Necrotizing Soft Tissue Infection

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17.1 Introduction

Necrotizing fasciitis (NF) better called as necrotizing soft tissue infection (NSTI) is infrequent but highly lethal infections. Necrotizing soft tissue infections (NSTIs) are fulminant infections of any layer of the soft tissue compartment associated with widespread necrosis and systemic toxicity. Delay in diagnosing and treating these infections increases the risk of mortality. Early and aggressive surgical debridement with support for the failing organs significantly improves the survival. These infections were first described by Jones in 1871, and at that time they were termed "hospital gangrene" [1]. According to Martin et al., necrotizing fasciitis (NF) is essentially a "severe inflammation of the muscle sheath that leads to necrosis of the subcutaneous tissue and adjacent fascia" that is difficult to diagnose early and even more difficult to manage effectively. Early clinical suspicion, appropriate antimicrobials, and surgery are key to improving survival. The problem is that it is difficult to diagnose as in one survey, the correct diagnosis was initially suspected in only 2 % of admissions [2, 3].

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17.2 History

The description of NF by Hippocrates in the fifth century BC, and that of a Confederate physician in the American civil war, is no different from the presentation of today: "A purple or blue spot is first perceived … the skin in the affected spot melts away in 24 hr whilst a deep blue and purple, almost black, areola surrounding the dead mass, spreads rapidly in ever increasing circles." In Peking, a missionary surgeon reported similar presentations among opium addicts in 1924: "A chill may usher in the general symptoms. Irregular patches, dusky hue, blisters or large bullae develop, may break and discharge a dark serous fluid." In the days before the advent of antimicrobials, NF was treated successfully with 'bear-claw scratch debridement' and Carrel's tubes irrigating the tissues with Dakin's solution of chlorinated soda [4–6].

17.2.1 Types

Four types of NF have been described (Table 17.1).

17.2.1.1 Type I NF (Polymicrobial/Synergistic)

Type I is found in 80 % of cases where it results from synergistic mixture of anaerobic, aerobic, and facultatively anaerobic bacteria (e.g., *E. coli*, *Pseudomonas* spp., and *Bacteroides* spp.). Type I NF particularly affects the immunocompromised or those with underlying abdominal pathology. The common aerobic species isolated from these infections are *Streptococci, Staphylococci, Enterococci*, and the family of Gram-negative rods. *Bacteroides* species are the most common anaerobes involved [7–9].

17.2.1.2 Type II NF

Type II is found in about 20 % of cases, which is usually monomicrobial and due to Gram-positive organisms, and the commonest type II NF is caused most frequently by group A *β-hemolytic streptococcal* alone or occasionally with *Staphylococcus aureus*. It carries a very high mortality of 43–58 %. Historically, monomicrobial *S. aureus* NF is uncommon, but occurs in neonates.

17.2.1.3 Type III NF

The commonest Gram-negative causes of NF remain *Vibrio* spp., such as *V. damselae* and *V. vulnificus*, which were responsible for 0.53 cases per 100,000 in Hong Kong in the late 1990s. *V. vulnificus*, associated with raw oyster ingestion, is the commonest cause of seafood-related deaths in the USA, particularly affecting patients with liver disease and iron overload. Wound contamination with seawater accounts for 25 % of cases. Virulence factors and digestive enzymes contribute to the high mortality of 30–40 % despite prompt diagnosis and aggressive therapy [10].

Table 17.1 Types of necrotizing fasciitis

Types of NF	Etiology	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 comorbidities
Type II (20–30 % cases)	Often monomicrobial, skin or throat derived	Usually group A β-hemolytic streptococcus (GAS), occasionally ± *S. aureus*	Aggressive, protean presentations easily missed	>32 %. Depends if associated myositis or toxic shock
Type III (commoner in Asia)	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)

17.2.1.4 Type IV NF: Fungal

Rarely NF can be caused by *Candida*, especially in immunocompromised patients. In contrast, zygomycotic necrotizing infections (*Mucor* and *Rhizopus* spp.) affect immunocompetent patients after severe trauma and are responsible for nearly 32 % of NF cases in some countries. Fungal invasion most commonly follows traumatic wounds or burns, and aspergillus or zygomycetes may be isolated [11].

17.3 Pathophysiology

NSTI is the condition where the microbial virulence overweighs the host defense system. Impaired host immunity or local tissue hypoxia as in atherosclerosis, burns, cancer or other immunocompromised states, chronic alcoholism, corticosteroid use, diabetes mellitus, hypoalbuminemia, intravenous drug abuse, malnutrition, obesity, occult diverticulitis, peripheral vascular disease, postoperative infection, and trauma predispose to NSTI. The pathogenesis of the development of NF depends on the causative organism(s). Synergistic NF is a comparatively slow process, evolving over days. Often, following complicated abdominal surgery and ischiorectal or perineal abscesses, synergistic NF develops particularly where gut flora breaches the mucosa, entering tissue planes. A slowly evolving bruise on the abdominal wall or perineal infection may reflect underlying malignancy. Gas-forming organisms and anaerobic infection may produce crepitus. Surgically, classical "dishwater fluid" due to lysis of polymorphs and serous discharge, together with macroscopic fascial necrosis, myositis, or myonecrosis, may be demonstrated. "Crescendo" pain, necessitating progressively stronger analgesia, is typical as occlusion of perforating nutrient vessels, and infarction of the nerves produces progressive skin ischemia and pain. Muscle hypoxia and swelling alter oxygen tension, increasing intracompartmental pressures, sometimes resulting in compartment syndrome [12]. Type II is initially more insidious than type I, but progresses far more rapidly. The disease may appear to have arisen spontaneously with no obvious focus. In such cases, hematogenous infection from many foci, including the throat, ascending vaginitis, primary peritonitis, or necrotizing proctitis, reaches the fascial layer. Hence, initial symptoms are ascribed to influenza, gastroenteritis, or muscle strain. This mechanism may explain the association of streptococcal infection with seemingly minor sporting injuries in athletes. The streptococcal capsule and protein M, protein F, streptolysin O, hyaluronidase, streptokinase, and pyrogenic exotoxins have their specific roles to play in the pathogenesis of streptococcal infections. Direct inoculation of GAS though wounds or associated with surgery is less common: examples include injection sites, caesarean section, plastic surgery, and even minor cosmetic procedures [13]. Hence the earliest clinical feature common to all types of NF is exquisite, agonizing pain, quite out of proportion to any external signs. The degree of pain may be lessened in diabetic neuropathy or following powerful analgesia. It is common to find patients prescribed with narcotic analgesics for "severe cellulitis" before the true diagnosis is suspected. As nerves supplying the necrotizing areas of skin die, the central areas become anesthetic, while laterally, the tissues overlying the deep spreading fascial infection

remain tender. Infection in the deeper layers finally ascends, producing edema of the epidermal and dermal layers (peau d'orange) and a "woody" firmness of the tissues. Hemorrhagic bullae progress to cutaneous gangrene, with sensory and motor deficits resulting from fascial and nerve destruction [14]. Fifty percent of type II NF cases are associated with toxic shock syndrome leading to a mortality of 40–67 % with up to half of patients needing amputation [15].

17.4 Clinical Features

Perhaps the biggest hurdle in early diagnosis and management of an NSTI is how to make the diagnosis. The commonly involved sites are the extremities (36–55 %), trunk (18–64 %), and perineum (up to 36 %). Events commonly predisposing patients to NSTIs include mild trauma, insect bites, drug reactions, illicit drug injections, perirectal abscesses, major traumas, and surgical procedures. Although patients may have an underlying risk factor, 30 % of the NSTIs do occur in healthy individuals [16]. The initial nonspecific signs such as tenderness, swelling, erythema, and pain at the affected site mimic nonsevere soft tissue infections such as cellulitis and erysipelas. The initial nonspecific signs are tenderness. Symptoms are much more than signs in initial phase, but by the time patients present, appearances are usually those of late NF, with visible bruising, bullae, and cutaneous necrosis due to progress of the necrotizing process. A thorough history should suggest the causative organisms in most cases. Goh et al. analyzed nine case series with a total of 1463 patients [17]. Diabetes mellitus was a comorbidity in 44.5 % of patients. Contact with marine life or ingestion of seafood in patients with liver disease was risk factors in some parts of Asia. The top three early presenting clinical features were swelling (80.8 %), pain (790.0 %), and erythema (70.7 %). These being nonspecific features, initial misdiagnosis was common and occurred in almost three-quarters of patients. Clinical features that helped early diagnosis were pain out of proportion to the physical findings, failure to improve despite broad-spectrum antibiotics, presence of bullae in the skin, and gas in the soft tissue on plain X-ray. Specific enquiries should be made about minor trauma; soft tissue injury penetrating lesions including insect or human bites, recent surgery, skin infection, or ulcers; injection sites; and illicit intravenous drug usage. Many cases, however, remain idiopathic [18]. Fever (>38 °C) is found in around 44 % of the cases, and tachycardia (>100 beats/min) is usually found in 59 % cases. Infected sites have erythema (80 %), induration (66 %), tenderness (54 %), fluctuance (35 %), skin necrosis (23 %), and bullae (11 %) [19].

We analyzed our patients of necrotizing fasciitis of the lower limb. The study reviewed 118 cases (78 males and 40 females) with mean age of 45 + 16.5 years (range 12–95 years) of lower limb necrotizing fasciitis admitted to the Department of Surgery, BHU in India between 1995 and 2007. Most patients ($n = 97$) presented with fever. Other presenting symptoms included painful swelling, bullae, erythema, ulcer, and necrosis. Comorbid conditions such as diabetes, tuberculosis,

malignancy, and immunosuppressive therapy were associated in 72 (61 %) cases. Amputations were done in 24 patients. Thirty-one patients developed septic shock. Renal dialysis was done in 16 patients, and ventilatory support was needed in 12 patients. The most common organism identified was beta-hemolytic streptococci ($n=42$). Eighteen patients died, a mortality of 15 %. The authors consider early diagnosis and aggressive surgical intervention to be crucial for the successful treatment of the disease [20] (Figs. 17.1, 17.2, and 17.3).

Type III may be associated with raw seafood ingestion or wound exposure to seawater justifies culture for *Vibrio* spp. A history of tonsillitis, close contacts with impetigo, or recent nonsteroidal anti-inflammatory drug (NSAID) usage suggests streptococcal infection. Patients present with fever and myalgia, severe pain, nausea, vomiting, and diarrhea. Diagnosis in initial phases is particularly difficult, since patients seen earlier in the infection were more easily misdiagnosed with muscle strains or viral illnesses. Other common misdiagnoses include gastroenteritis, sunburn, or an "allergic rash." A widespread macular "toxic erythema" may be present in a minority of patients. Misdiagnosis of NF is particularly common in children as it is rare and then usually associated with recent varicella zoster. Despite severe pain and appearing quite unwell, some patients initially have only a mild erythema, cellulitis, or swelling overlying the affected area. Since lymphatic channels are obstructed early, lymphangitis and lymphadenitis are rare. Overall, an exquisitely tender area evolves into a smooth, swollen area of skin with distinct margins progressing to dusky blue/purple, "bruising" violaceous plaques and finally full-thickness necrosis with hemorrhagic bullae [21]. Later on patients present with gangrenous patches, and the patients are very toxic and may involve various organs with hypotension, tachycardia, renal shutdown, respiratory problems, etc.

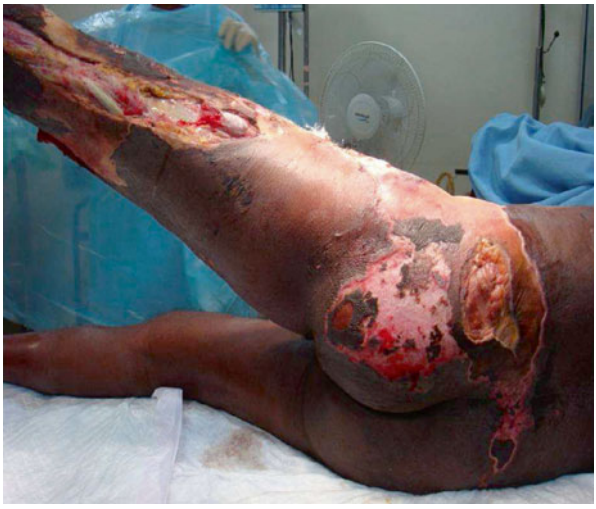

Fig. 17.1 Necrotizing fasciitis after thorn prick

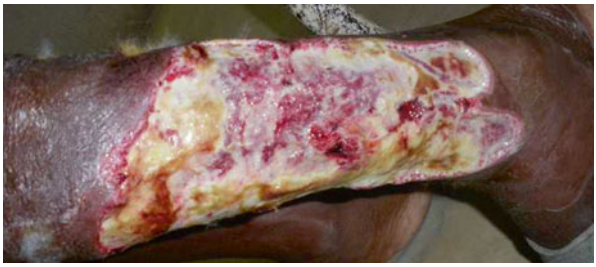

Fig. 17.2 Necrotizing fasciitis of the leg

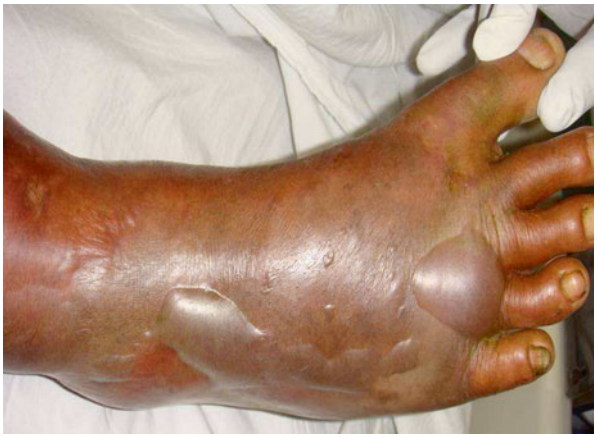

Fig. 17.3 Initial presentation with bullae

17.4.1 Investigations

17.4.1.1 Hematology

Disseminated intravascular coagulation and thrombocytopenia are common in any severe sepsis. A rapidly falling hemoglobin in the presence of a stable hematocrit may suggest intravascular hemolysis. The leukocyte count is less helpful for diagnosis. Although leukocytosis is common in type II, leukopenia is commoner in association with toxic syndrome. Infection with leukotoxin-producing organisms, e.g., Panton–Valentine leukocidin (PVL)-producing *S. aureus* or GAS, often leads to lymphopenia [22].

17.4.1.2 Biochemistry

Acute renal failure is quite common in severe sepsis, and dosing of renally excreted antimicrobials should be adjusted accordingly. Bacterial infection, inflammation, thrombosis, and necrosis all increase serum C-reactive protein (CRP). A very high CRP level is common. CRP levels of >16 mg/dL, with a sensitivity of 89 % and specificity of 90 %, have been reported in type II [23]. 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, but CK levels of 600 U/L gave a sensitivity of 58 % and a specificity of 95 % for cases of NF. One-third of patients with type II are hypocalcemic on

admission, due to calcium precipitation with fat necrosis [24]. Hypocalcaemia may also be a sign of severity in synergistic NF. Hypoalbuminemia and hyponatremia are common: in a series of 21 matched, consecutive cases, a serum sodium level of <135 mmol/L was found to be significantly associated with NF [25]. Severe metabolic acidosis may be found in NF. A high serum lactate combined with low sodium levels may be predictive of mortality. With serum lactate levels ≥6 mmol/L, the mortality was 32 %, whereas a lactate of <6 mmol/L and a serum sodium of <135 mg/L were associated with a mortality of 19 % [26].

17.4.1.3 Culture

Blood cultures are positive in 11–60 % of patients in type II, but the yield in type I synergistic fasciitis is lower. Routine culture of throat and vaginal swabs may be useful to establish a primary focus. Blister fluid is often sterile. Percutaneous needle aspiration of the advancing edge is painful. A tissue biopsy is the investigation of choice. Fungal cultures, especially in immunosuppressed or trauma patients, and enrichment cultures are useful, especially where patients have had recent antibiotic treatment [27].

17.4.1.4 Radiological

Plain X-ray of the area may show gas. Ultrasound may also show gas, but it mainly shows the edema and collection. The computed tomography scan findings suggestive of NSTI include the extent of abnormal soft tissue gas dissecting along the fascial planes, fascial stranding, and asymmetric thickening of fascial planes. The sensitivity of CT to identify NSTI is 100 %, specificity is 81 %, positive predictive value is 76 %, and negative predictive value is 100 % [28]. Magnetic resonance imaging (MRI) with gadolinium can differentiate necrotic and inflamed or edematous tissue. T2-weighted images on MRI are probably the best radiological adjunctive investigation, but are more sensitive than specific [29]. Chest X-ray may reveal early changes of fluid overload or changes of adult respiratory distress syndrome. Radiology of the affected areas is generally unhelpful, although occasionally MRI of the suspected area of fasciitis may be helpful, but should not delay surgery.

17.4.1.5 Histology

The characteristic findings include subcutaneous necrosis, polymorphonuclear cell infiltration, fibrinous vascular thrombosis with necrosis, and microorganisms within the destroyed fascia and dermis. Gram staining may also reveal Gram-positive clostridial bacilli. Histopathology can also identify fungal infection and invasive fungal infection with vascular thrombosis. Fine-needle or large-bore needle aspiration is another method to establish the diagnosis [30].

17.5 Scoring Systems for Prediction of NF

The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) scoring system has been useful in the diagnosis of NF when severe soft tissue infection was already suspected. It has 13 variables (including age, sex, serum potassium, and platelet

count); the most reliable indicators of underlying NF were found to be CRP, creatinine, hemoglobin, leukocyte count, sodium, and serum glucose. A score of 6 using the LRINEC system "raises the suspicion," with a score ≥8 being "strongly predictive" of NF. For patients scoring >6, the positive predictive value for NF was 92 % and the negative predictive value was 96 %. The LRINEC score may also indicate outcome: mortality of those patients with LRINEC score of <6 was 11 %, compared with 21 % for those scoring >6 [26, 31].

17.6 Treatment of NF

It is a dire emergency, and urgent surgical referral improves survival and needs a team approach with expertise from critical care, surgery, reconstructive surgery, and rehabilitation specialists [32]. The principles of treatment are fluid resuscitation and correction of electrolyte and acid–base imbalance, early initiation of antibiotics, surgical debridement of the affected area, and supportive measures for organ failure. In addition to antimicrobial therapy, complete debridement of infected tissue is key to successful treatment. Resuscitation with intravenous fluids and colloids, and inotropic agents, is usually necessary. Blood cultures, baseline full blood count, urea and electrolytes, liver function tests, clotting studies, and CRP and CK levels should be performed. Serum lactate and CRP are markers of severity of the infection and help guide therapy [33].

17.6.1 Antibiotic Therapy

As the condition is sporadic, it is not possible to have randomized double-blind controlled trials. Whereas antibiotic therapy may be guided by the Gram stain of aspirates or biopsies, the poor sensitivity and the fulminant nature of the infection make broad-spectrum empirical therapy covering most types of NF seem sensible. Subsequent antibiotic prescribing may be based on culture data [34]. Intravenous benzyl penicillin and clindamycin, imipenem, vancomycin, linezolid, and daptomycin are the drugs of choice in NF. Early initiation of antimicrobial therapy is essential and adjunctive to debridement. The current empirical antimicrobial regimes are piperacillin–tazobactam at 3.375 g every six hours with clindamycin 400–600 mg every 4–6 h with ciprofloxacin 400 mg every 12 h in type I infections. For type II infections, penicillin (2–4 million units very 4–6 h) with clindamycin is recommended. Injection linezolid (600 mg every 12 h) or vancomycin (30 mg/kg/day in two divided doses) may be considered in those allergic to penicillin. For type III clostridial infections, combination of penicillin with clindamycin is effective. In case of *Vibrio* or *Aeromonas* infection, doxycycline in a dose of 1 g every 12 h is effective. Clindamycin suppresses the toxin production by *S. aureus*, hemolytic *streptococci*, and clostridia and should be included when these organisms are present or suspected [35]. For suspected *Vibrio* spp. NF, therapy with doxycycline 100 mg twice daily plus intravenous ceftazidime 2 g eight hourly is recommended

[36]. Drotrecogin α (activated protein C) has not been used effectively in NF, and its use is limited to those patients not actively bleeding or within 24 h of surgery. After resuscitation, potent antibiotics, and surgical debridement, some patients still do not respond, and in these cases intravenous immunoglobulins may be tried.

17.7 Surgical Treatment of NF (Figs. 17.4, 17.5, and 17.6)

Surgery is vital in reducing the mortality of NF. In cases of doubt about the viability of tissues, the tissue oxygen tension can be measured with a probe using transcutaneous soft tissue oximetry. The oxygen tension is significantly lower in NF than cellulitis (52 % in NF, cf. 84 % in patients with simple cellulitis) with a sensitivity of 100 % and a specificity of 97 % [12]. Aggressive surgery removes the source of infection and toxins, and removal of infarcted tissue improves the penetration of antibiotics. The area of necrosis often extends beyond what is anticipated based on external appearance of the skin due to thrombosis of the dermal capillary beds that precedes skin necrosis. All obviously necrotic skin, subcutaneous tissue, fascia, and muscle must be excised. When there is crepitance present over an area of normal-appearing skin, an exploratory incision should be made through the involved area to determine whether the underlying tissues are viable. The presence of soft tissue gas does not mandate excision as long as the underlying tissues are viable. This crepitance often resolves after the necrotic tissue is removed. Amputation is done in 25–50 % of the cases where the affected extremity is either nonviable or would not be functional following debridement [37]. Early thorough and repeated

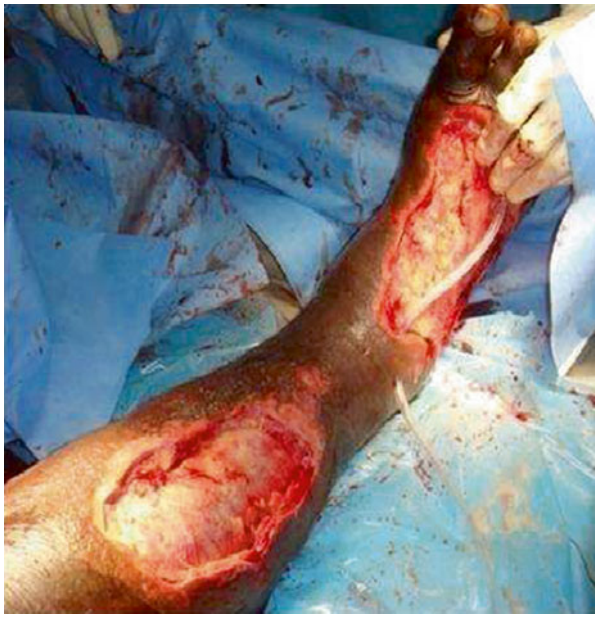

Fig. 17.4 Debridement of wound

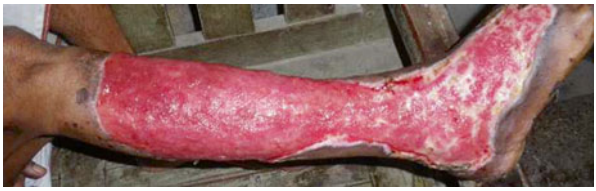

Fig. 17.5 Healthy granulation tissue after debridement

Fig. 17.6 Skin grafting after proper bed preparation

debridement is essential. Inadequate or delayed surgery is associated with a mortality of 38 % (8/21), compared with a mortality of only 4.2 % (2/48) in those who underwent aggressive surgery at recognition. Delaying surgery by 24 h increased the mortality associated with *Vibrio* spp. NF from 35 to 53 %, with 100 % mortality if surgery was not performed within 3 days [38–40].

Anesthesia for patients with NF is often difficult. The incision is often larger than expected, and the patient is cardiovascularly unstable with multiorgan failure, coagulopathy, and blood loss. Massive third-space fluid loss necessitates aggressive fluid replacement which may have a dilutional effect on the doses of antimicrobials administered. The rate of spread of NF may be very fast. Most patients need intensive care initially. Some surgeons believe that all infected material should be removed in one operation, but usually a "second-look" procedure is usually advisable. Repeat debridements are often necessary with a mean of 3–4 such procedures during admission. Extensive debridement produces large areas that need covering. Negative-pressure therapy [vacuum-assisted closure or (VAC) dressing] with a continuous pressure of 40–100 mmHg is useful for wound coverage and encourages granulation before and after skin grafting [41].

17.8 Hyperbaric Oxygen

Hyperbaric oxygen switches off α-toxin production, so it is believed to increase the bactericidal action of neutrophils since at low oxygen tensions peroxide-dependent killing mechanisms are less efficient. However, the overall evidence of benefit in non-clostridial NF is weak. Despite reports of rapid amelioration of clinical and mental status after only one hyperbaric oxygen session, there are few published data to support the use of hyperbaric oxygen in NF. Hyperbaric oxygen chambers are usually not available, but if facilities exist, it may be used [42].

Table 17.2 Clinical score predictive of death for patients with necrotizing soft tissue infections

Parameters	Score
Heart rate more than 110 beats per minute	1
Temperature less than 36 °C	1
Serum creatinine more than 1.5 mg/dL	1
Hematocrit more than 50 %	3
Age more than 50 years	3
White blood cell count more than 40,000/mcL	3
Points 0–2, 6 % mortality; 3–5, 24 % mortality; 6 or more, 88 % mortality	

Anaya et al. [37]

17.9 Outcome

Generally, synergistic NF has a better immediate prognosis, although underlying malignancy or other comorbidities account for later demise. The absence of myonecrosis or myositis in beta-streptococcal infection is associated with a better prognosis as myositis and organ failure increase mortality from 9 to 63 %. In the past, the mortality rate in NSTI was as high as 46 %. A decade ago, pooled analysis determined it to be nearly 34 %. Anaya et al. looked into clinical predictive markers for mortality looking into heart rate, temperature, serum creatinine, hematocrit, age, and WBC count and calculated the mortality [37] (Table 17.2). Kalaivani et al. analyzed their patients and found increasing age, raised creatinine, and delay in the first debridement were mainly associated with increasing mortality [43].

Conclusion

NF is an aggressive disease and delay in recognition and effective treatment increases the mortality of NF; thus, early diagnosis and management of NF is essential. In cases where the diagnosis is uncertain, repeated clinical assessment and a multiparametric approach integrating a range of diagnostic modalities and multidisciplinary involvement will optimize the diagnosis. Antimicrobial management should be tailored to the nature of the infecting organism and infection control aspects considered as soon as the diagnosis is entertained. Early surgical referral is essential, both for diagnostic confirmation and therapeutic removal of as much infected tissue as possible, although a "second look" is advisable.

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