Necrotizing Fasciitis of the Extremities

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Abstract

Necrotizing fasciitis (NF) describes a life threatening soft tissue infection characterized by a rapid spreading infection of the subcutaneous tissue and in particular the fascia. Various synonyms for this type of infection are used, often due to the difficult diagnosis. Necrotizing fasciits of the extremities is found after simple skin lacerations and often in rural, farming or garden setting environments. Many of the infections are found in immunologically healthy people, but persons revealing a compromised wound healing are endangered additionally, e.g., diabetes. In the majority of the microbiological analyses, *streptococci* alone or a mixture with mainly anaerobic bacteria may be detected. The management of infected extremities requires a rapid diagnosis, dedicated aggressive surgical management as soon as possible, and a wide debridement extending the border of the infected fascia. Timely surgical revisions within the first day or days together with antibiotic treatment are the only measures to stop the infection. Depending on the status of the patient a hyperbaric oxygenation treatment seems to be useful in order to limit the infection. In fulminated cases early amputations, maximal intensive care treatment of the septic patient are required, where all means are warranted to save the patients life. As a consequence, early clinical diagnoses with thorough surgical debridement of the infected liquid necrotic fascia as well as correct antibiotic treatment are needed. Secondary plastic reconstruction of the soft tissue defects will generally be required.

Key Words

Necrotizing fasciitis · Soft tissue infection · Soft tissue reconstruction

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Introduction

Necrotizing fasciitis (NF) is an infection accompanied by spreading crepitating edema and blister formation. It was first described by Hippocrates in the fifth century as erysipelas [1]. In the eighteenth century a detailed description of NF was provided by British naval physicians and in the early nineteenth century, it was named as gangrenous ulcer, putrid ulcer, malignant ulcer, phagedenic ulcer, phagedena, and phagedena gangrenosa and hospital gangrene [2]. In 1871, during the civil war, J. Jones, an American Surgeon, mentioned more than 2,000 cases very possible NF. Afterwards Pfanner described in 1818 in the German medical literature the clinical picture of necrotizing erysipelas and found *streptococci* related to the disease [3, 4]. In 1924, Meleney used the name hemolytic streptococcal gangrene [5]. Since then, various names have been given to NF (Table 1). Finally, in 1952, Wilson used the term necrotizing fasciitis (NF). The anogenital manifestation of NF was first described by Fournier in 1883 and is since then called Fournier's Gangrene [6, 7].

The early onset of this type of soft tissue infection is a discrepancy between pronounced pain and clinical appearance. The aggressive progression induces finally skin and fascia necrosis, coagulopathia and cellulites. Five diagnostic criteria can be defined (Table 2, [8]). The missing isolation of *clostridium perfringens* does not necessarily exclude gas gangrene nor prove NF. In patients suffering from NF, more often diabetes, hypertonic blood pressure, arterial occlusive disease, and obesity are found as well as higher percentage of alcohol

Table 1. Synonyms of NF.

Hemolytic streptococcal gangrene
Non-clostridia gas gangrene
Non-clostridia crepitate cellulites
Necrotizing erysipelas
Gangrenous erysipelas
Bacterial synergistic gangrene
Necrotizing cellulites
Synergistic necrotizing cellulites

Table 2. Diagnostic criteria of NF (mod. by Fischer 1979).

Extensive necrosis of fascia with extension to the adjacent skin
Medium to severe intoxication and reduced mental state
Primary exclusion of muscles
No vascular occlusive disease
Histology with leukocyte infiltration, focal fascia necrosis and surrounding tissue, micro-thrombosis

and drug abuse, immunosuppressant therapy and HIV-infections. Even a varicella zoster virus infection in combination with the use of NSAIDs is discussed as risk factor [9]. It is more likely to appear in elderly people, but children also can be affected. In the literature various reasons have been related to the primary focus and include minor skin lesions, bites of insects and wounds after surgical procedures [10]. Initial microbiological tests discover in a high amount *streptococci* (app. 30%), a mixture of different bacteria and less common pseudomonas aeruginosa (app. 5%, Table 3).

Table 3. List of possible bacteria isolated in NF.

Gram-positive aerobic bacteria	*Streptococci* group A
	Streptococci group B
	Enterocooci
	Staphylococci
	Bacillus
Gram-negative aerobic bacteria	*Escherichia coli*
	Pseudomonas aeruginosa
	Enterobacter cloacae
	Klebsilla
	Proteus
	Serratia
	Acinetobacter calcoaceticus
	Citrobacter freundii
	Pasteurella multocida
Anaerobic bacteria	*Bacteroides*
	Clostridium
	Peptostreptococci
Marine Vibrio sp	*Vibrio vulnificus*
	Vibrio parahemolyticus
	Vibrio damsela
	Vibrio alginolyticus
Fungi	*Candida*
	Aspergillus
	Rhizopus

Therapeutic Strategy

Diagnostics

Due to an increased amount of invasive streptococcal infections in the US during the 1980s, a ''streptococcal septic shock syndrome (STSS)'' was defined. This is characterized by a systemic sepsis with multiple organ failure, especially the kidney. Today, NF caused by *streptococci* group A is classified as a subgroup of this infection. Also myositis caused by *streptococci* – mostly due to direct inoculation/contamination – should be differentiated. In such cases rapid lyses of the involved muscle, with edema formation, focal development of a compartment syndrome with consecutive necrosis is observed [11–16]. Therefore necrotizing soft tissue infections (NSTI's) characterize various diseases. Clinically they can be separated in superficial infections involving cutis/subcutis and deep infections affecting fascia and muscle (NF, myositis). These deep infections are further classified as type I (polymicrobial) and type II (monomicrobial). Bacterial factors play an important role in NSTI. In the cases of invasive streptococcal infections, surface proteins (M1, M3) increase adhesion and prevent phagocytosis and exotoxines (A, B, C, streptococci super-antigen) induce the release of cytokines and could bind to T-cell receptors causing further release of TNF-α, IL-1 and IL-6 ending in a STSS [17, 18]. Although M-types 1 and 3 are common other types have been isolated in invasive infections; however, a stable genetic change was observed in M-type 1 group A *streptococci* in the 1980s, resulting in its ability to produce nicotinamide adenine dinucleotide glycohydrolase (NADase) and might be one factor in severe invasive infections [19]. The rapid tissue destruction is a result of toxin-induced vascular occlusion. As the infection progresses more toxins are produced and tissue destroyed. This microvascular occlusion contributes to shock and organ dysfunction.

In the case of NF early diagnosis is critical with respect to the survival of the patient. This is primarily a clinical diagnosis with no typical changes in lab diagnostics. Serum creatinine phosphokinase (CPK) might be useful in detecting deeper soft-tissue infections. Even a mild leukocytosis could be combined with an increasing percentage of immature neutrophils and should be a reason to be suspicious. Renal

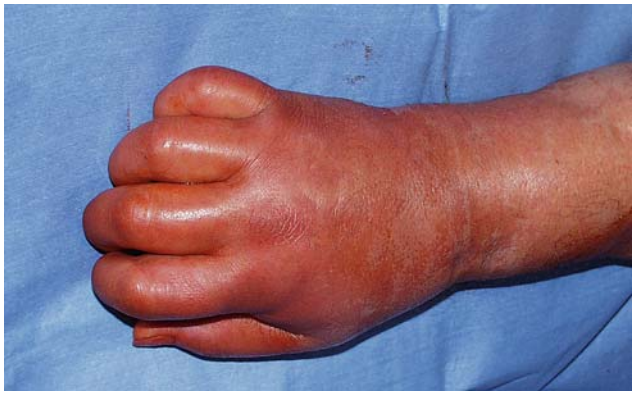

Figure 1. Early clinical appearance of a NF in the hand.

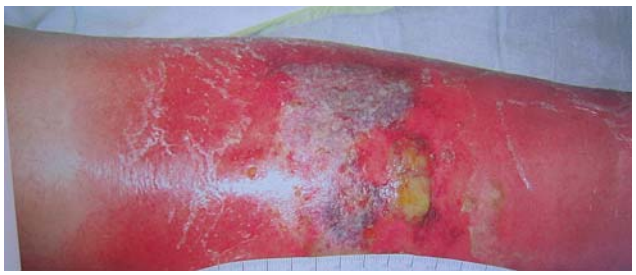

Figure 2. Appearance of skin necrosis of NF in the lower leg.

Table 4. Clinical signs of Necrotizing Fasciitis.

Skin	Blurred picture of erythema
	Extensive edema
	No swelling of lymph nodes
	Discolored wound drainage
	Vesicle/bullae
	Necrosis
	Crepitus
Pain	Early on not explained by the clinical appearance
	Extending the margin of infection
	Decreased/anesthesia at apparent site of infection
Systemic signs	Fever
	Tactile temperature
	Diaphoresis
	Tachycardia
	Toxic delirium

Table 5. List of serious soft tissue infections.

Necrotizing fasciitis (NF)
Clostridia gas gangrene
Streptococci myositis
Erysipelas
Streptococcal septic shock syndrome (STSS)
Staphylococcal septic shock syndrome

impairment precedes hypotension, as well as hypoalbuminemia and hypocalcemia are early signs. Especially in the extremities the bacteria are inoculated mostly through a minor skin lesion. The infection is in the early stage characterized by un-proportional local pain due to fascia necrosis. After this, skin changes are visible with edema and erythema (Figure 1). The typical pattern of skin necrosis with or without blisters is found later; however, the necrosis generally spreads rapidly in the proximal direction. The necrosis of the fascia has already much further spread, compared to the changes of the skin (Figure 2). Crepitating skin can be recognized in about 50% of the patients and is suspicious of a poly-bacterial infection. The typical clinical signs are listed in Table 4. Since the time to surgery needs to be diminished no demanding diagnostics like histology or bacterial isolation is possible. To support the diagnosis of NF ultrasound can be used demonstrating fluid between the muscle and subcutaneous tissue because of fascia necrosis. Sometimes X-rays can reveal gas formation which could be easily palpated. CT or MRI could be of some use, but with little impact on the final decision to proceed to the operative treatment. MRI has some impact due to soft tissue and multiplanar imaging and might be helpful in case the source of infection lies deep inside the body. During surgery an excision biopsy could be done, but the typical discoloration of the fascia (yellow to green) and the possibility to manually dissect the fascia (like chewing gum) will assure the diagnosis.

In contrast to myositis caused by *streptococci* the muscles appear normal and not as necrotic with a discoloration, brown to grey, comparable to loam.

STSS is more often found in association with pharyngitis, or small lesions of the skin or mucosa (scratches, insect bites). This syndrome appears in normally healthy people of all ages, in children more often seen following chickenpox infection [16]. Isolation of *streptococci* group A is typical – also in normally sterile body compartments – and of course the signs of a systemic shock. However, 50% of the STSS cases are accompanied by NF. The typical serious soft tissue infections are listed in Table 5.

Surgical Approach

The relevance of a surgical management could be proved by Kaiser and Cerra. A reduced surgical treatment was followed by a significant increase of death rate [20]. There is no space for incision and drainage or limited evacuation of the abscess. The only surgical

option is the radical surgical excision of the infected subcutaneous tissue in particular including the grey pale fascia. In these cases, the fascia is grey, has lost all its strength and can more or less be pealed off. It is essential to resect the infected fascia and to debride into healthy tissue. Furthermore, it is essential to follow up by surgical re-interventions after a short time – even again on the same day in fulminant cases or at least the subsequent day. In general this regime is followed a few days until the spreading in the proximal direction has been stopped. An amputation in the extremities is not the primary treatment, but in cases where the whole tissue is necrotic and most muscles involved, this might be the only option to stop further spreading and systemic sepsis with multiple organ failure. These amputations have to be performed as open amputations, again requiring second look operation and secondary closure. After primary intensive care and control of the infection and sepsis (mostly after 1 week) reconstructive procedures are initialized reaching from secondary wound closure and skin grafting to flap coverage saving viable tissue and restore function.

Histology

Histology of the excised tissue reveals infiltration of fascia by polymorphic nuclear cells, with peri-vascular focus. Sometimes bacteria are detectable. Later, a co-liquation necrosis of the fascia is visible, involving subcutaneous tissue and skin. The tissues cannot be differentiated anymore and muscle tissue is involved as well.

Antibiotic Treatment

Demanding a radical debridement, therefore the resulting wound areas are extensive in most cases and therefore the increased fluid turnover already justifies an intense care treatment. An adjusted antibiotic regime is mandatory. In undefined cases Gram-negative, Gram positive and anaerobic bacteria must be addressed. Mono-therapy includes imipenem-cilastatin, meropenem, ertapenem, piperacillin/tazobactam and tigecycline. A combination-therapy adds vancomycin, linezolid or daptomycin to a carbapenem or β-lactam/β-lactamase inhibitor combination, if methicilin-resistant *staphylococci* are possible. Another combination therapy includes penicillin, clindamycin and fluoroquinolone or aminogycoside to cover Gram-negative bacteria. In a case of streptococcal infection clindamycin should be included into the medication, since it has been shown to inhibit the toxin production (m-protein and exotoxin) in severe cases [21]. Especially streptolycin O (SLO) induces changes to the leukocytes. It is specific to phenoloxidase important in the mechanism of host defense and much reduced in NF-cases due to *streptococci* infection. This significant immunosuppressive effect is accompanied by the effect that phenoloxidase catalyses the transformation of tyrosine to dehydroxy-phenylalanine necessary to produce catecholamine, one reason a patient with NF might need catecholamine substitution. Additionally, some immunotherapies (e.g., immunoglobulins) are also suggested by some authors [13]. The mechanism is believed to be related to the neutralization of superantigen activity and reduction of TNF-α and IL-6.

Intensive Care Therapy

Various efforts have been made to categorize patients with respect to the risk of mortality. Negative parameters are age above 50 years, WBC > 40,000 cells/mm^3, hematocrit > 50%, HR > 100, temperature < 37°C and creatinine > 15 mg/dl [22]. If the patient develops a septic shock or STSS an acute respiratory distress syndrome (ARDS) is also very likely (app. 50%) and needs mostly intubation and mechanical ventilation to achieve adequate oxygen supply.

Every patient with signs of sepsis or impaired immune response should have intensive care treatment, since organ failure is very common in the time course of NF. The patients are at an extremely high risk to run into systemic sepsis with a poor prognosis. Good oxygenation, cardiac output and control of homeostasis are the primary goals in treating a systemic sepsis and septic shock according to the current guidelines [23]. These guidelines have to be included stepwise in the treatment of sepsis due to necrotizing fasciitis. Additional treatment options to enhance systemic toxin and mediator reduction have been discussed, such as continuous hemofiltration [24]. Due to the variation and limited number of patients in single centers, this approach has been only applied in isolated cases [25].

Therapeutic Options

Besides the basic treatment including intensive care medicine and surgical debridement numerous adjuvant therapies have been recommended with respect to the systemic management of these infections as well as possibilities for local wound treatment.

Systemic Adjuvant Therapy

Hyperbaric Oxygenation (HBO)

Necrotizing Infections are considered to be one of the primary indications for HBO as well as decompression disease, gas embolism, CO- and smoke intoxication,

Table 6. Characteristics and co-morbidity of the patients with NF.

Patients				Characteristics of necrotizing fasciitis		Co-morbidity				
No	Age (years)	Sex	History (h)	Origin of infection	Extend of gangrene	Cardio-pulmonary	Occlusive arterial disease	Massive overweight	Alcoholism	Diabetes
1	50	F	120	Thumb	Hand					
2	49	M	72	Lateral left thigh	Thigh, glutei, trunk					X
3	77	F	48	Dorsal thigh	Glutei, trunk, thoracic	X		X		
4	47	M	16	Lower leg	Leg				X	
5	53	M	92	Hand	Forearm	X			X	
6	52	M	36	Finger	Arm					
7	27	M	56	Finger	Arm					
8	57	F	12	Thigh		X				

anaerobic infections (*clostridia* infections) and radionecrosis [26]. HBO-therapy is able to increase blood oxygen content by 25% and thereby tissue oxygenation tenfold [27]. Other effects related to this treatment are vasoconstriction, reduced leukocyte sequestration, lipid peroxidation, free radical scavenging and reduction of tissue edema resulting in an increased tissue perfusion/microcirculation [28–30]. Another important effect, thought to be helpful in treating NF by improving host defense, is the activation of leukocytes. Also reparative processes might be stimulated due to fibroblast migration, proliferation and collagen synthesis [22, 31, 32]. These effects might be very helpful to support healing/granulation tissue formation of these mostly difficult wounds [33]. Various treatment regimes are recommended to be followed-up; however the most intense is that in accordance with crush injury with three treatments within the first 48 hours (2–2.5 ATA, 1–2 h O_2-breathing), followed by two treatments the next 48 h and finally 48 h once a day. Since the use of HBO-treatment is connected with high medical and technical expenditure, especially if the patient is critically ill due to sepsis and needs breathing support, estimation is necessary, also the literature is controversial about the effects on morbidity and mortality rates [12, 34, 35]. However, this therapy needs to be considered focusing an increasing network and therapeutic standard in HBO-Treatment. Another possibility to increase oxygen in the body is an intravenous application (Regelsberger's intravenous Oxygen Therapy). However the effect needs to be proved for NF, also with respect to an increase of granulocytes [36]. Therefore the major focus in NF should be related to intensive care management and the vital surgical therapy with no delay.

Topical Wound Treatment

Antiseptic Treatment

After primary surgical treatment in most cases a topical wound treatment is used. Various substances according to the isolated bacteria can be chosen. Mostly the following antiseptic substances are recommended: Polyhexamid, Povidon-Iodine, Silver Sulfadiazine, Actate Mafenid. Also wine vinegar and citric acid have been applied, especially to modify the wound environment and lower the pH in cases of *pseudomonas* infections.

Vacuum Sealing

Vacuum Sealing is a widely used approach to condition destroyed soft tissue in order to allow granulation and a safe secondary reconstruction [37]. It is extremely useful in cleaned wounds of the extremities and the abdomen and reduces surgical interventions to intervals between 2 and 5 days. In acute stages of necrotizing fasciitis, however, vacuum sealing is not indicated during the early states of purulent infections and infected tissue necrosis. But subsequently, when infected and destroyed soft tissues have been removed, vacuum sealing seems to be very useful for conditioning the defects and occasionally allowing limited tissue closure using skin graft; if not, a complex reconstruction is required [38].

Characteristic Clinical Case

The clinical cases with NF and primary focus on the extremities are listed in Tables 6 and 7. Most of these have had minor injuries with rapid spreading of the infection. One exemplary case is described to illustrate the significance of early operative treatment and excision of the devastated tissue.

Table 7. Clinical course and treatment procedures of the patients with NF.

Pat. no	No re-deb	Additional resections	Bacterial characterization	Days on ICU	Reconstructive procedures	No reco-proc	Outcome
1	2	Partial thumb amputation	Polybacterial	1	Amputation revision	1	Survival
2	26	Muscle thigh	Polybacterial	11	Skin transplantation	2	Survival
3	5	Muscle glutei, trunk	*Streptococci* group A	24			Death
4	7	Muscle	*Streptococci* group A	3	Secondary closure, skin transplantation	2	Survival
5	5		*Streptococci* group A	6	Secondary closure, skin transplantation	3	Survival
6	5	Finger amputation	*Streptococci* group A	6	Groin flap, skin transplantation	4	Survival
7	8	Forearm amputation	Polybacterial	12	Secondary closure	1	Survival
8	2		*Streptococci* group A	4	Secondary closure	1	Survival

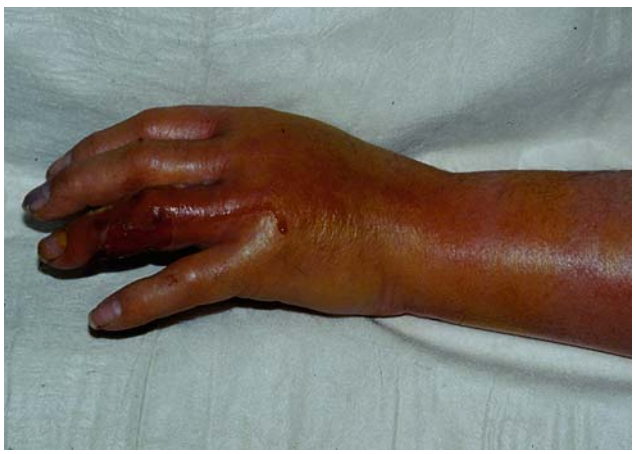

Figure 3. Appearance of the hand at the time of hospital admission.

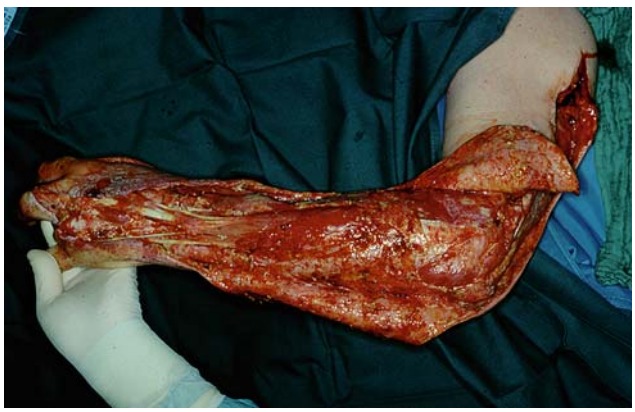

Figure 4. Situation after extensive debridement and amputation of the necrotic ring finger.

A 52-year-old gentleman was visiting a garden market. By lifting various flowers, He experienced a minor scratch, while handling various flowers, on the ulna side at the middle phalanx of the left ring finger. This happened on a Thursday afternoon and since there was no obvious skin lesion he did not care about it. During the next night and day he experienced increasing swelling and pain of the whole hand – not only the finger. On Saturday morning he consulted a local surgeon, who admitted him immediately to the hospital. The patient had already clear signs of local infection (Figure 3), systemic sepsis with reduced blood pressure, tachycardia and fever up to 40°C. Immediately, he was brought to the surgery room where a primary excision of the possibly involved tissue was done, up to the elbow. However, the patient did not recover very well afterwards in the intensive care unit. Finally he was brought back to surgery – on the same day – and a radical debridement was performed, including the amputation of the ring finger and excision of all obvious involved fascias (Figure 4). After this, four more wound care procedures were done in the operating theatre. Finally after 6 days the wounds could be closed with a pedicle groin flap and skin graft. Three more reconstructive procedures were followed including flap division, and two more correction with a

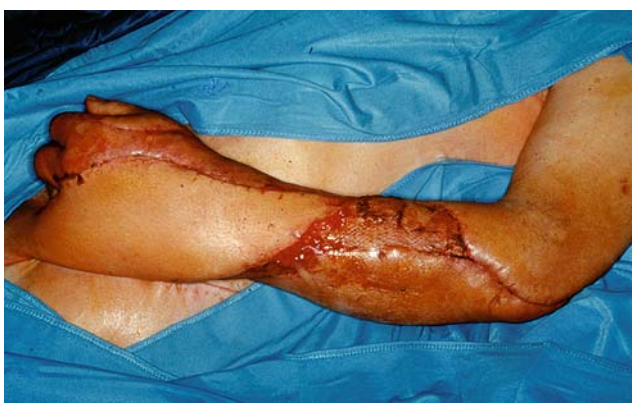

Figure 5. Soft tissue coverage of the area with the exposed tendons with a groin flap.

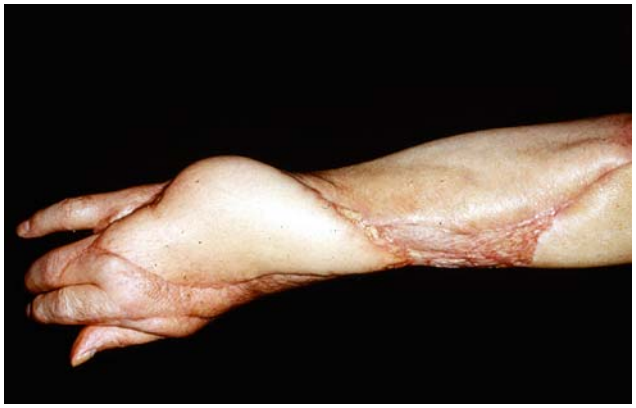

Figure 6. Clinical picture of the forearm after the reconstruction was performed. Further debulging had not been done yet.

final skin graft (Figures 5 and 6). During the treatment period at the intensive care unit also HBO-therapy was followed daily starting at day 1 for 5 days.

Conclusion

Necrotizing fasciitis (NF) is a life threatening soft tissue infection, characterized by foudroyant spreading necrosis of the involved fascias. Since a high variety of bacteria can be isolated the two different types of NF can be differentiated: Type 1 characterized by a poly-bacterial infection of aerobic and anaerobic bacteria and Type 2 with *streptococci* group A as source of infection [39]. The type 2 infections are less common, but are more often found in the case of the involvement of extremities. Every fascia in the body can be destroyed by this disease. Early diagnosis is critical to the survival of the patient and must rely on the clinical picture. When there is doubt, there should be no delay in performing surgery with radical debridement. The suggested treatment strategy with adequate early surgical and intensive care medicine could help reduce the up to 70% lethality rate, as stated in some publications, to less than 10% [40–42]. Infections of the extremities are less likely lethal, whereas an intra-abdominal occurrence leads mostly to the death of the patient. Higher age, diabetes, arterial occlusive disease, immunosuppressant status and the onset of NF due to iatrogenic infections is linked to a much worse prognosis. NF is an infection still observed very seldom; however, some data indicate an increase of this type of infection in the last decade, therefore clinicians should be aware and alert in cases of a significant soft tissue infection to rule out NF.

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