Ditsios K, Chitas K, Christidis P, Charatsis K, Katsimentzas T, Papadopoulos P. Necrotizing Fasciitis of the Upper Extremity – A Review. *Orthopedic Reviews*. 2022;14(3). doi:10.52965/001c.35320

Reviews

Necrotizing Fasciitis of the Upper Extremity – A Review

Konstantinos Ditsios[1], Konstantinos Chitas[1], Panagiotis Christidis[2] [a], Konstantinos Charatsis[1], Triantafyllos Katsimentzas[1], Pericles Papadopoulos[1]

[1] 2nd Academic Department of Orthopedic Surgery, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, General Hospital of Thessaloniki "G. Gennimatas", Greece, [2] Department of Orthopaedic Surgery, General Hospital of Katerini

Keywords: Necrotizing Fasciitis, upper extremity, upper limb, surgical debridement, review

https://doi.org/10.52965/001c.35320

Orthopedic Reviews

Vol. 14, Issue 3, 2022

Necrotizing fasciitis is a soft tissue infection that habitually originates from the fascial sheaths, expands at a volant pace, leads to extensive necrosis of the subcutaneous tissues, and eventually ends up in a life-threatening condition with notably elevated amputation and mortality rates. Factors that induce interruption of skin integrity, such as trauma or intravenous drug use, are the most common inciting events. Specific clinical signs heralding its presence are usually absent in the early stages, often resulting in misdiagnosis. Early recognition, prompt and aggressive surgical debridement, antibiotic use, and supportive care constitute the fundamental principles to lean on for a better prognosis. Necrotizing fasciitis of the upper extremity is relatively rare and consequently holds a limited place in the literature. Only a few studies assess it as a separate entity, with most of them being case reports or small case series. We, therefore, performed a review of the current literature, to assemble the dispersed results of different studies and clarify the various aspects of upper limb necrotizing fasciitis. In this systematic review, we present the epidemiological data, the causative events, the most frequent underlying diseases, the risk factors, the amputation and mortality rates, the pathogenic microorganisms, the clinical characteristics, the diagnostic tools, the medical and surgical management concerning necrotizing fasciitis of the upper limb. Finally, the results indicating its differentiation compared to necrotizing fasciitis of other anatomic sites are remarkably highlighted.

1. INTRODUCTION

The term necrotizing fasciitis (NF) refers to a group of relatively uncommon, rapidly progressive, and potentially fatal soft-tissue infections. NF usually spreads across the fascial planes expeditiously and extensively, resulting in the necrosis of superficial and deep fasciae and subcutaneous fat. Skin and muscles are usually spared in the early stages, clinical manifestations are nonspecific at the time of admission, prompt diagnosis and appropriate treatment are usually delayed, and the infection quickly aggravates and evolves into an emergent, life-threatening condition.[1,2]

The earliest report of the disease dates to the fifth century BC when Hippocrates first described "erysipelas" in patients with quickly spreading and highly lethal soft-tissue infections.[3,4] The first clear description of "modern" NF was given by Dr . Joseph Jones, a military surgeon of the Confederate Army during the U.S. Civil War. In 1871, he used the term "hospital gangrene" to describe 2.642 cases of soldiers that developed "virulent" infections with "grayish and greenish slough", having a mortality rate of 46%.[2–5] In 1883, Jean Alfred Fournier reported five cases of necrosis of the perineum; consequently, this type of NF is named after him as "Fournier's gangrene".[4] In 1924, Meleney first found a correlation between NF and Beta-Haemolytic Streptococcus Group A in a series of 20 patients in a hospital in Beijing, calling the disease "acute hemolytic streptococcal gangrene".[4,5] Since then, the condition has been known under different terms, such as "phagedema", "nonclostridial gas gangrene" and "necrotizing erysipelas".[6] Fi-

a **Corresponding author:**
Panagiotis Christidis MD, MSc
Resident Doctor
Department of Orthopedic Surgery,
General Hospital of Katerini, 60100
Katerini, Greece
+30 6940 730227
panagiotischristidis13@gmail.com

nally, the term "Necrotizing Fasciitis" was introduced in 1952 by Dr. B. Wilson noticed in a series of 22 patients that the infection affected the fascial planes but seemed to spare the underlying muscles.[2–5] Over the years, this term was further expanded, becoming known as NSTIs (Necrotizing Soft-Tissue Infections), to include cases of cellulitis and superficial skin infections, as they may be early presentations of necrotizing fasciitis.[3]

NF is usually triggered by a puncturing event that breaks off skin integrity (trauma, animal or insect bites, invasive medical procedures) or even by hematogenous spread, chronic wounds, and abscesses. The most frequent inciting factor, particularly in the United States, is intravenous drug use (IVDU). However, approximately 11%-20% of cases are idiopathic.[7,8] NF demonstrates a wide variety of causative microorganisms, depending on geographical region and demographics. Mixed flora cases predominate over single organism infections and the most recurrent pathogens are gram-positive organisms (usually Streptococcus and Staphylococcus species).[7]

Early recognition of the disease is crucial, and any delay can lead to a worse prognosis with higher amputation and mortality rates.[4] NF is notably challenging to diagnose, as it has an unpredictable clinical course, often quite subtle with nonspecific symptoms in the early stages. This can lead to a false impression of less serious conditions like cellulitis, misdiagnosis, delay of diagnosis, and inadequate treatment. The paramount sign is pain disproportionate to the physical findings. As many as 50% of cases may initially present without skin changes. The classic "hard signs" of skin necrosis and crepitus can be absent in the majority of cases.[7,9–11] Although diagnosis is usually clinical, the use of imaging and laboratory tools is essential. Gas in soft tissue planes can be seen in plain X-ray studies. LRINEC score (Laboratory Risk Indicator for Necrotizing Fasciitis) can detect clinically early cases of necrotizing fasciitis, using routinely measured variables (C-Reactive Protein, Total White Cell count, Hemoglobin, Sodium, Creatinine, Glucose).[12]

The progression of the disease is usually fulminant, and NF quickly deteriorates to a life-threatening condition, potentially leading to septic shock, SIRS (Systemic Inflammatory Response Syndrome), concomitant multisystem organ failure, and eventually death.[2,8] High clinical suspicion, prompt diagnosis, and immediate and aggressive surgical intervention remain the cornerstones in the treatment of NF. A multidisciplinary approach is often mandatory. Emergent interventions such as airway protection, hemodynamic support, and early intravenous initiation of broad-spectrum antibiotics, followed as quickly as possible by extensive debridement and excision of the affected necrotic tissue are the "gold standard". Repeated surgical debridement may be required.[1,2,11,13,14] Unfortunately, even with optimal treatment, NF retains significant morbidity and has mortality rates of 25% - 35%.[1]

All body parts can be affected by NF, but the extremities remain the most frequent site of infection, making up 45% - 74% of all cases, according to different studies. About two-thirds of these cases concern the lower extremities, while NF of the upper limb is less common, being involved in approximately 6% - 27% of the patients.[3,4,7,15–20] Because of its rarity, few studies assess upper limb NF, with most of them being limited to case reports, small case series, series of mixed anatomic sites, or big national database studies with an absence of extensive details relating to certain parameters of upper extremity NF.

We have therefore performed a review of the literature to investigate the various features of the disease, quote the epidemiological and microbiological data, analyze the comorbidities and the predisposing factors, highlight the clinical signs indicating its presence, underline the laboratory and imaging findings and focus on the appropriate conservative and invasive treatment that is recommended to be followed.

2. MATERIAL AND METHODS

This study provides a review of the published literature referring to the Necrotizing Fasciitis of the upper extremity. Publications relating to this subject were identified using different electronic resources, including PubMed, Scopus, and Web of Science. The keywords used have been ''necrotizing fasciitis'', "upper extremity" and ''upper limb''. The results returned 359 published papers. Studies written in other languages than English, cases of underage patients, reports dealing with NF affecting sites other than the upper extremity, papers with the wrong subject matter, and duplications were excluded.

3. EPIDEMIOLOGY

3.1. DEMOGRAPHICS AND ANATOMIC SITE OF INFECTION

Among different studies, the annual incidence of NF varies between 500 and 1.500 cases reported in the United States each year, and its prevalence globally is estimated to be around 0,40 – 0,53 cases per 100.000 population annually. Its incidence is believed to be increasing over the last decade, mostly thanks to the amelioration of the reporting system, the augmentation of the diagnostic accuracy, and consequently the decrease of the formerly several misdiagnosed cases. Additionally, this can be attributed to the increased age and number of comorbidities in the population, as well as to the antibiotic abuse and its negative impact on the virulence of the pathogens.[1,4,16,18]

Although NF can affect all body parts, the extremities are the most common site of infection, described to be affected in 45 – 74% of all cases, with the lower extremities being most prevalent. NF of the upper extremities is less frequently reported, presenting frequencies varying between 6% and 27%.[3,4,7,15–20] According to Anaya et al., in a large series of 166 patients with established NF, the extremities were the most common site of infection (57.8%), followed by the abdomen and the perineum.[19] In a systematic review by Angeles et al., consisting of 12 studies including 317 limbs, the upper extremity was involved in 32% of the cases.[20] Nevertheless, NF of the upper extremity is believed to be under-reported and is expected to become more frequent, due to the increasing intravenous drug use.

Table 1. Demographics and Anatomic site of infection

Value	Total (data from 35 surveys) n=379 (100%)	Total (data from 30 surveys) n=208 (100%)
Age, y, mean (range)	56,4 (20 – 86)	
Gender		
Male	257 (67,8%)	
Female	122 (32,2%)	
Affected side		
Right		105 (50,5%)
Left		99 (47,6%)
Both		4 (1,9%)
Anatomic site involved		
Shoulder		43 (20,7%)
Arm		99 (47,6%)
Forearm		119 (57,2%)
Hand and fingers		146 (70,2%)

Although NF can affect all age groups, the elderly, and middle-aged people (over 50 years old) are more susceptible to it. While a male-to-female ratio of 3:1 has been reported for the total of NF cases, mainly associated with the prevalence of Fournier's Gangrene in men, as far as the upper extremity is concerned, a gender predilection has not been proved.[4]

From the reviewed literature, 35 articles provide information about patients' gender and age.[5,6,8,10,13–18,21–45] On a total of 379 patients with NF of the upper extremity, 257 were male (67,8%) and 122 were female (32,2%). The average age of these patients was 56,4 and ranged between 20 and 86 years old (underage patients were excluded from the data selection). A sum of 30 articles, presenting the cases of 208 patients suffering from upper limb NF, gave information concerning the affected side and the sites of the upper extremity that were involved. No statistically important difference was found between the right (n=105 cases, 50,5%) and the left (n=99 cases, 47,6%) upper limb, while 4 cases (1,9%) developed bilateral infection. The most frequently affected site was the forearm (n=146, 70,2%), followed by the hand (n=119, 57,2%). The epidemiologic data of the reviewed articles are presented in Table 1.

3.2. MORTALITY AND AMPUTATION RATES

The average mortality rate of NF remains a controversial issue. It is generally accepted that without treatment, the mortality rate can reach 100% and that despite the advances in critical care management, antibiotics, and surgical treatment, mortality rates remain elevated and comparable to these of 46%, observed by Dr. Joseph Jones at his first description of NF back in 1871. Among different studies, NF presents a remarkably wide range of mortality rates, varying from 6% to 76%.[4,6,12,19,46]

It seems that in NF that is affecting the extremities, mortality rates are lower compared to these of other anatomical regions (e.g., head, neck, trunk, perineum) since NF at these locations is commonly more widespread upon presentation and tends to be more difficult to treat, while NF of upper extremity frequently appears in intravenous drug users; hence in younger patients with fewer comorbidities.[17] Pessa and Howard demonstrated a mortality rate of 18% in NF of extremities, significantly lower compared to these of abdominal (44%) and perineal (33%) infections.[47] Angeles et al. in their systematic review consisting of 324 limbs reported 71 deaths, attributing to NF of the extremities a mortality rate of 21,9%.[20] According to Anaya et al., out of 96 patients suffering from NF of the extremities, 21 deceased (mortality rate 21,9%) and 25 lost a limb (amputation rate 26%), while Ogilvie et al. found that the mortality rate of NF of the extremities was only 9,3% (14 deaths among 150 cases).[19,48]

As far as NF of the upper extremity is concerned, retrospective studies report mortality rates of 10% to 36%, while rates of amputation range from 11% to 38%. Nawijn et al. conducted a retrospective cohort study consisting of 122 patients with upper extremity NF and observed a 30-day mortality rate of 11% and an amputation rate of 14% (13 patients died and 17 underwent an amputation).[17] Similarly, a database study led by Uehara et al. pointed to a mortality rate of 15,5% and an amputation rate of 11,2% (18 patients died and 13 patients underwent upper limb amputation from a total of 116 patients affected by NF of the upper extremity).[18] Table 2 illustrates the number and the percentage of patients with upper extremity NF that eventually died or lost a limb, among different studies.[6,10,15,17,18,44–46] The combined results extracted from the reviewed literature give a mean death rate of 15,9% and an average amputation rate of 14,7%, significantly smaller compared to these of NF involving other anatomic sites.

Table 2. Death and amputation rates of upper extremity NF reported in different studies

Author/Year	Patients	Amputation (%)	Death (%)
Nawijn et al. 2019	122	17 (13,9%)	13 (10,7%)
Corona et al. 2016	7	1 (14,3%)	2 (28,6%)
Uehara et al. 2014	116	13 (11,2%)	18 (15,5%)
Yeung et al. 2011	29	11 (37,9%)	8 (27,6%)
Espandar et al. 2011	9	1 (11,1%)	2 (22,2%)
Cheng et al. 2008	14	0 (0%)	5 (35,7%)
Tang et al. 2001	10	5 (50%)	3 (30%)
Schecter et al. 1982	33	2 (6,1%)	3 (9,1%)
Total	**340**	**50 (14,7%)**	**54 (15,9%)**

4. AETIOLOGY

NF of the upper extremity is usually attributed to the inoculation of the pathogen into the subcutaneous tissue, which can occur via any break in an epithelial or mucosal surface. A skin lesion may be found in up to 80% of the cases. Skin traumas, lacerations, burns, bites (from animals, insects, or even humans), iatrogenic invasive causes (venipuncture, percutaneous catheter injections, intra-articular injections, insulin injections, postoperative complications), chronic skin infections, fistulas, neglected wounds, ulcers, and abscesses have been incriminated as causative factors.[1] In Asia, the consumption of raw or undercooked seafood and fish fin injuries are often the source of the infection.[4,49] However, the most reported triggering cause, especially in the United States, is intravenous drug use (IVDU). According to Angoules et al., in a group of 392 patients suffering from NF of the extremities, multiple punctures in the affected site due to intravenous drug use were observed in 129 patients (32,9%) and trauma in 45 of them (11,5%).[20] Schecter et al. found that the entry portal was intravenous drug injection in 22 out of 33 patients with NF of the upper extremity (66,7%) and similarly, Gonzalez et al. pointed out the same in 10 out of 12 patients (83,3%).[5,10] Finally, Nawijn et al. in their retrospective cohort study consisting of 122 patients with upper extremity NF demonstrated that the main causes were intravenous drug use (35 cases, 28,7%), open wound (21 cases, 17,2%), blunt trauma (14 cases, 11,5%), bite (10 cases, 8,2%) and operative procedures (4 cases, 3,3%).[17]

Nevertheless, many times there is an absence of an obvious external portal of entry for pathogens. Idiopathic necrotizing fasciitis accounts for 11%-20% of all cases in various studies. This form has been assumed to arise from microbial entry through unrecognizable lesions of the epidermis. Blunt trauma may presumably be the cause; contact sports athletes can, therefore, be a susceptible group to this condition. Remote infections are another suggested aetiologic mechanism for idiopathic necrotizing fasciitis, possibly through hematogenous spread from distant sites (e.g., in cases with streptococcal pharyngitis).[1,7,8]

5. ASSOCIATED CONDITIONS

NF often occurs in patients predisposed to infection because of some underlying chronic disease. Some conditions are remarkably more often associated with the development of NF, especially diabetes mellitus, which is a risk factor that appears in 21% - 71% of the cases.[17,20,34,44,50] Other frequently encountered medical conditions include immunodeficiency, malignancy, chronic heart failure, peripheral vascular disease, pre-existing hypertension, liver cirrhosis and failure, chronic renal failure, respiratory insufficiency, an altered state of consciousness. The notable frequency and the great participation of intravenous drug use at the outset of NF of the upper extremity have already been underlined. As evidenced in several articles, some comorbid conditions such as smoking, chronic alcoholism, malnutrition, and obesity are also significant risk factors for the development of NF.[3,4,33] Uehara et al. in their database study containing 116 patients with upper extremity NF described the presence of diabetes mellitus in 38 patients (32,8%), renal failure in 22 patients (19%), lung dysfunction in 13 patients (11,2%), and liver cirrhosis or failure in 5 of them (4,3%).[18] It is worth mentioning that in up to 30% of all cases, NF can be manifested in previously healthy patients, without any predisposing factors.

The role of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) has also been pointed out, though the exact way in which they contribute to the emergence of NF remains somehow controversial. It is mainly believed that they act in two distinctive ways; on the one hand with their immunosuppressive effect, thus inhibiting the antibacterial defenses of the patient, and on the other hand by impeding some clinical manifestations of NF, like fever, obstructing that way the prompt diagnosis of NF.[4]

6. PATHOPHYSIOLOGY

The infection usually begins at the level of hypodermis and in the superficial fascia, as the outermost layers (dermis and epidermis) are not affected in the early stages. The development of NF is the result of the synergistic action between the virulence factors of the causative pathogens and the specific factors of the host (comorbidities, predisposing factors, level of the immune response). The offending organism(s) release toxins and initiate a cascade of endoge-

nous cytokine reaction that contributes to widespread tissue destruction. The speed at which the disease settles, the extension of the infection, and the concomitant necrosis are defined by the different bacteria and the enzymes they produce. The presence of a hypoxic environment favors the growth of anaerobic bacteria. The resulting necrosis of the hypodermis and the superficial fasciae is mainly related to the direct effect of the bacterial enzymes that destroy the tissues and the fat and secondarily to vascular reasons. Invasive pathogen(s) cause thrombosis to the nutrient vessels that are in the epidermis, leading to extensive tissue ischemia, aggravated by the presence of oedema. Subsequently, tissue ischemia promotes infectious dissemination that eventually leads to skin necrosis at a later stage. This is also one of the reasons that explain the intense pain phenomena that are usually observed, as well as the signs of regional hypoesthesia and anesthesia that sometimes are manifested, especially when some cutaneous or subcutaneous nerve branches are also affected. The existing fascial and hypodermic necrotic spread is nearly always greater than the apparent overlying skin changes, which are usually confirmed later in the operating room. Additionally, during the surgical cleaning, there is an effusion of a stinky, viscous fluid, commonly described as "dishwater pus" which is the result of the action of bacterial toxins and massive tissue destruction. Even though in most the cases the underlying muscles are spared, sometimes they are also affected, particularly when there is a delay in the surgical procedures and in the commencement of the debridement. Lymphangitis and lymphadenopathy are rarely encountered due to thrombosis of the lymphatic vessels. The gas formed by anaerobic bacteria may lead to crepitus.[4]

7. MICROBIOLOGY

Cultures obtained from the site of injury in the operating room during surgical debridement are indispensable, tend to give positive results in 80% of the cases, and remain the key to the microbiological diagnosis of NF, which is achieved in approximately 75% of all cases. Blood cultures turn out to be positive only in 25% of the cases. From a microbiological point of view, NF can be classified into four types based on microbiological findings and culture results.[3,4,6,24,29,51]

Type 1, also known as the polymicrobial/synergistic type, is the most encountered type, constituting 70% to 90% of all cases. It tends to affect elderly and chronically ill/immunocompromised patients or patients with several comorbidities, such as diabetes mellitus, often after surgical procedures. It results from a mixed aerobic and anaerobic flora with two or more pathogens being implicated (on average 4,4 different species are found).

Type 2, also known as the monomicrobial type caused by Gram-positive organisms, comes second in terms of frequency, accounting for 10% to 15% of all cases, but is the most recurrent type in upper limb NF. It tends to affect previously healthy individuals of any age without underlying illness, presents a predilection for the extremities, typically occurs after small incisions, and is believed to be highly correlated with the use of NSAIDs. It is predominantly due to group-A beta-hemolytic Streptococcus (Streptococcus pyogenes) and occasionally to Staphylococcus aureus. By secreting toxins that cause leukocyte destruction and tissue necrosis, S. aureus is usually found in the fulminant form of NF, is associated with an elevated risk of the toxic syndrome, and is difficult to manage, especially when methicillin-resistant S. aureus (MRSA) is involved. Unfortunately, the incidence of monomicrobial infections caused by S. aureus has increased over the past decade.

Type 3 includes single organism infections involving the Clostridium species or Gram-negative bacteria. Clostridium species are anaerobic bacteria with C. perfringens being the most common of them. Clostridium infections are more frequent among drug addicts, usually result from external injuries (deep wounds or crush injuries causing local devascularization) or surgical wounds, and are related to higher mortality and amputation rates if not properly treated. This Type also includes marine-related organisms, such as Vibrio vulnificus which is frequently isolated in Asia and is linked to the consumption of raw or undercooked seafood and fish fin injuries. Aeromonas hydrophilia, usually found in freshwater or low salinity water and in the soil, also produces infections that belong to this group. They tend to spread extremely rapidly and typically include hemorrhagic blisters, lesions, and purpuric necrosis.

Type 4 includes fungal infections, commonly from Candida spp. and Zygomycetes. These infections usually occur after trauma, mainly affect immunocompromised patients, and demonstrate an aggressive and rapidly extensive clinical course.

It is essential to highlight that there is a big discrepancy between different studies depending on their country of origin, because of the variation of the endemic microbial flora of each geographic area and the nonidentical habits of each people. Therefore, in studies from countries where people tend to contact contaminated seawater, raw or undercooked seafood, and are susceptible to fish fin injuries, we observed a prevalence of marine-related pathogens such as Vibrio vulnificus and other Gram-negative organisms. Indeed, in a retrospective study from Hong Kong by Yeung et al., 8 out of 29 patients (27,6%) were infected by Vibrio spp. and in total 12 of them (41,4%) developed Type 3 NF of the upper limb.[44] Similarly, Tang et al. in a retrospective study containing 10 patients with upper extremity NF coming from Hong Kong, found 5 infections from Vibrio spp. (50%) and a total of 6 cases with Type 3 NF (60%).[45] Kuo et al. conducted a retrospective study consisting of 67 cases from Taiwan with NF of the limbs caused by Vibrio vulnificus, which is quite rare in other areas.[49]

From the reviewed literature, 30 studies including 255 patients with upper limb NF provided detailed information about culture results.[5,6,8,10,13–17,21–24,26–33,35–39,41,43–45] The cultures obtained were positive in 232 patients (91%). An explicit predominance of Type 2 NF can be noticed, confirming the divergence of upper extremity NF compared to NF affecting other anatomic sites in terms of microbiology. Group A beta-hemolytic Streptococcus was the most

Table 3. Culture results, sorting based on NF Types and isolated pathogens from patients with upper extremity NF

	Total n=255 (100%)
Patients with specific organisms isolated (positive cultures), n (%)	232 (91,0%)
Type 1	60 (25,9%)
Type 2	126 (54,3%)
Type 3	43 (18,5%)
Type 4	3 (1,3%)
Group A beta-haemolytic Streptococcus	98 (42,2%)
Other Streptococcus species	48 (20,7%)
Staphylococcus aureus Of which Methicillin-resistant Staphylococcus aureus (MRSA)	45 (19,4%) 21 (9,1%)
Other Staphylococcus species	16 (6,9%)
Bacteroides spp.	10 (4,3%)
Enterococci spp.	11 (4,7%)
Escherichia coli	3 (1,3%)
Clostridium spp.	10 (4,3%)
Vibrio spp.	17 (7,3%)
Klebsiella spp.	7 (3,0%)
Pseudomonas spp.	4 (1,7%)
Aeromonas spp.	3 (1,3%)
Other	38 (16,4%)
Patients without specific organisms isolated (negative cultures)	**23 (9,0%)**

cultured pathogen, grown in 98 cases (42,2%), followed by other Streptococcus species (20,7%) and Staphylococcus aureus (19,4%). Other aerobic and anaerobic microorganisms were less often noticed. Table 3 exhibits the aggregate culture results collected, concerning upper limb NF.

8. DIAGNOSIS

8.1. PHYSICAL EXAMINATION FINDINGS

A review of the literature reveals a variety of different clinical presentations, mainly depending on the development of the infection. Consequently, two groups of signs and symptoms may be considered: the early and the advanced. As the pathological process begins in the deep tissue and fascia, early clinical findings may be subtle. Thus, the clinical diagnosis of necrotizing fasciitis remains challenging, especially in the early stages, as it can mimic other infections such as cellulitis, abscess, tenosynovitis, or gout arthritis.[4,16,33,52]

Angoules et al. In a systematic review including 317 extremities (102 upper limbs) with necrotizing fasciitis reported that erythema (73%), pain (63%), and oedema (49%) were the most common clinical findings followed by induration of the skin, purulence, fluctuance, local warmth and bullae.[20]

In another study, Yeung et al. retrospectively reviewed 29 patients with upper extremity necrotizing infections and reported that erythema, tenderness, and pain out of proportion to the clinical findings, were the most prevalent symptoms in the early stages. Later, as the disease develops, hemorrhagic bullae, skin anesthesia or crepitus, and gangrenous changes may appear (the classical "hard signs" of the disease).[44]

Furthermore, Schecter et al. In a study of 33 cases of upper extremity necrotizing fasciitis concluded that all patients had erythema, oedema, tenderness, and warmth while bullae, crepitus, and skin necrosis were less common findings.[10]

Gonzalez et al. also described similar physical examination findings in 12 cases of upper extremity necrotizing infection while Singh et al. in a series of 48 cases (14% involving the upper extremity) reported pain, erythema, swelling, and tenderness as the most common signs and symptoms.[2,5]

Systemic manifestations should not be overlooked, although in cases of upper extremity necrotizing infections, they are not common, and the patients may be systematically well. Fever, tachycardia, and hypotension are alarming signs. Symptoms of septic shock or multiple organ failure may appear in the late stages and as a result, the patient demonstrates hypotension, elevated white blood cell count, coagulopathy, weakness, changes in mental status, and metabolic acidosis.[2,4,44]

Extreme awareness is required in cases of the acute/fulminant type of the disease because of the subtle early course and the rapid progress. Iwata et al. described 5 cases of fulminant type, with a lack of skin inflammatory signs such as redness and warmth, while purpura was the only initial clinical sign.[32] Kato et al. have also described a case of the fulminant type with petechiae as the first clinical sign.[53] Therefore, it is important to suspect necrotizing fasciitis when the patient presents with purpura or petechiae and a lack of inflammatory skin signs at the onset.

8.2. BEDSIDE AND LABORATORY TESTS

Laboratory results during the process of this disease may not always be specific. However, certain laboratory findings can help the clinical doctor to differentiate necrotizing fasciitis from other skin infections. Leukocytosis is a common finding in these patients and a white blood cell count >20000/L is strongly suggestive of the disease. Pathological laboratory values that represent the failure of one or more organs is also typically present in these patients. Elevated blood urea and serum creatinine reflect renal failure while high levels of serum creatine kinase are noted in severe sepsis or Multiple Organ Dysfunction Syndrome.[2,52]

Some laboratory-based scoring systems have been proposed for establishing the early diagnosis of necrotizing fasciitis and determining the prognosis. Laboratory Risk Indicator for Necrotizing Fasciitis score (the LRINEC score), proposed by Wong et al., is one of them.[12] This model uses the laboratory values of c-reactive protein, white blood cells count, hemoglobin, creatinine, glucose, and sodium. A score of at least 6 should raise the suspicion of necrotizing

fasciitis while a value of 8 or more suggests that there is a 75% chance of having the disease. On the other hand, a meta-analysis performed by Bechar et al. assessing the validity of the LRINEC score showed that clinical cases of NF involving the extremities have a more subtle presentation and delayed onset of sepsis compared to the cases of groin or trunk.[54] Another prospective cohort study by Hsiao et al, including 106 patients with NF and 825 patients with cellulitis, concludes that the LRINEC score may not be an accurate tool to detect the NF and differentiate this disease from cellulitis.[55] Another system that was used by Yeung et al. in their study is the ALERTS (Abnormal Liver Function, Extent of infection, Renal impairment, Thrombocytopenia, and Shock) numerical score, which is effective in predicting associated mortality.[44] Fournier's Gangrene Severity Index (FGSI) is another scoring system that is effective in determining the mortality risk and the need for immediate surgical debridement.[4]

Two bedside tests that can be used by the clinicians, as supplementary diagnostic tools, in cases of ambiguous diagnosis are the "finger test" and the frozen section biopsy.

The finger test, as proposed by Andreasen et al., is performed under local anesthesia, by which, a 2cm incision is made down to the deep fascia followed by exploration with the index finger. The presence of "dishwater pus", along with the lack of bleeding and lack of tissue resistance in blunt dissection are findings associated with NF.[56] Frozen section biopsy may also be a reliable diagnostic tool that can be performed by local anesthesia and can promote early diagnosis of necrotizing fasciitis. Stamenkovic et al., in their study of 19 cases of NF, described the procedure and the histological criteria for establishing the NF diagnosis which includes polymorphonuclear infiltration, thrombosis of the perforating vessels, necrosis of the fascia, and absence of muscle involvement.[57] It is also highlighted, in the same study, that this method is of value only early in the development of the infection before the necrotizing process extends to all the soft tissue layers.

8.3. IMAGING

Plain radiographs have low specificity and sensitivity in recognizing NF and are unremarkable until the infection is advanced, but they can show the gas formation and soft tissue swelling.[58] Care must be taken to differentiate necrotizing fasciitis from an extensive subcutaneous emphysema.[59]

Advanced imaging is an important adjunct to clinical and laboratory examination and can provide invaluable information to establish the diagnosis and plan the surgical treatment. Wysoki et al., in a retrospective study of 20 patients with necrotizing fasciitis, reported that the hallmarks of necrotizing fasciitis are asymmetrical thickening of deep fascial layers and soft tissue gas. Furthermore, fat infiltration, focal fluid collections, and muscle enhancement can be appreciated.[43] In another study, McGillicuddy et al. noted several CT findings that suggest necrotizing fasciitis, which included fascial air, muscle/fascial oedema, fluid tracking, lymphadenopathy, and subcutaneous oedema.[60]

MR imaging can also help determine the extent of necrosis and differentiate necrotizing from non-necrotizing fasciitis.[61] Intravenous administration of gadolinium-based contrast material can distinguish whether a muscle is viable or necrotic and delineate abscesses. Schmid et al. in their study highlight the high sensitivity of MRI regarding the diagnosis of NF with its characteristic findings of thickening and fluid collections along deep fascial sheaths.[62] In other studies, the sensitivity and specificity of MRI in diagnosing necrotizing fasciitis have been reported up to 100% and 86% respectively.[63] From another perspective, although MRI scans have high sensitivity and specificity in detecting NF, they consume a considerable amount of time and may further delay the appropriate treatment.[3]

Ultrasound imaging, which has rarely been reported in the literature, is a less expensive diagnostic tool that can aid in the early diagnosis of the disease. Shyy et al. present two cases of upper extremity NF and report that the main sonographic findings are thickening of the subcutaneous tissue, perifascial fluid, air within the soft tissue, and deep fascia with an irregular or distorted appearance.[37] In another case report of upper extremity NF, Wronski et al. note that increased echogenicity of subcutaneous fat tissue, perifascial fluid, and a gas layer just above the deep fascia consists of the main sonographic findings.[34] Yen et al. in a prospective observational review of 60 patients with clinically suspected NF conclude that ultrasonography has a sensitivity of 88.2% and specificity of 93.3% regarding the diagnosis of NF.[64] However, there is no perfect imaging modality that has been validated to date that can be used to establish the diagnosis of necrotizing fasciitis.

9. TREATMENT

The goal of treatment is the eradication of the infection while maintaining the maximum possible function of the extremity. Early recognition, appropriate antibiotic treatment, and surgical intervention are mandatory.

9.1. MEDICAL MANAGEMENT

Because of the destruction of soft tissue structures, that characterizes necrotizing fasciitis, the adequate delivery of antibiotics in the infection site is compromised. Therefore, treatment with antibiotics alone is of little value in the management of the disease. However, they play an important role combined with surgical debridement and that is the reason why the immediate administration of broad-spectrum antibiotics in patients with suspected necrotizing fasciitis is justified.[4] The empirical antibiotic treatment depends on the microbiological classification of the disease and is based on history, Gram stain, and cultures.[65] One study by Elliot et al. assessing 198 patients reported an average of 4.5 microorganisms per infection and they concluded that the initial regimen should include antibiotics effective against aerobic gram-positive cocci, gram-negative rods, and a variety of anaerobes.[66]

An update of the guidelines for the treatment of skin and soft tissue infections published by the Infectious Dis-

eases Society of America (IDSA) in 2014, states that the best choice for a mixed infection is a combination of ampicillin-sulbactam plus ciprofloxacin plus clindamycin. For monomicrobial necrotizing fasciitis, caused by group A streptococci, they report that both clindamycin and penicillin should be used.[67]

Yeung et al., assessing 29 patients with upper limb necrotizing fasciitis, recommend the administration of quinolones and Augmentin as empirical treatment for necrotizing fasciitis, and penicillin for group A streptococcus infections.[44] In another study, which included 20 patients with extremity NF (2 upper limbs), the most common empiric antibiotic treatment was Meropenem plus clindamycin.[6]

For type I infections (polymicrobial/synergistic) anaerobic coverage is very important; metronidazole, clindamycin, or carbapenems are effective. For type II infections antibiotics against Staphylococcus aureus and Streptococcus pyogenes should be administrated; therefore, penicillin, first or second-generation cephalosporins, and macrolides can be used, while some researchers propose the additional usage of clindamycin along with the beta-lactam agent.[30] Type III infections can be managed with penicillin and clindamycin, which cover the Clostridium species and finally, type IV infections should be treated with anti-fungal agents such as amphotericin B and fluoroconazoles. If infection by Vibrio species is suspected, combination therapy with third-generation cephalosporins and doxycycline is recommended.[49]

The empirical antibiotic treatment can always be readjusted according to the results of tissue/blood cultures and sensitivity patterns and should be continued until the infection is controlled. Elliot et al. in their study state that most patients received antibiotic therapy for an average of 12.8 days while other studies propose the administration of the antibiotic agents for up to 5 days after local signs and symptoms have resolved.[4,66] Clinicians should not neglect the fact that patients with NF often present in a condition of sepsis or septic shock; therefore, analgesia, aggressive fluid replacement, nutritional support, and blood pressure support are of utmost importance.[20]

Intravenous immunoglobin (IVIG) as antitoxin therapy has also been described recently in literature but there is no strong evidence, to our knowledge, that suggests their beneficial effect in the management of the disease.[4,31]

9.2. SURGICAL MANAGEMENT

Appropriate and early surgical debridement remains the cornerstone of treatment in cases of necrotizing fasciitis. The goal is to remove all the necrotic tissues while preserving the motor and sensory function of the extremity. Many studies support that early and aggressive surgical debridement increases the rate of survival and that delay in surgical treatment greater than 24h since admission, affects the mortality rate. Kuo et al., studying 67 cases of necrotizing fasciitis (74.7% regarding upper extremities), report that delay of more than 24h from injury to surgery was significantly associated with increased mortality.[15] Sunderland and Friedrich, after reviewing a series of studies, conclude that delay in surgical debridement greater than 24h from admission is the most important predictor of mortality.[7] In another study of 65 patients with NF (40% concerning upper and lower limbs) McHenry found that those who died in hospital had a longer mean time interval (90 hours) from admission to surgery than those who survived (25 hours).[68] All these findings demonstrate the important role of early and aggressive surgical management.

Often, a series of debridement and close monitoring of the progression of the disease is mandatory to control the infection, and not so rarely do surgeons end up amputating the limb. Cheng et al., in a retrospective review, identified 14 patients with upper limb NF that underwent an average of two surgical debridements and reported a mortality rate of 35,7%. None of the patients was submitted to amputation but a split-thickness skin-graft reconstruction was required in 7 out of 9 survivors.[15] In another study, regarding 31 patients with upper extremity NF, Hankins and Southern found that the median number of operations for each patient was 2,04 (range 0-7) while Singh et al., report an average number of 2,57 procedures per patient in their study of 48 cases (14% upper extremity infections).[2,30] In a previously reported study, Yeung et al. stated that the mean value of debridement per patient was 2 and the mortality rate 28%. In all, 11 amputations were performed: three above-elbow, two below-elbow, and six entailed digits. 10 patients had their wounds treated with skin grafts and 4 with flap coverage.[44]

Sharma and colleagues proposed a risk-adjusted scoring system that surgeons can use to anticipate which infections may require additional debridement and plan their operative schedule. This scoring system is based on the infection's known characteristics- patient factors, microbiology, infection site- and the researchers recommend additional wound debridement with a score of a total of 12 points or greater.[69]

The risk factors for increased mortality rate and extremity amputation have been also described in the literature. Anaya et al., in a retrospective review of 166 patients (58% extremity infections), identified WBC >30000, creatinine >2mg/dl, heart disease, and clostridial infection as independent predictors of mortality. Independent predictors of limb loss were found to be clostridial infections, heart disease, and shock.[19] Tang et al., studying 12 patients with upper limb NF, suggested the criteria for possible amputation that included high anesthesia risk, necrotic underlying muscles, extensive infection with a large area of necrosis, septic shock requiring ionotropic support, and vascular insufficiency. Considering these criteria were performed 5 amputations, ranging from digital amputation to shoulder disarticulation.[45] In another retrospective cohort study of 122 patients with upper extremity NF, Nawijn and colleagues found that ASA (American Society of Anesthesiologists) classification and base deficit at admission can predict the prognosis of patients, while a necrotizing infection of the non-dominant arm is a risk factor for amputation. They also stated that necrotizing infections of the upper limb have a relatively low mortality rate, but a relatively high amputation rate compared with cases of NF regarding

other anatomical sites.[17] Uehara et al. in their study of 116 patients with upper extremity NF report that sepsis and diabetes mellitus are associated with a higher rate of amputations, while renal dysfunction and advanced age are associated with higher rates of in-hospital mortality.[18]

Management of the large, complex wounds that often result after surgical debridement of upper limb necrotizing fasciitis, can pose serious challenges even for experienced surgeons. Especially in patients who will be submitted in reconstruction with flaps or free tissue transfers, maintaining the wound clean and protecting it from desiccation is of utmost importance. The use of negative pressure wound therapy (NPWT) has been widely reported in the literature and many studies support its beneficial effect on wound healing. Corona et al., in their study of 20 patients with extremity NF (40% upper limb) used the above-mentioned technique for surgical wound management in 75% of the cases and reported a mortality rate of 30% and four amputations. Although they could not prove a clear improvement in results, they support the application of NWPT for three reasons: improved wound isolation, reduced nursing time, and patient comfort.[6] In another study, Huang assessed the efficacy of NPWT in patients with limp NF. They compared two groups of 12 patients. The first group was treated with vacuum-assisted wound closure (VAC) and the other group with conventional wet-to-dry dressings. They noticed that although the patient cost was not significantly different, the VAC technique could decrease the morbidities associated with wound care.[70] In another case report, Collins presents the successful, concomitant use of NWPT, ciNPT (closed incision negative pressure therapy), and hydro polymer foam dressings for wound management of an upper extremity necrotizing infection.[14]

Reconstruction of the soft tissue deficits post debridement using free tissue transfers is poorly mentioned in the literature. Gawaziuk et al., in a retrospective review of 12 patients with NF (58,8% involving upper extremity) treated with FTT and 212 patients (18,9% upper extremity) treated with no FTT, concluded that FTT was not associated with worse outcomes such as increased rate of amputation, prolonged hospital stay or more operations and remains a feasible option.[28] The main flaps that have been described are anterolateral thigh, latissimus dorsi, radial forearm, and groin.[25,28]

From another perspective, Mattison et al., studied the clinical and economic benefits of single-specialty management of upper extremities NF. The researchers, retrospectively reviewed 54 cases with upper extremity necrotizing fasciitis, concluded that patients managed primarily by the plastic surgery team demonstrated higher APACHE II scores compared to patients managed by multiple services. In addition, they noted that the patients admitted directly to a plastic surgery team had shorter average lengths of hospital and ICU stays, and decreased the total number of procedures, resulting in decreased hospital charges. Therefore, they advocate the single-specialty management of NF, and in cases that is not possible, they propose

improved communication between the teams initially managing the patient and the reconstructive team.[71]

10. CONCLUSION

Necrotizing fasciitis is a rare but, potentially, life-threatening condition with high mortality rates. Upper limp is a relatively uncommon site of infection and the literature pertaining to their management is limited in case reports, small case series, and small retrospective studies. For this reason, we conducted a review of the current literature, to gather the findings of various studies, exhibit its basic characteristics, and subline the differences that necrotizing fasciitis of the upper extremity presents compared to other anatomic sites. First, the relatively lower mortality rates of upper limb NF were confirmed. Interruption of the skin integrity from events, such as trauma, constitutes the most common causative factor and if the upper extremity is concerned, intravenous drug use (IVDU) is the most frequent among them. Moreover, the increasing intravenous use of recreational substances explains the resultant growth in the incidence of upper limb NF. Numerous conditions are associated with this pathology, such as diabetes mellitus, immunodeficiency, malignancy, renal and liver failure, and peripheral vascular disease. Depending on the pathogenic microorganism that is responsible for this type of infection, NF can be categorized into four distinct types. Contrary to NF of other anatomic sites that are usually due to mixed polymicrobial flora, NF of the upper extremity is most attributed to monomicrobial infection from Gram-positive pathogens (predominantly Group A beta-hemolytic Streptococcus and secondarily Staphylococcus aureus). The clinical course of the disease may vary and, especially, the cases involving the upper extremities may have the more subtle presentation and delayed onset of sepsis. A delay in diagnosis may prove to be fatal, hence, the clinicians must have a high index of suspicion and must be able to differentiate this condition from other necrotizing soft tissue infections. Laboratory-based scoring systems, imaging modalities, and histological examination can be useful tools in establishing the diagnosis, which may be secured by explorative surgery. Antibiotics administration and early and aggressive surgical debridement have been proven to affect the mortality rates and remain the cornerstone of treatment. In some cases, a series of debridement is mandatory to control the disease and, not rarely, the surgeon may be obliged to amputate the limp to preserve the life of the patient. Postoperative management of the surgical wound is another important matter and many new promising technologies have been proposed in literature. Despite the surgical advances, the pharmacological improvement and the intensive care developments, necrotizing fasciitis remains a condition with high mortality and morbidity rates and implementation of new management technologies does not seem to affect the outcome. Consequently, necrotizing fasciitis of the upper extremity remains a field still investigated in a relatively low level, and we hope that this study could function as a stimulus for new studies.

FUNDING

No funding was received.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors made a substantial contribution and reviewed the document carefully prior to submission. KD, KC, PC, and KC designed and coordinated the study. All aforementioned authors along with TK and PP performed the authorship of the initial draft. KD, KC, PC, KC, TK, and PP significantly contributed to the linguistic formatting and correction of the manuscript, revised it critically for important intellectual content, and was responsible for the final proofreading of the article.

Submitted: December 10, 2021 EDT, Accepted: March 28, 2022 EDT

REFERENCES

1. Whitaker CM, Low S, Gorbachova T, Raphael JS, Williamson C. Imaging and Laboratory Workup for Hand Infections. *Hand Clin*. 2020;36(3):285-299. doi:10.1016/j.hcl.2020.03.002

2. Misiakos EP, Bagias G, Patapis P, Sotiropoulos D, Kanavidis P, Machairas A. Current Concepts in the Management of Necrotizing Fasciitis. *Front Surg*. 2014;1. doi:10.3389/fsurg.2014.00036

3. Gawaziuk JP, Liu T, Sigurdson L, et al. Free tissue transfer for necrotizing fasciitis reconstruction: A case series. *Burns*. 2017;43(7):1561-1566. doi:10.1016/j.burns.2017.04.007

4. Lille ST, Sato TT, Engrav LH, Foy H, Jurkovich GJ. Necrotizing soft tissue infections: Obstacles in diagnosis. *J Am Coll Surg*. 1996;182(1):7-11.

5. Neeki MM, Dong F, Au C, et al. Evaluating the Laboratory Risk Indicator to Differentiate Cellulitis from Necrotizing Fasciitis in the Emergency Department. *West J Emerg Med*. 2017;18(4):684-689. doi:10.5811/westjem.2017.3.33607

6. Gonzalez MH, Kay T, Weinzweig N, Brown A, Pulvirenti J. Necrotizing fasciitis of the upper extremity. *J Hand Surg Am*. 1996;21(4):689-692. doi:10.1016/s0363-5023(96)80029-3

7. Wronski M, Slodkowski M, Cebulski W, Karkocha D, Krasnodebski IW. Necrotizing fasciitis: Early sonographic diagnosis. *J Clin Ultrasound*. 2011;39(4):236-239. doi:10.1002/jcu.20766

8. Melillo A, Addagatla K, Jarrett NJ. Necrotizing Soft Tissue Infections of the Upper Extremity. *Hand Clin*. 2020;36(3):339-344. doi:10.1016/j.hcl.2020.03.007

9. Aizawa T, Nakayama E, Kubo S, Nakamura K, Azuma R, Kiyosawa T. Severe Functional Loss of the Hand due to Necrotizing Fasciitis with Underlying Vasculitis Neuropathy. *J Hand Microsurg*. 2019;11(S 01):S42-S45. doi:10.1055/s-0039-1683945

10. Bluman EM, Mechrefe AP, Fadale PD. Idiopathic Staphylococcus aureus necrotizing fasciitis of the upper extremity. *J Shoulder Elb Surg*. 2005;14(2):227-230. doi:10.1016/j.jse.2004.06.003

11. Anaya DA, McMahon K, Nathens AB, Sullivan SR, Foy H, Bulger E. Predictors of mortality and limb loss in necrotizing soft tissue infections. *Arch Surg*. 2005;140(2):151-157. doi:10.1001/archsurg.140.2.151

12. Hsiao CT, Chang CP, Huang TY, Chen YC, Fann WC. Prospective validation of the laboratory risk indicator for necrotizing fasciitis (LRINEC) score for necrotizing fasciitis of the extremities. *PLoS ONE*. 2020;15(1):e0227748. doi:10.1371/journal.pone.0227748

13. Shyy W, Knight RS, Goldstein R, Isaacs ED, Teismann NA. Sonographic findings in necrotizing fasciitis: Two ends of the spectrum. *J Ultrasound Med*. 2016;35(10):2273-2277. doi:10.7863/ultra.15.12068

14. Pessa ME, Howard RJ. Necrotizing fasciitis. *Surg Gynecol Obstet*. 1985;161(4):357-361. doi:10.1002/9781118482117.ch27

15. Zarb Adami R, Odeyinde S, Hazari A. Isolated digital necrotizing fasciitis: An unusual presentation. *J Hand Surg Eur Vol*. 2017;42(7):747-748. doi:10.1177/1753193416676423

16. Espandar R, Sibdari SY, Rafiee E, Yazdanian S. Necrotizing fasciitis of the extremities: A prospective study. *Strateg Trauma Limb Reconstr*. 2011;6(3):121-125. doi:10.1007/s11751-011-0116-1

17. Angel MF, Zhang F, Jones M, Henderson J, Chapman SW. Necrotizing fasciitis of the upper extremity resulting from a water moccasin bite. *South Med J*. 2002;95(9):1090-1094. doi:10.1097/00007611-200209000-00038

18. Wysoki MG, Santora TA, Shah RM, Friedman AC. Necrotizing fasciitis: CT characteristics. *Radiology*. 1997;203(3):859-863. doi:10.1148/radiology.203.3.9169717

19. Balakrishnan C, Erella VS, Vandemark S, Mussman J. Groin Flap for Salvage of Upper Extremity Following Necrotizing Fasciitis: A Case Report. *Can J Plast Surg*. 2005;13(3):153-155. doi:10.1177/229255030501300301

20. Ginting KE, Caparelli M, Kundu N. Necrotizing Soft Tissue Infection After Intravenous Drug Injection: A Multidisciplinary Approach to Surgical Management at a Community Hospital. *Am Surg*. 2020;86(9):1215-1217. doi:10.1177/0003134820933596

21. Hankins CL, Southern S. Factors that affect the clinical course of group A ß-haemolytic streptococcal infections of the hand and upper extremity: A retrospective study. *Scand J Plast Reconstr Surg Hand Surg*. 2008;42(3):153-157. doi:10.1080/02844310802038223

22. Schecter W, Meyer A, Schecter G, Giuliano A, Newmeyer W, Kilgore E. Necrotizing fasciitis of the upper extremity. *J Hand Surg Am*. 1982;7(1):15-20. doi:10.1016/s0363-5023(82)80006-3

23. Bento-Rodrigues J, Judas F, Pedrosa Rodrigues J, et al. Fasceíte necrosante após mobilização e infiltração intrarticular do ombro com betametasona. *Acta Med Port*. 2013;26(4):456-459.

24. Stamenkovic I, Lew PD. Early Recognition of Potentially Fatal Necrotizing Fasciitis. *N Engl J Med*. 1984;310(26):1689-1693. doi:10.1056/nejm198406283102601

25. Andreasen TJ, Green SD, Childers BJ. Massive infectious soft-tissue injury: Diagnosis and management of necrotizing fasciitis and purpura fulminans. *Plast Reconstr Surg*. 2001;107(4):1025-1035. doi:10.1097/00006534-200104010-00019

26. Bechar J, Sepehripour S, Hardwicke J, Filobbos G. Laboratory risk indicator for necrotising fasciitis (LRINEC) score for the assessment of early necrotising fasciitis: A systematic review of the literature. *Ann R Coll Surg Engl*. 2017;99(5):341-346. doi:10.1308/rcsann.2017.0053

27. Uehara K, Yasunaga H, Morizaki Y, Horiguchi H, Fushimi K, Tanaka S. Necrotising soft-tissue infections of the upper limb: Risk factors for amputation and death. *Bone Jt J*. 2014;96-B(11):1530-1534. doi:10.1302/0301-620x.96b11.34888

28. Kamal RN, Paci GM, Born CT. Extensive subcutaneous emphysema resembling necrotizing fasciitis. *Orthopedics*. 2013;36(5):671-675. doi:10.3928/01477447-20130426-34

29. Sharma K, Mull A, Friedman J, et al. Development and Validation of a Prognostic, Risk-Adjusted Scoring System for Operative Upper-Extremity Infections. *J Hand Surg Am*. 2020;45(1):9-19. doi:10.1016/j.jhsa.2019.10.010

30. Sunderland IR, Friedrich JB. Predictors of Mortality and Limb Loss in Necrotizing Soft Tissue Infections of the Upper Extremity. *J Hand Surg Am*. 2009;34(10):1900-1901. doi:10.1016/j.jhsa.2009.08.018

31. Collins J. Surgical intervention and customised dressings in an extremity wound caused by necrotising fasciitis: A case study. *J Wound Care*. 2019;28(Sup5):S21-S27. doi:10.12968/jowc.2019.28.sup5.s21

32. Paz Maya S, Dualde Beltrán D, Lemercier P, Leiva-Salinas C. Necrotizing fasciitis: An urgent diagnosis. *Skeletal Radiol*. 2014;43(5):577-589. doi:10.1007/s00256-013-1813-2

33. Atiyeh BC, Zaatari AM. Necrotizing fasciitis of the upper extremity. *J Emerg Med*. 1994;12(5):611-613. doi:10.1016/0736-4679(94)90412-x

34. McHenry CR, Piotrowski JJ, Petrinic D, Malangoni MA. Determinants of mortality for necrotizing soft-tissue infections. *Annals of Surgery*. 1995;221(5):558-565. doi:10.1097/00000658-199505000-00013

35. McGillicuddy EA, Lischuk AW, Schuster KM, et al. Development of a computed tomography-based scoring system for necrotizing soft-tissue infections. *J Trauma - Inj Infect Crit Care*. 2011;70(4):894-899. doi:10.1097/ta.0b013e3182134a76

36. Singh G, Bharpoda P, Reddy R. Necrotizing Fasciitis: A Study of 48 Cases. *Indian J Surg*. 2015;77(S2):345-350. doi:10.1007/s12262-013-0835-2

37. Theodorou SJ, Theodorou DJ, Resnick D. Imaging findings of complications affecting the upper extremity in intravenous drug users: Featured cases. *Emerg Radiol*. 2008;15(4):227-239. doi:10.1007/s10140-008-0709-2

38. Nazerani S, Maghari A, Kalantar Motamedi MH, Ardakani JV, Rashidian N, Nazerani T. Necrotizing fasciitis of the upper extremity, case report and review of the literature. *Trauma Mon*. 2012;17(2):309-312. doi:10.5812/traumamon.6398

39. Ogilvie CM, Miclau T. Necrotizing soft tissue infections of the extremities and back. *Clin Orthop Relat Res*. 2006;447:179-186. doi:10.1097/01.blo.0000218734.46376.89

40. Schmid MR, Kossmann T, Duewell S. Differentiation of necrotizing fasciitis and cellulitis using MR imaging. *Am J Roentgenol*. 1998;170(3):615-620. doi:10.2214/ajr.170.3.9490940

41. Angoules AG, Kontakis G, Drakoulakis E, Vrentzos G, Granick MS, Giannoudis PV. Necrotising fasciitis of upper and lower limb: a systematic review. *Injury*. 2007;38(Suppl 5). doi:10.1016/S0020-1383(07)80005-2

42. Hakkarainen TW, Kopari NM, Pham TN, Evans HL. Necrotizing soft tissue infections: Review and current concepts in treatment, systems of care, and outcomes. *Curr Probl Surg*. 2014;51(8):344-362. doi:10.1067/j.cpsurg.2014.06.001

43. Mikić D, Takić-Radovanović T, Luković M, et al. Teška forma streptokoknog nekrotizujućeg fasciitisa ruke - Dijagnostički i terapijski izazov. *Vojnosanit Pregl*. 2015;72(8):745-749. doi:10.2298/vsp140724069m

44. Crosby SN, Snoddy MC, Atkinson CT, Lee DH, Weikert DR. Upper extremity myonecrosis caused by edwardsiella tarda resulting in transhumeral amputation: Case report. *J Hand Surg Am*. 2013;38(1):129-132. doi:10.1016/j.jhsa.2012.10.009

45. Yeung YK, Ho ST, Yen CH, et al. Factors affecting mortality in Hong Kong patients with upper limb necrotising fasciitis. *Hong Kong Med J*. 2011;17(2):96-104.

46. Chen LL, Tayban K, Caravanos C, Shaz D, Halpern NA. Necrotizing fasciitis associated with malignancy. *J Am Assoc Nurse Pract*. 2020;32(2):109-112. doi:10.1097/jxx.0000000000000251

47. Ito M, Takahashi N, Saitoh H, et al. Successful treatment of necrotizing fasciitis in an upper extremity caused by Clostridium perfringens after bone marrow transplantation. *Intern Med*. 2011;50(19):2213-2217. doi:10.2169/internalmedicine.50.5829

48. Wong CH, Wang YS. The diagnosis of necrotizing fasciitis. *Curr Opin Infect Dis*. 2005;18(2):101-106. doi:10.1097/01.qco.0000160896.74492.ea

49. Mattison G, Leis AR, Gupta SC. Single-specialty management and reconstruction of necrotizing fasciitis of the upper extremities: Clinical and economic benefits from a case series. *Ann Plast Surg*. 2014;72(SUPPL. 1). doi:10.1097/SAP.0000000000000173

50. Dias L, Markeson D, Evgeniou E, Misra A. Necrotising fasciitis of the thumb. *BMJ Case Rep*. Published online 2012. doi:10.1136/bcr-2012-006380

51. Nawijn F, Verhiel SHWL, Lunn KN, Eberlin KR, Hietbrink F, Chen NC. Factors Associated with Mortality and Amputation Caused by Necrotizing Soft Tissue Infections of the Upper Extremity: A Retrospective Cohort Study. *World J Surg*. 2020;44(3):730-740. doi:10.1007/s00268-019-05256-9

52. Elliott D, Kufera JA, Myers RAM. The microbiology of necrotizing soft tissue infections. *Am J Surg*. 2000;179(5):361-366. doi:10.1016/s0002-9610(00)00360-3

53. Bastug A, Kislak S, Mutlu NM, et al. Necrotizing fasciitis due to Streptococcus mitis caused by accidental human bite. *J Infect Dev Ctries*. 2016;10(1):100-102. doi:10.3855/jidc.7040

54. Kuo YL, Shieh SJ, Chiu HY, Lee JW. Necrotizing fasciitis caused by Vibrio vulnificus: Epidemiology, clinical findings, treatment and prevention. *Eur J Clin Microbiol Infect Dis*. 2007;26(11):785-792. doi:10.1007/s10096-007-0358-5

55. Puvanendran R, Huey JCM, Pasupathy S. Necrotizing fasciitis. *Can Fam Physician*. 2009;55(10):981-987. doi:10.2106/00004623-200308000-00005

56. Reichert JC, Habild G, Simon P, Nöth U, Krümpelmann JB. Necrotizing streptococcal myositis of the upper extremity: A case report. *BMC Res Notes*. 2017;10(1). doi:10.1186/s13104-017-2743-1

57. Rein JM, Cosman B. Bacteroides necrotizing fasciitis of the upper extremity: Case report. *Plast Reconstr Surg*. 1971;48(6):592-594. doi:10.1097/00006534-197112000-00018

58. Weidle PA, Brankamp J, Dedy N, Haenisch C, Windolf J, Jonas M. Complication of a closed colles-fracture: Necrotising fasciitis with lethal outcome. A case report. *Arch Orthop Trauma Surg*. 2009;129(1):75-78. doi:10.1007/s00402-008-0748-x

59. Kato N, Ueno H. Necrotizing fasciitis appearing with petechiae as the first clinical sign. *J Dermatol*. 1993;20(6):378-380. doi:10.1111/j.1346-8138.1993.tb01302.x

60. Lujan-Hernandez J, Schultz KS, Rothkopf DM. Rapidly Progressive Soft Tissue Infection of the Upper Extremity With Aeromonas veronii Biovar sobria. *J Hand Surg Am*. 2020;45(11):1091.e1-1091.e4. doi:10.1016/j.jhsa.2020.02.003

61. Tang WM, Ho PL, Fung KK, Yuen KY, Leong JCY. Necrotising fasciitis of a limb. *J Bone Jt Surg - Ser B*. 2001;83(5):709-714. doi:10.1302/0301-620X.83B5.10987

62. Giuliano A, Lewis F, Hadley K, Blaisdell FW. Bacteriology of necrotizing fasciitis. *Am J Surg*. 1977;134(1):52-57. doi:10.1016/0002-9610(77)90283-5

63. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis*. 2014;59(2). doi:10.1093/cid/ciu296

64. Yen ZS, Wang HP, Ma HM, Chen SC, Chen WJ. Ultrasonographic screening of clinically-suspected necrotizing fasciitis. *Acad Emerg Med*. 2002;9(12):1448-1451. doi:10.1197/aemj.9.12.1448

65. Iwata Y, Sato S, Murase Y, et al. Five cases of necrotizing fasciitis: Lack of skin inflammatory signs as a clinical clue for the fulminant type. *J Dermatol*. 2008;35(11):719-725. doi:10.1111/j.1346-8138.2008.00556.x

66. Kapi E, Dogan ZDA, Seyhan T, Kilinc N. Unusual cases of necrotizing fasciitis: a clinical experience from Turkey. *Eur J Plast Surg*. 2018;41(1):31-40. doi:10.1007/s00238-017-1310-2

67. Huang WS, Hsieh SC, Hsieh CS, Schoung JY, Huang T. Use of vacuum-assisted wound closure to manage limb wounds in patients suffering from acute necrotizing fasciitis. *Asian J Surg*. 2006;29(3):135-139. doi:10.1016/S1015-9584(09)60072-5

68. Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: A tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med*. 2004;32(7):1535-1541. doi:10.1097/01.ccm.0000129486.35458.7d

69. Cheng NC, Su YM, Kuo YS, Tai HC, Tang YB. Factors affecting the mortality of necrotizing fasciitis involving the upper extremities. *Surg Today*. 2008;38(12):1108-1113. doi:10.1007/s00595-008-3799-2

70. Chauhan A, Wigton MD, Palmer BA. Necrotizing fasciitis. *J Hand Surg Am*. 2014;39(8):1598-1601. doi:10.1016/j.jhsa.2014.04.010

71. Corona PS, Erimeiku F, Reverté-Vinaixa MM, Soldado F, Amat C, Carrera L. Necrotising fasciitis of the extremities: implementation of new management technologies. *Injury*. 2016;47:S66-S71. doi:10.1016/s0020-1383(16)30609-x