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NECROTIZING FASCIITIS

Pathoprofile

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INTRODUCTION

Necrotizing fasciitis (NF), commonly known as flesh-eating disease, is a rare and life-threatening soft-tissue infection characterized by the rapid necrosis of subcutaneous tissue and fascia.[1,2] There are four subtypes of NF, each classified based on the causative microorganism, with NF types I and II accounting for ~70-80% and ~20-30% of cases, respectively.[3] Differing only in clinical manifestations and speed of pathogenesis, the pathophysiology of all types of NF is similar.[3] Bacteria invades subcutaneous tissue, proliferates, and releases endotoxins and exotoxins, leading to expanding tissue necrosis, toxic shock syndrome (TSS), and death in 15-45% of cases.[4-6]

DIAGNOSIS

NF has the potential to spread aggressively and, thus, early diagnosis is vital in preventing mortality and morbidity.[1] Multivariate analysis reveals that a delay of 24 hours in NF treatment can decrease the survival rate by 18%.[2,7] However, in the early stages of NF, the paucity of pathognomonic signs often results in a misdiagnosis of cellulitis, erysipelas, or an abscess.[2,8] Therefore, a high-degree of clinical suspicion is required to distinguish NF from other soft-tissue infections.[1,2] Following clinical assessment, various tests may be performed to confirm diagnosis. The 'finger test' is among the most effective diagnostic procedures.[2] A 2-cm incision is made and the surgeon inserts their index finger to probe the deep tissue; a test is NF-positive if the subcutaneous tissue easily dissects off of the deep fascia.[1,2] A laboratory evaluation may also be used to identify characteristics of NF such as leukocytosis with a neutrophil predominance, and the elevation of acute phase reactants such as C-reactive protein and platelets. Radiological imaging can also be useful for a timely diagnosis.[9] MRI scans exhibit a success rate of 93-100% in diagnosis by identifying necrosis and edema along the thickened fascial planes, and fascial fluid generated from liquefactive tissue necrosis.[1,2] Furthermore, CT scans may display increased attenuation of subcutaneous fat, fascial thickening, soft-tissue edema, and tracking along fascial planes.[1]

RISK FACTORS

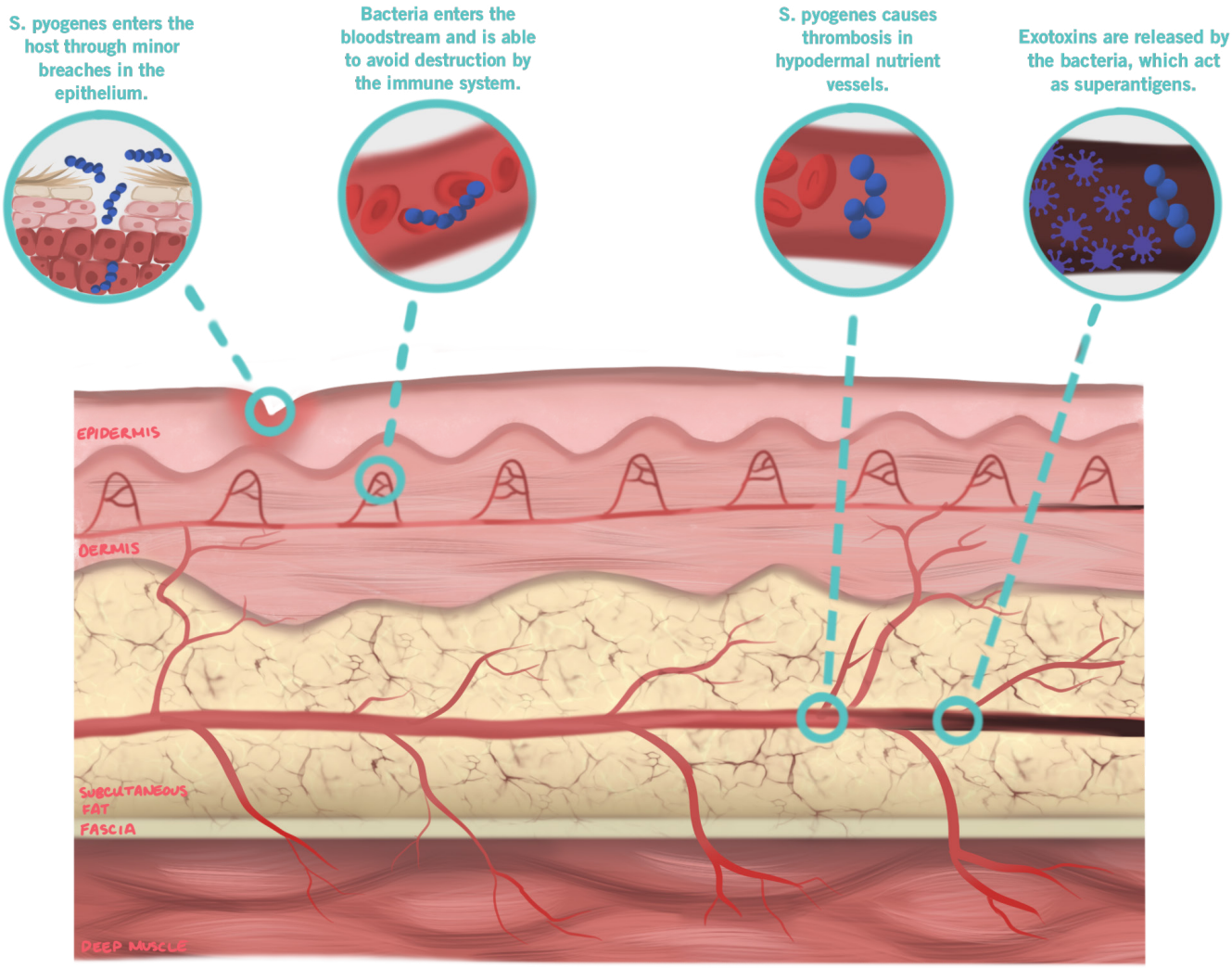
Although NF can infect healthy individuals of all ages, immunocompromised patients are most susceptible to the disease due to weakened immune defences against pathogens.[1] In fact, diabetes mellitus is the most common comorbidity, presenting in 18-60% of cases.[1,2] Additional immunocompromised states strongly associated with NF include liver cirrhosis, obesity, alcohol abuse, peripheral vascular disease, cancer, and advanced age.[1,2] Intravenous drug use and surgical procedures also increase the risk of developing NF as they may lead to bacterial invasion and localized tissue damage.[10]

MECHANISM (TYPE II NECROTIZING FASCIITIS)

Infection by group A Streptococcus (e.g. *S. pyogenes*) is the most common cause of NF.[11] Unlike Clostridium bacteria, which enter directly through deep penetrating injuries, *S. pyogenes* enters the bloodstream and deep tissue through minor breaches in the epithelium, or penetrates through mucus membranes.[12] Through the expression of the anti-phagocytic M protein, *S. pyogenes* avoids destruction by the host immune system and begins infecting the hypodermis.[12,13] The anaerobic environment and the synergy between virulence factors and host proteins promotes bacterial growth and facilitates necrosis of the fascia by bacterial enzymes.[13] Invasive bacteria then cause thrombosis of hypodermal nutrient vessels, leading to ischemia, infectious dissemination, skin necrosis, intense pain, or anesthesia.[13] If NF continues to progress, exotoxins released by *S. pyogenes* (e.g. streptococcal pyrogenic exotoxin A, streptococcal superantigen, etc.) or M protein fragments may act as superantigens by overstimulating inflammatory T-cells resulting in TSS, organ failure, and death.[12] Necrotic spread in the fascia progresses several inches per hour, with death resulting as soon as 12-24 hours after initial infection.[12,14]

TREATMENT

Surgical debridement of affected tissues is the primary treatment for NF.[13] This life-saving procedure is performed as early as possible, and often repeated 5 to 40 times depending on the clinical course of the infection.[13] The initial debridement surgery typically involves a wide-deep cut or multiple shallow cuts at the edge of the infected area, to release pus or hemorrhagic fluid and prevent further spread of the infection.[13,15] Once an incision is made, infected tissue is



removed while carefully trimming potentially salvageable soft tissue, until healthy tissue is revealed.[13] If debridement proves insufficient, patients may choose amputation, which could involve fewer procedures and reduced blood loss.[15] Although no definitive requirements exist, amputation is often performed if there is extensive necrosis of underlying muscles, TSS, vascular insufficiency, or patient history of diabetes or hypotension.[13]

Treatment of NF with antibiotic therapies is minimally effective. However, using a combination of broad and narrow-spectrum antibiotics alongside surgical intervention can help prevent the spread of infection.[13] Due to the possible development of large wounds or TSS with NF and its treatment, nutritional supplementation is required to replace lost proteins and fluids.[12] Several other treatments, including hyperbaric oxygen therapy (HBOT) and IV immunoglobulin (IVIg) therapy, have been proposed but remain controversial.[16] HBOT, which involves inhalation of 100% oxygen, is said to decrease edema, infection spread, and increase antibiotic efficacy, but has yet to be strongly supported in clinical settings.[17] Similarly, IVIg therapy is hypothesized to bind and inhibit exotoxins released by NF-causing bacteria; however, these observations remain restricted to small studies of critically-ill NF patients.[16,18]

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