of the disease [47]. Despite severe pain and an unwell appearance, some patients initially have only mild erythema, cellulitis or swelling over the affected area. Since lymphatic channels are obstructed easily in GAS infection, lymphangitis and lymphedema are rare [1-4, 13, 16, 50]. Invariably, an extremely tender area evolves into a smooth swollen area of skin with distinct margins which progresses into skin changes and the sequence include

erythema, then bronzing and induration of the skin followed by breakdown with purple bullae formation within 3 to 5 days and finally, the dull blue grey hue of frank skin necrosis. The hemorrhagic bullae indicate the occlusion of deep blood vessels in the fascial and muscle compartment .The overlying cutaneous sensation can vary from intense tenderness early in the disease process to anesthesia as the superficial nerves are destroyed [1-5]. Patients in the late stages of NF appear apathetic and indifferent to their surroundings [1, 2]

A thorough history should suggest the causative organism in most cases [1-5]. A thorough history concerning sea water exposure or fish sting associated with liver and spleen dysfunction could suggest infection with *Vibrio* and *Aeromonas* which are well known water-borne organisms that cause NF [54]. A history of tonsillitis, close contact with impetigo or recent nonsteroidal anti-inflammatory agent (NSAID) usage suggests streptococcal infection [55]. Since GAS vaginitis is associated with serous discharge and easily overlooked a search for the infective focus should include vaginal examination and cultures. With puerperal GAS NF, the baby should undergo septic screen and prophylactic antimicrobials [55, 56]. Specific inquiries should be made about minor trauma, soft tissue injury, penetrating lesion including insect or human bites, recent surgery, skin infection or ulcer, injection sites and illicit intravenous drug usage. Misdiagnosis of NF is particularly common in children as it is rare and usually associated with recent infection with Varicella Zoster [57] (Figure 4). Many cases, however, remain idiopathic.

General Physical Findings
Fever ($>38^0$) is often absent (44%) but tachycardia (>100 beats/min) is usually found (59%) while hypotension (<100 mmhg) and tachypnea (>20/min) are less frequent and found in 21% and 26%, respectively [58]. Although NF can occur anywhere on the body it is more common in extremities (36-55%) trunk (18-64%), and perineum (up to 36%) [58, 59].

Laboratory Diagnostic Procedures
Serum Biochemistry
Multiple organ dysfunction may reflect liver and renal disorders, coagulopathy and elevated creatinine kinase due to severe sepsis [1-4]. Raised serum creatinine kinase (CK) indicates myositis or myonecrosis as well as the effects of circulating toxins or ischemia. Involvement of adjacent muscle raises CK and is not present in all cases of NF. CK levels of 600 U/L gave a sensitivity of 58% and a specificity of 95% for cases of NF [60, 61]. In the presence of acute renal failure due to severe sepsis, the dosing of renally excreted antimicrobials must be adjusted. Bacterial infection, inflammation, thrombosis and necrosis increase C-reactive protein(CRP) [3, 4]. A very high CRP level is common, particularly in GAS NF; CRP levels of >16mg/dl has a sensitivity of 89% and specificity of 90% in GAS NF [63]. Hypocalcaemia is noted in about one third of these patients due to calcium precipitation with fat necrosis[62, 63]. Hypocalcemia may also be a sign of

severity in synergistic NF [66]. Hypoalbuminemia and hyponatremia are common when less than 135 mmol/L is found to be significantly associated with NF [62]. Severe metabolic acidosis is often seen in GAS NF. High serum lactate levels of >6 mmol/L have a reported mortality of 32%, whereas a lactate of <6 mmol and a serum sodium of <135 mmol/L were associated with 19% mortality [64].

Hematology
Rapidly falling hemoglobin in the presence of a stable hematocrit may suggest intravascular hemolysis; however, one should also take into consideration the dilution effect of any fluids used for resuscitation while interpreting the results [62]. The leucocyte count is less reliable in the diagnosis due to a wide range of values. Although leucocytosis is common in GAS NF, leucopenia is common in association with STSS [64]. Infection with leucotoxin-producing organisms (e.g., Panton-Valentine leucocidin (PVL), producing *S aureus* or GAS) often leads to lymphopenia [59]. Disseminated intravascular coagulation and thrombocytopenia are common in any severe sepsis and are likely to be seen in NF [1-3].

Laboratory Scoring System for Predilection of NF
The laboratory risk indicator (LRINEC) for NF was developed with the hope of increasing the diagnostic yield of NF, even early in its evolution [63] (Table 2). Among the various variables studied, the ones that were reliable in predicting NF are included in the scoring system and include CRP, creatinine, hemoglobin, leucocyte count, sodium and serum glucose [63, 65] (Table 2).

A score of 6 using the LRINEC system raises the suspicion of NF and a score of 8 is strongly suggestive of the diagnosis (Table 2). For patients scoring >6, the positive predictive value for NF was 92% and the negative predictive value was 96%. The LRINEC score may also be indicative of outcome. Patients with a score <6 and those with a score >6 have 11% and 21% mortality, respectively [66].

Microbiology
Gross staining of affected tissues can be used for microbiological diagnosis in NF [1-4, 19]. Blood and debrided tissues should be sent for culture [1-4]. Microscopic examination may reveal coagulative necrosis of the superficial fascia, subcutaneous fat and occasionally the deep fascia. Inflammatory cellular infiltration, thrombosis of blood vessels and necrosis of subcutaneous glands may be present with or without apparent bacterial infiltration [1-4]. Blood cultures are positive in 11% to 60% of patients with GAS NF, but the yield in synergistic fasciitis is lower [2, 19]. Routine culture of throat and vaginal swabs may be useful to establish a primary focus [49]. Blister fluid is often sterile [67]. Percutaneous needle aspiration of the advancing edge is painful and hence a tissue biopsy is the investigation of choice [68]. Tissues and aspirates should be gram stained and cultured aerobically and anaerobically [67]. Fungal culture is necessary, especially in immunocompromised or trauma

patients, and enrichment culture is useful, particularly when patients had recent antibiotic treatment [68, 69]. Routine histological examination of tissue is important since intra-laboratory contamination of fungal culture plates can be excluded if histological fungal stains are negative [68]. In terms of monomicrobial infections, *Streptococcal spp* (especially group A*), S aureus, V vulnificus, A Hydrophilia, Enterobacteriaceae (Escherichia coli), Pseudomonas spp & Klebsiella spp), Clostridium perfringes* (gas gangrene) and anaerobic streptococcus are common [1-4]. Although *Aeromonas hydrophilia* and *Vibrio vulnificus* are rare organisms, they produce virulent factors that can lead to fatal sepsis more rapidly than in cases with *Streptococcus pyogenes*, resulting in up to 50% mortality rate within 48 hours after admission [70-72]. Most patients infected with *Vibrio vulnificus* have a history of underlying chronic illness, cirrhosis, alcoholic liver disease, gouty arthritis, chronic renal failure, diabetes mellitus or chronic use of steroids [73].

Table 2 Laboratory risk indicator for necrotizing fasciitis scoring system(LRNEC)

Variables	Score
Hemoglobin(g/dl)	
>13.5	0
11-13.5	1
<11	2
Total White blood cells count (/mm^3)	
<15	0
15-25	1
>25	2
Glucose(mmol/L)	
<10	0
>10	1
C-reactive protein(mg/dl)	
<150	0
>150	4
Sodium(mmol/L)	
>135	0
<135	2
Creatinine (μmol/L)	
<141	0
>141	2

Bedside Tests
Finger tests and frozen section have been used as complimentary diagnostic modalities in patients with an equivocal diagnosis [1-4]. The finger test is a bedside procedure in which a 2 cm incision is made under local anesthesia down to the deep fascia and gentle probing of the index finger is performed at the level of the deep fascia [1-4]. Lack of bleeding, presence of characteristic dishwater pus and lack of tissue resistance to blunt finger dissection indicate a positive finger test and NF [74] (Figure 3). Non-bleeding, non-contractile muscle suggests myonecrosis and myositis which in combination with GASNF increases the mortality to 80 to 100% [74] (Figure 2). Another reasonable approach is bedside incisional biopsy down to the fascial layer and an immediate frozen section, culture and gram stain [1, 2]. Gram staining, in addition to histological staining of tissues, is important

since a paucity of leucocytes in the presence of gram positive cocci may be seen in GAS NF or CA-MRSA due to leucocidin–mediated destruction of WBC [75]. Non-suppurative necrosis of the subcutaneous fat with minimal inflammatory reaction should raise the suspicion of zygomycosis [68].

Low tissue oxygen saturation measured by near infra-red spectroscopy throughout the involved lower extremities is valuable in differentiating NF from non-severe tissue infection. Sensitivity is 100% and specificity is 97% at a cut-off saturation level of <70% and this noninvasive method may offer a reliable assessment of lower extremities at risk for NF [32].

Imaging Studies

Radiological studies are only considered as adjunct measures for uncertain cases and cannot be usually performed to exclude NF, since many false negative results can occur with definite NF [2-4]. Moreover, the extent of debridement can be determined only by physical findings in surgery [4]. A plain radiograph is usually not beneficial, although there are reports of gas seen on plain x-rays in 32% of cases of NF compared to 3% of non NF patients [76]. It is, however, more sensitive than clinical examination for detecting crepitus [4]. Ultrasound findings correlate reasonably well with histological fat changes in NF, but correlation with fascial and muscle abnormalities is poor. It can be helpful in differentiating Fournier's gangrene from an acute scrotum [77]. CT scanning has been demonstrated to show asymmetric fascial thickening, fat stranding and soft tissue gas, which are valuable clues in assessing a patient with suspected NF[78]. It can also provide information about co-existent deep collection and it is helpful in determining the extent of spread of infection [78]. Magnetic resonance imaging with gadolinium can differentiate necrotic and inflamed or edematous tissue. T2 weighted images on MRI with fat suppression are probably the best radiological adjunctive investigation to demonstrate deep fascial involvement and is more sensitive than specific [79].

Management

The key aspects of management include early diagnosis, resuscitation of the patient, administration of broad spectrum antibiotics followed by radical surgical debridement, intensive care support and finally, reconstruction of the resulting wound [1-5, 7, 10, 12].

Resuscitation, Antibiotic Therapy and Critical Care

The degree of respiratory, hemodynamic, renal and metabolic compromise must be quickly assessed. If required, early resuscitation should be instituted and the intensive care unit promptly informed [1-5, 11, 15]. Resuscitation with IV fluids, colloids and inotrophic agents is usually necessary. The pain score should be documented regularly allowing for the effects of analgesia

[47]. Blood cultures, baseline full blood count, urea electrolytes, liver function tests, clotting studies, CRP and CK levels are performed [1-5]. Serum lactate and CRP are markers of severity of the infection and help to guide therapy [1-5]. Non-steroidal analgesia is generally stopped in patients with soft tissue infection [1, 2]. The patient's tetanus status should be determined and updated, if necessary [1-3].

Antimicrobial Treatment in NF

All patients should receive broad spectrum IV antibiotics to cover streptococci, staphylococci, gram negative rods and anaerobes [1-5] (Table 3). A combination of clindamycin and cefuroxime is used with any adjustments made once culture results have returned [1-5]. Penicillin has been shown to fail in this type of infection because the offending bacteria may reach a stationary phase of growth and would stop expressing critical penicillin binding proteins [2, 3]. Clindamycin, however, has greater efficacy due to multifactorial reasons. Clindamycin is not affected by the stage of bacterial growth, as it can switch off exotoxin production even in stationary phase organisms and inhibit M protein synthesis, thus promoting phagocytosis and suppressing the effects of bacterial toxins in mediating septic shock[74, 85, 86]. Clindamycin also lasts longer than penicillin and has some anaerobic cover [83, 84]. Emerging clindamycin resistance of streptococci pyogenes, however, may have serious implication in the treatment of severe streptococcus pyogenes infection [82]. The advocated initial treatment includes ampicillin or ampicillin–salbactum necrotizing combined with metronidazole or clindamycin. The coverage of anaerobes is quite essential for type I disease. Metronidazole or clindamycin or the use of beta lactams inhibitor or carbapenems is an appropriate choice of anaerobes [1-4]. If patients have histories of prior hospitalization or antibiotic exposure, broader gram negative coverage should be necessary as an initial empirical therapy. Ampicillin sulbactam, pippercillin-tazobactam, ticarcillin–clavulanate, higher generation cephalosporins or carbapenems are the primary agents in this setting [2-4] (Table 3). In type II disease, the causative organism is mostly GAS, but may be methicillin-sensitive (MSSA) or methicillin-resistant staphylococcus (MRSA) [4]. In place of amoxicillin/penicillin, first generation cephalosporin such as cefazolin or vancomycin is used for treatment of MRSA [1-4]. Antimicrobials are narrowed based on the results of initial blood, wound and tissue culture, but should be continued until the infection is under control for at least 48 hours after the temperature and WBC have returned to normal or there is stabilization of the clinical condition. In order to cover adequately for synergistic and exotoxin producing gram positive NF, a suggested empirical protocol includes intravenous clindamycin 1.2 to 1.8 g six hourly together with intravenous imipenem 0.5 – 1 g six hourly[2]. When MRSA is suspected, some recommend intravenous linezolid 600 mg twice daily or daptomycin 6mg/kg as a preference to vancomycin, as the latter has no effect on exotoxin production [2]. For suspected Vibrio spp NF, therapy with doxycycline100 mg twice daily plus intravenous ceftazidime 2 g eight hourly is recommended [32]. Ciprofloxacin may be an alternative [83].

Table 3 First-line antimicrobial agent by infection type

Mixed Infection	Streptococcus infection
Ampicillin-Sulbactam	Penicillin
Or	Plus
Piperacillin-tazobactam	Clindamycin
Plus	
Clindamycin	S aureus infection
Plus	Cefazolin
Ciprofloxacin	Vancomycin (resistant strains)
Imipenem/cilastatin	Clindamycin
Meropenem	
Cefotaxime	Clostridium infection
Plus	Clindamycin
Metranidazole or clindamycin	Penicillin

Adjunctive Therapies

The use of hyperbaric oxygen (HBO) therapy in the management of NF is controversial. Some studies have reported a survival benefit with fewer debridement and thus quicker wound closure with adjunctive HBO [84, 85]. However, there has been no prospective randomized trial to assess the benefit of HBO [1-5]. Cycles of HBO are indicated to sterilize microscopic invisible residual post-surgical foci. The principle behind its use is to increase the tissue oxygenation in both healthy tissue and in zones of infected hypoxic areas; this prevents extension of the disease and the need for further debridements [84, 85]. For synergistic infection particularly involving *Clostridium spp*, HBO switches off alpha toxin production. HBO is believed to increase the bactericidal action of neutrophils since at a low oxygen tension, peroxide dependent killing mechanisms are less efficient [84, 85].

Intravenous immunoglobulin (IVIG) is a reasonable and desirable option to neutralize streptococcal toxins[86, 87]. Alhough there are several authors who argue in favor of high dose IVIG in severe GAS infection, the studies have evaluated a small number of patients and there is little evidence of any benefit in gram negative sepsis and considerable debate regarding its mode of action [86, 87]. IVIG, however, is believed to promote clearance of GAS by the immune system, neutralize streptococcal superantigens and act as an immunomodulatory agent [88]. In GAS NF with additional myositis and myonecrosis where superantigens abound, usage of IVIG has been reported to have dramatic effect on outcome [88]. However, all of these patients would require additional surgical debridement. Suggested IVIG dosage varies, but most authors recommend 2g/Kg with an option of a second dose, if necessary after 24 hours [88, 89]. Infusion is started initially at a rate of 20ml/h, increasing incrementally after 10 minutes to a maximum of 160mL/h [2, 90]. Side effects are seldom reported, but the major contraindications include selective IgA deficiency or a history of anaphylaxis with immunoglobulins [87, 88]

Surgical Treatment
Surgical debridement is the mainstay of treatment of NF and results in significantly improved mortality compared to cases in which surgery is delayed even for a few hours [1-5]. Inadequate or delayed surgery was associated with mortality of 35% compared with mortality of only 4.2% in those who underwent aggressive surgery at disease recognition (P=0.0007) [90]. Delaying surgery by 24 hours increased the mortality associated with Vibrio spp NF from 35% to 53%, with 100% mortality if surgery was not performed within 3 days [91]. In another study, delaying the surgery by 24 hours quadrupled the mortality [92]. Surgical consultation is indicated with the following conditions: 1) disproportionately severe pain to clinical findings 2) skin color changes such as ecchymosis 3) altered mental status 4) elevated band formed in differential WBC count 5) metabolic acidosis and 6) emergence of hemorrhagic bullae especially in cirrhotic patients [93]. When NF is suspected, patients are subjected to surgical intervention as soon as possible for a "search and destroy" objective of aggressive and extensive debridement [1-5]. Involved tissues should be resected thoroughly until there is no further evidence of infection. Anesthesia for patients with NF is often difficult as these patients often have cardiovascular instability, multiorgan failure, coagulopathy, or third space loss [1-5]. Aggressive fluid replacement could lead to dilutional effect on the doses of antimicrobial agents administered. Initial surgery is the most important determinant for survival and the wound must be inspected closely after the initial debridement. If further debridement is needed, the patient must be swiftly returned to the operating room. A second surgery is typically done 12 to 24 hours after the initial debridement [1-5] (Figure 2). While there are reports of a mean of 3-4 debridements required during the admission[13, 94], others report anywhere from 5 to 40 sessions of surgery. In one study, an average of 33 debridements and grafting procedures were required [95]. Removal of the tissues with an adequate margin is recommended rather than leaving only actively infected or necrotic tissue, which could lead to relapse due to residual infected tissue [1-4]. Once the infection is controlled, daily dressing is needed at the bedside under sedation followed by secondary suturing of the wounds with or without split skin grafts to cover the exposed underlying tissues. Dressing changes with alginate or hydrogel may facilitate granulation [3]. If the debridement has created a significant cavity, then conforming foam dressings can be inserted to fill the dead space [3]. Other forms of surgery such as amputation may be necessary for NF of the extremities. A defunctioning colostomy should be considered if perineal wounds are regularly contaminated with feces [1-3]. The vacuum-assisted wound closing (VAC) device has been found to be effective for non-healing limb wounds with reduced morbidity compared to conventional technique [96, 97]. This is employed to promote healing and to close wounds. This has also helped to reduce the size of the defects. The adhesive seal around the wound combined with continuous or intermittent negative external pressure using pressures of 40 to 100 mmHg facilitates removal of excess wound exudates and decreases edema with increased rates of granulation tissue formation, lowered bacterial counts and enhanced flap survival [96, 97]. Nutritional support is required from the first day of admission for compensation for lost proteins and fluid from the large wounds [2-4]. Metabolic demands are similar to those of other major trauma or burns. In general, patients with severe tissue defects will require twice their basal calorie requirements [1-5]. A nasogastric tube for feeding is sometimes required to maintain adequate enteral nutrition. Recurrent cases of NF are uncommon with only few case reports including MRSA and a case of complement C4 deficiency where GAS NF was succeeded by streptococcal pneumonia NF [31, 98]

Antimicrobial Prophylaxis for Contacts of GAS NF
This is a controversial issue despite the recognition that sporadic secondary cases of iGAS (infective GAS infection) occurred following close contact with an index case of GAS NF[2]. Around 27% of household contacts are reported to be GAS carriers [77, 99]. The secondary iGAS cases within the household of an index case are reported to be 200 times more likely to occur (294 per 100,000 contacts), but international guidelines on prophylaxis vary widely in their recommendation [11]. The UK health protection agency, based on several clusters of infection in a limited survey in 2004, recommended antimicrobial prophylaxis limited to mothers and babies if infected during the neonatal period [56].The recommendation included warning close contacts to seek early medical advice in the event of signs and symptoms of streptococcal infection [56]. The Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA) do not recommend routine testing for GAS colonization or administration of chemoprophylaxis to household contacts [100]. However, where prophylaxis is prescribed to an elderly or at risk patient, the rest of the household should receive chemoprophylaxis, as the source of GAS may not necessarily be the person with iGAS infection [100]. Household contacts should be informed about the clinical manifestation of pharyngeal and iGAS infection and advised to seek immediate medical attention if symptomatic [100].

Outcome
The mortality rates for NF vary considerably with the best centers claiming less than 10% and others as high as 75% [1-5, 22, 25, 51, 58, 59, 73, 94]. The larger, more comprehensive retrospective studies have narrowed these rates between 25% and 40% [11, 13, 83]. The outcome is also region- specific with truncal (44%) and perineal (28%) having higher mortality than extremities (22%), presumably due to the option of amputation of the limb in the event of an extensive infection [101, 102]. There is a host of variables associated with higher mortality. These include delayed initial debridement, age >60, female gender, hypotension, acidosis, bacteremia , total body surface area involved more than $250cm^3$, renal failure, hyponatremia, elevated blood lactate, peripheral vascular

disease and number of co-morbidities[11-13]. Generally, synergistic NF has a better immediate prognosis although underlying malignancy or other co-morbidities account for later demise [1-5]. The absence of myonecrosis or myositis in GAS NF is associated with a better prognosis, as myositis and STSS increase mortality from 9% to 63% [74]. Although an early study found no relationship between mortality of GAS NF with the M type, a recent European survey found that *emm*3, *emm*1, and *emm*87 caused most cases of NF with *emm*3 and *emm*87 having the highest case of fatality rates. Also, the various exotoxin produced and the STSS also influenced the outcome [21, 103].

Conclusion

NF is a rare but devastating infection of the fascia and subcutaneous tissue. The presentation of the disease is variable. Type I cases manifest with frank tissue necrosis and septicemic shock occurring over hours. Type II cases develop over hours to days usually with a precipitating traumatic event and can deteriorate quickly. Type III cases have a more insidious and non- specific presentation and require a high index of suspicion in order to make the diagnosis. Since delay in recognition and effective treatment increases the mortality of NF, early diagnosis and management of NF are essential for a better outcome. In cases where diagnosis is uncertain, repeated clinical assessment and a multiparametric approach integrating a range of diagnostic modalities and multidisciplinary involvement will optimize the diagnosis. All patients should be treated promptly with appropriate antibiotics, which are tailored to the nature of the infecting organism. Radical surgical debridement, along with second surgeries when needed, is the definitive management and is also frequently diagnostic in patients who have not presented with classical dermatological signs. The role of HBO therapy and intravenous immunotherapy has been reported to be beneficial and would require further study.

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