

Necrotizing Fasciitis: Current Concepts, Pathogens and Management

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Abstract: Necrotizing fasciitis (NF) is a severe disease of sudden onset that spreads rapidly. The disease is more common in the adults and is rare in the children. The infection enters the body through a break in the skin such as cut or burn. Majority of the cases involve methicillin resistant *Staphylococcus aureus* (MRSA), anaerobic species, *Enterobacteriaceae*, hemolytic streptococcus group A are isolated alone or in combination. Streptococcal infections also associated with toxic-shock syndrome. Symptoms include inflammation, fever, and fast heart rate, diarrhea, vomiting, and crepitus may be present, discharge of fluid said to resemble "dish water". Fournier's gangrene is a form of NF occurring about the male genitals. Gold standard for diagnosis is surgical exploration, with LRINEC score. Patient with a LRINEC score ≥ 6 have higher rate of mortality and amputation. Medical imaging is helpful to confirm diagnosis. Initial treatment includes a combination of intravenous antibiotics including piperacillin/tazobactam, vancomycin, and clindamycin or ampicillin-sulbactam combined with metronidazole, clindamycin or carbapenems (imipenem). Aggressive surgical debridement is always necessary. Amputation of infected limb(s) may be necessary. Ancillary therapies, neither a substitute for surgical debridement nor proven efficacy have been described. Some studies recommend using intravenous immunoglobulin (IVIG). Nutritional support is imperative. High mortality rates if left untreated. High index of suspicion and knowledge is essential for early diagnosis and outcomes of NF.

Keywords: Necrotizing fasciitis, Flesh-eating bacteria, Pathogens, Surgery, Management

I. Introduction

Necrotizing fasciitis (NF), also known as flesh-eating disease, is an infection that results in the death of the body's soft tissue [1]. Necrotizing fasciitis has been described at least since the time of Hippocrates [2]. NF affects 0.4 to 1 person per 100,000 per year in the United States. In areas of the world it is as common as 1 in every 100,000 people [3]. Both sexes are affected equally [2]. It becomes more common among older people and is rare in children [3]. The term "necrotizing fasciitis" first came into use in 1952 [3,4]. It is a severe disease of sudden onset that spreads rapidly. Risk factors include poor immune function such as from diabetes or cancer, obesity, alcoholism, intravenous drug use, and peripheral vascular disease [2]. Typically the infection (pathogens) enter the body through a break in the skin such as cut or burn [1]. Between 55-80% of cases involve more than one type of bacteria. Methicillin-resistant *Staphylococcus aureus* (MRSA) is involved in up to a third of cases [3]. Symptoms include red or purple skin in the affected area, severe pain, fever, and vomiting [1]. The most commonly affected areas are the limbs and perineum [2]. It is not typically spread between people [1]. The disease is classified into four types, depending on the infecting organism [3]. Medical imaging is helpful to confirm the diagnosis [3]. Frequently a combination of antibiotics are used such as penicillin G, clindamycin, vancomycin, and gentamicin [3]. Delays in surgery are associated with high risk of death [3]. Despite high quality treatment the risk of death is between 25% and 35% [2]. Prevention is by good wound care and handwashing [1]. The paper reviews the current literature on management of Necrotizing fasciitis.

II. Pathogens

The term necrotizing fasciitis encompasses two distinct bacteriologic entities. In type 1 NF, at least one anaerobic species (most commonly *Bacterioides* or (*Peptostreptococcus*) is isolated in combination with one or more facultative anaerobes species such as streptococci (other than group A) and members of the *Enterobacteriaceae* (e.g. *E. coli*, *Enterobacter*, *Klebsiella*, *Proteus*). An obligate aerobe such as *P. aeruginosa* is only rarely a component of such a mixed infection. Cases in which only anaerobes are present appear to be rare [5]. In type 11 (corresponding to the entity also known as hemolytic streptococcus gangrene), group A streptococci are isolated alone or in combination with other species, most commonly *S. aureus*. Streptococcus gangrene also a form of gangrenous cellulitis. Streptococcal infections are also associated with toxic-shock syndrome [6].

Hemolytic streptococcus gangrene occurs after minor trauma, stab wounds, or surgery, particularly in the context of diabetes and peripheral vascular disease, but cirrhosis and corticosteroid therapy have also been predisposing factors [6]. In outbreaks of streptococcal toxic-shock like syndrome, chills, fever (or profound hypothermia and shock), confusion, vomiting, diarrhea, tachycardia, hypotension, and multiorgan failure are prominent features. NF is present in about half of cases of streptococcal toxic shock-like syndrome [7]. Nonsteroidal anti-inflammatory (NSAIDs) were linked to an increased risk of NF in retrospective reports, perhaps by masking and delaying local and systematic inflammatory signs, but prospective studies have not confirmed the use of NSAIDs as a risk factor for NF or increased complications in this setting [8]. Unlike many earlier cases of hemolytic gangrene, which affected older individuals with underlying diseases, more recently streptococcal toxic shock-like has occurred primarily in young previously healthy adults after minor trauma. In 70% of patients, soft tissue findings progressed to hemolytic streptococcal gangrene with development of vesicles, violaceous bullae and necrosis of subcutaneous tissues typical of NF (or myositis) and requiring surgical debridement [9]. The mortality rate was 30%. In young children, the skin lesions of varicella can be superinfected with group A Streptococci and become a risk factor for group A streptococcal necrotizing fasciitis [10].

In patients with severe, invasive group A streptococcal infection, a primary site of infection generally involving skin and soft tissue is identifiable in roughly 75% of cases, with necrotizing fasciitis in most of these patients [11]. There is a high rate of streptococcal bacteremia. The pathogenesis of streptococcal toxic shock appears to involve microbial and host factors. The predominant group A streptococci isolated in several outbreaks have expressed the common M protein type M1 or M3 (although other M types are also associated with this syndrome) and possess pyrogenic exotoxin gene type A or C and express pyrogenic exotoxin in vitro. Examination of type M1 and M3 isolated from cases of streptococcal toxic shock-like syndrome has suggested their possible clonal origin [12].

Genome microarray analysis has demonstrated that M1 and M3 strains carry several additional unique virulence factors that may be responsible for the apparent association of these strains with invasive infection [13]. Host susceptibility to streptococcal toxic shock syndrome may be related to an absence of suitable protective antibodies against the M protein of invading pyrogenic exotoxins; such seronegative individuals would be at heightened risk to invasive streptococcal infection and toxic shock syndrome [11]. Because the streptococcal pyrogenic exotoxins act as super antigens, which activate T cells by binding to human leucocyte antigen (HLA) class II molecules, protection against or heightened susceptibility to streptococcal toxic shock may correlate with certain HLA-DQ polymorphism [14]. The majority of infections are caused by organisms that normally reside on the individual's skin. These skin flora exist as commensals and infection reflects their anatomical distribution (e.g. perineal infections are caused by anaerobes). Sources of MRSA may include working at municipal waste water treatment plants, exposure to secondary waste water spray irrigation, exposure to runoff from farm fields fertilized by human sewage sludge or seepage, hospital setting—using dirty needles [15-17]. The risk of infection during regional anesthesia is considered to be very low, though reported [18].

III. Clinical Presentations

Necrotizing fasciitis is an uncommon severe infection involving the subcutaneous soft tissues particularly the superficial (and often deep) fascia. It is usually an acute process but rarely may follow a subacute progressive course. Necrotizing fasciitis can affect any part of the body but is most common on the extremities particularly legs. Other sites of predilection are the abdominal wall, perianal, and groin areas and postoperative wounds [19].

The portal of entry is usually a site of trauma (e.g. laceration, abrasions, burn, insect bite), a laparotomy performed in the presence of peritoneal soiling (e.g. penetrating abdominal trauma or perforated viscus) or another surgical procedure (hemorrhoidectomy, vasectomy), perirectal abscess, decubitus ulcer, or intestinal perforation. The last may be secondary to occult diverticulitis [20], rectosigmoid neoplasm, or a foreign body or chicken bone or toothpick. NF from such intestinal sources may occur in the lower extremity (extension along psoas muscle), as well as in the groin or abdominal wall (via colocolocutaneous fistula). Particular clinical settings in which NF may develop include diabetes mellitus, alcoholism, and parental drug abuse [21,22]. In the newborn NF can be a serious complication of omphalitis. Initial swelling and erythema about the umbilicus can progress over several hours to several days and result in purplish discoloration and periumbilical necrosis. Involvement of the anterior abdominal wall frequently extends to the flanks and even onto the chest wall [23].

The affected area is initially erythematous, swollen, without sharp margins, hot, shiny, exquisitely tender and painful [24]. Lymphangitis, and lymphadenitis are infrequent. The process progresses rapidly over several days, with sequential skin color changes from red purple to patches of blue gray. Within 3 to 5 days after onset skin breaks down with bullae (containing thick or purple fluid) and frank cutaneous gangrene (resembling thermal burn) can be seen. By this time the involved area is no longer tender but has become anesthetic

secondary to thrombosis of small blood vessels and destruction of superficial nerves located in the necrotic, undermined subcutaneous tissue [25].

People usually complain of intense pain that seem excessive given the external appearance of the skin. Patient initially has signs of inflammation, fever and fast heart rate. With progression of disease often within hours, tissue becomes progressively swollen; the skin discolored and develops blisters. Crepitus may be present and there may be discharge of fluid, said to resemble “dish water”. Diarrhea and vomiting are also common symptoms. In the early stages, signs of inflammation may not be apparent if the bacteria are deep within the tissue. If they are **not** deep, signs of inflammation, such as redness and swollen or hot skin, develop very quickly. Skin color may progress to violet, and blisters may form with subsequent necrosis (death) of the subcutaneous tissues. Furthermore, people with necrotizing fasciitis have fever and appear sick. Mortality rates are as high as 73% if left untreated [26]. Without surgery and medical assistance, such as antibiotics, the infection will rapidly progress and will eventually lead to death [27]. When NF affects the groins it is known as Fournier gangrene [2].

Aleksandar and associates reported 13 cases of NF in a pediatric orthopedic population [28]. Dutta and colleagues reported a fatal NF case in a 27 year-old female patient after spinal anesthesia [18]. CDC confirmed that if you are healthy, have a strong immune system, and practice good hygiene and proper wound care, your chances of getting NF (“flesh-eating bacteria”) are extremely low [1].

Fournier’s Gangrene: A form of NF occurring about the male genitals is known as Fournier’s gangrene, also known as idiopathic gangrene of the scrotum, streptococcal scrotal gangrene, and perineal phlegmon [29]. It may be confined to the scrotum, or it may extend to involve the perineum, penis, and abdominal wall. Predisposing factors include diabetes mellitus, local trauma, paraphimotic, periurethral extravasation of urine, perirectal or perianal infection [30], and surgery in the area (circumcision, herniorrhaphy). In cases originating in the genitalia, the infecting bacteria probably pass through Buck’s fascia of the penis and spread along the dartos fascia’s of the scrotum and penis. Colle’s fascia of the perineum, and Scrupa’s fascia of the anterior wall abdominal wall. Anaerobic bacteria play an important role and contribute to the typical foul odor associated with this form of NF. Mixed cultures containing facultative organisms (*E. coli*, *Klebsiella*, enterococci), along with anaerobes (*Bacterioides*, *Fusobacterium*, *Clostridium*, anaerobic or microaerophilic streptococci), have been obtained from studied cases. Rarely group A streptococcal gangrene evolving from streptococcal balanitis can also involve male genital area [31].

The infection commonly starts as cellulitis adjacent to the portal of entry. Early in the course of Fournier’s gangrene, the evolved area is swollen, erythematous, and tender as the infection begins to evolve the deep fascia. Pain is prominent; fever and systemic toxicity are marked. Swelling and crepitus of the scrotum quickly increase, and dark purple areas develop and progress to extensive scrotal gangrene. If the abdominal wall becomes involved in an obese patient with diabetes, the process spread extremely rapidly [32].

Miscellaneous Necrotizing fasciitis: Necrotizing fasciitis of the face and eyelids, neck, and lip are uncommon but life threatening forms of disease [33-35]. It is most often caused by group A streptococci, alone or with *S. aureus*, and represents streptococcal gangrene; occasionally, it represents mixed infections of group A streptococcus with Enterobacteriaceae or oral Bacteriesspp. Although NF of the head and neck is often considered a single entity, in fact it represents two conditions, etiologically [36]. Craniofacial NF is commonly caused by group A streptococci, whereas cervical NF often represents a polymicrobial process (e.g. group A streptococci, various other streptococcal species, *Bacterioides* or *Peptostreptococcus* spp). In mixed infections, crepitus may be a feature, as may necrosis of the epidermis and superficial fascia. Trauma is the usual precipitating cause of NF of the periorbital areas, face; dental oral pharyngeal infections predispose to cervical NF. The mortality associated with cervical NF is about four times high as that from craniofacial necrotizing fasciitis [36].

Various pathogens have been occasionally recovered from wounds and often from blood cultures of patients with NF [37]. NF in neutropenic children receiving cancer chemotherapy may be caused by *P. aeruginosa* or Enterobacteriaceae [38]. The acute cellulitis caused by *V. vulnificus* and other *Vibrio* species may extend to the superficial and deep fascia and produce NF. Similarly, MRSA may cause NF usually in HIV-infected or other immunocompromised host [39].

IV. Diagnosis

Early diagnosis is difficult as the disease often looks early on like a simple superficial skin infection [3]. While a number of laboratory and imaging modalities can raise the suspicion for NF, the gold standard for diagnosis is surgical exploration in the setting of high suspicion. When in doubt, a small “key hole” incision can be made into the affected tissue, and if a finger easily separates the tissue along the fascial plane, the diagnosis is confirmed and extensive debridement should be performed [2]. Computed tomography (CT scan) is able to detect about 80% of cases while MRI may pick up slightly more [40].

Diagnostic scoring system

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score can be utilized to risk stratify people having signs of cellulitis to determine the likelihood of NF being present. It uses six serologic measures: C-reactive protein, total white cell count, hemoglobin, sodium, creatinine and glucose. A score greater than or equal to 6 indicates that NF should be seriously considered. The scoring criteria includes:[41].

- a).CRP(mg/L) \geq 150:4 points
- b).WBC count($\times 10^3/\text{mm}^3$) <15:0 point,15-25: 1 point,>25: 2 points
- c).Hemoglobin(g/dl) >13.5: 0 point,11-13.5: 1 point <11: 2 point
- d).Sodium(mmol/L) <135: 2 points
- e).Creatinine(umol/L)>141: 2 points
- f).Glucose(mmol/L)>10: 1 point [41,42].

As per derivation study of the LRINEC score, a score of ≥ 6 is a reasonable cut –off to rule out in NF, but a LRINEC < 6 does not rule out the diagnosis. Diagnosis of severe cellulitis or abscess should be considered due to similar presentations [43]. But a validation study showed that patient with a LRINEC score ≥ 6 have higher rate of both mortality and amputation[44]. The study also showed that LRINEC score is a robust score capable of detecting even clinically early cases of NF. The variables used routinely measured to assess severe soft tissue infections. Patients with a LRINEC score of ≥ 6 should be carefully evaluated for the presence of NF[44]. The study by Falco and associates confirm that in the early stage of NF, clinical presentation can be ambivalent. Study showed that triple diagnostics consisting of an incisional biopsy with macroscopic, histologic and microbiologic findings was helpful in timely identification of NF[45]. *High index of suspicion and knowledge is essential for early diagnosis of NF*[46].

Classification

The disease (NF) is classified into four types, depending on the infecting organism [3]. The most common type is caused by mixture of bacterial types, and commonly occurs at sites of surgery or trauma, usually in abdominal or perianal areas and accounts for 70% to 80% of cases [3,47]. Type 1 is caused by Group A streptococci (often with a co-infection of *S.aureus*), and usually occurs on the head, neck arm or legs. It is less often associated with predisposing risk factors (such as surgery or compromised immune system). Type 11 is caused by *Vivrio.vulnificus*, which enters the skin via puncture wounds from fish or insects in the sea water[48,49]. The type four is due to fungal infection[3].

V. Management

Prompt diagnosis is of paramount importance because of the rapidity with which the process can progress. The reported mortality rate of NF has ranged from 24% to 34 % overall [37], and somewhat less (15%) for Fournier's gangrene[31]. Earlier clinical differentiation NF from cellulitis can be difficult because the initial signs-including pain, edema, and erythema are not distinct. However, the presence of marked systemic toxicity out of proportion to the local findings should alert the physician. CT scanning and magnetic resonance imaging (MRI) can demonstrate subcutaneous and fascial edema, as well as tissue gas, in patients with NF and distinguish this process from cellulitis [50]. Early treatment is often presumptive, thus, antibiotics should be started as soon as this condition (NF) is suspected. Initial treatment often includes a combination of intravenous antibiotics including piperacillin/tazobactam, vancomycin, and clindamycin or broad spectrum antibiotics which include ampicillin-sulbactam combined with metronidazole, clindamycin or carbapenems (imipenem)[51]. Cultures are taken to determine appropriate antibiotic coverage and antibiotics may be changed when culture results are obtained. Treatment for NF may involve an interdisciplinary care team. For example, in the case of necrotizing fasciitis involving the head and neck, the team could include otolaryngologist, speech pathologist, intensivists, microbiologists and plastic surgeons or oral and maxillofacial surgeons[52]. Maintaining strict asepsis during any surgical procedure and regional anesthesia techniques is vital in preventing the occurrence of the disease[18].

Surgical Intervention

People are taken to surgery based on a high index of suspicion, determined by the person's signs and symptoms. In NF aggressive surgical debridement (removal of infected tissue) is always necessary to keep it from spreading and is only treatment available. The diagnosis is confirmed by visual examination of the tissues and tissue samples for microscopic evaluation [52,18]. Amputation of the affected limb(s) may be necessary. Repeat explorations usually need to be done to remove additional necrotic tissue. Typically, this leaves a large open wound, which often requires skin grafting, though necrosis of internal (thoracic and abdominal) viscera-such as intestinal tissue-is also possible. The associated systemic inflammatory response is usually profound and most people will require monitoring in an intensive care unit. Because of the extreme nature of many of these

wounds and the grafting and debridement that accompanies such treatment, a burn center's wound clinic has staff trained in such wounds, may be utilized [52,18]. Some studies have proven an improved wound healing and a significant reduction of wound surface area in full-thickness wounds treated with VAC (vacuum assisted closure) devices as compared to conventional gauze therapy [53].

Several ancillary therapies, neither a substitute for prompt surgical debridement nor of proven efficacy has been described. One is the use of IV immune globulin to treat the streptococcal toxic shock-like syndrome accompanying the treatment of group A streptococcal NF [25]. Some studies recommend using intravenous immunoglobulin (IVIG), [54]. A higher dose of IVIG may be needed especially in severe streptococcal infections, but still yet to be demonstrated with randomized studies [55]. The other is the use of Hyperbaric oxygen treatment is sometimes used to treat necrotizing soft tissue infection in combinations with antibiotics and debridement, but there is lack of compelling evidence regarding its efficacy for this purpose [56]. This modality is not widely available and should not delay urgent debridement and conventional therapy with appropriate antibiotics and intensive care supportive measures [57]. Nutritional support is required from the first day of patient's admission to hospital (preferably the ICU), to replace lost proteins and fluid from large wounds and/or the resultant toxic shock. Metabolic demand are similar.

VI. Historical cases

- In 1994 A clusters of cases occurred Gloucestershire, in the west of England. Of five confirmed and one probable infection. The first two had acquired the *Streptococcus pyogenes* during surgery, the remaining four were community acquired [58]. The cases generated much newspaper coverage, with lurid headlines such as "Flesh Eating Bug Ate My Face:" [59].
- In 1997 Ken Kendrick, former agent owner of the San Diego Padres and Arizona Diamondbacks, contracted the disease in 1997. He had seven surgeries in a little more than a week and later recovered fully [60].
- In 2004 Eric Allin Cornell, winner of the 2001 Nobel Prize in Physics, lost his left arm and shoulder to the disease [61].
- In 2005 Alexandru Marin, an experimental particle physicist, professor at MIT, Boston University and Harvard University, and researcher at CERN and JINR died from the disease [62].
- In 2015 Edgar Savisaar, an Estonian politician. His right leg was amputated > he got the disease during trip to Thailand [63].

VII. Conclusion

Necrotizing fasciitis (NF) is an infection that results in the death of body's soft tissue. Delays in surgery are associated with high risk of death. High degree of suspicion is required with early diagnosis, appropriate empirical antibiotic therapy, and surgical intervention should be instituted.

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