Necrotizing fasciitis

Catherine L. Cherneski, BSc(Med), MD, John M. Embil, MD.

ABSTRACT

Necrotizing fasciitis is a devestating condition which has been recognized for several years. In North America a recent increase of cases has led to much media attention and public fear. Necrotizing fasciitis may occur as a consequence of infection with *Streptococcus pyogenes* or as a result of a polymicrobial synergistic infection caused by aerobic, anaerobic, gram positive and gram negative organisms, often in postoperative patients. Necrotizing fasciitis caused by *Streptococcus pyogenes* is mediated by superantigens. The management of necrotizing fasciitis requires a high index of suspicion for diagnosis followed by antimicrobial therapy and early surgical intervention. In cases caused by *Streptococcus pyogenes* with streptococcal toxic shock syndrome, intravenous immunoglobulin may be of benefit.

Keywords: Necrotizing fasciitis, *Streptococcus pyogenes,* superantigen.

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Over the last decade, there have been an increasing number of reports in the news media and medical literature of rapidly progressive and often fatal skin and soft tissue infections. The dramatization of necrotizing fasciitis, the so-called "flesh-eating disease", by the media has produced widespread fear among physicians and the general public, even though this is still a rare entity. There appears to exist much confusion as to what necrotizing fasciitis is, and what agent or agents are responsible for causing this disease. As necrotizing fasciitus is potentially curable, but rapidly fatal if not promptly recognized and treated appropriately, it is vitally important that physicians and health care providers be aware of the etiology, pathogenesis, complications and management of this disease. More commonly however, in day to day practice, the physician will be required to allay the fears that his patients have about necrotizing fasciitis.

Etiology. The predominant layers of skin affected in necrotizing fasciitis are the superficial fascia and the subcutaneous fat. The fascia, a strong fibrous-like tissue, is divided into 2 layers: the superficial and deep fascia. The superficial fascia is positioned just beneath the dermis. It separates superficial layers of skin and soft tissue from deeper layers and provides support for the skin. Deep to the superficial fascia is the subcutaneous fat, were nutrient arteries, veins, and nerves supplying the dermis and epidermis are located. Below the subcutaneous adipose tissue lies the deep fascia, which separates the subcutaneous fat from the muscle layer. Infections in these different tissue plains are associated with different clinical syndromes. For example erysipelas, a superficial infection of the dermis and epidermis, can be seen to have a distinct leading edge, while cellulitis, a deeper dermal infection, is associated with a more diffuse erythematous non-raised leading edge. Myonecrosis affects deeper tissue layers, specifically muscle.[1] In necrotizing fasciitis, infection results in a rapidly progressive inflammation and necrosis of the superficial fascia and subcutaneous fat, while deeper tissues and muscle remain unaffected. Ultimately, this leads to infarction of the overlying skin as a late finding. Cases of necrotizing fasciitis can be divided into 2 types based upon the bacteriology. Type 1 is a polymicrobial infection caused by a mixture of anaerobic and aerobic bacteria. This type of necrotizing fasciitis most commonly affects people with compromised vascular supply such as in the lower extremeties of persons with diabetes, whose foot infections may progress to necrotizing fasciitis. Type 1 infections also occur in situations where there

From the Department of Medicine, Section of General Internal Medicine, (Cherneski), Department of Medicine, Section of Infectious Diseases, (Embil), University of Manitoba, Canada.

Address correspondence and reprint request to: Dr. John M. Embil, Infection Control Unit, Health Sciences Center, MS 673-820 Sherbrook Street, Winnipeg, Manitoba, R3A 1RA, Canada. Tel. +1 (204) 787 4564 Fax. +1 (204) 787 4699. Email: jembil@hsc.mb.ca

is contamination with fecal organisms, such as in an intra-abdominal infection resulting from fecal spillage or a perineal infection. Type 2 necrotizing fasciitis is caused by *Streptococcus pyogenes (S.pygenes)*, which is also known as Group A Streptococcus (GAS). Those who are immunocompromised are at higher risk of infection with this organism, although it may also cause disease in previously healthy individuals after seemingly minor injury.[2,3] On gram stain, *S.pyogenes* appears as gram positive cocci in chains. It is a ubiquitous organism that causes a variety of invasive and non-invasive infections skin and soft tissue infections including pharyngitis, impetigo, erysipelas, and cellulitis. The potential for invasive disease is determined by a variety of factors including the status of the host's immune system, and the virulence of the organism.[2,4] Streptococci are classified according to the hemolytic reaction they produce on blood agar. The α-hemolytic streptococci (Viridans streptococci and *Streptococcus pneumoniae*) imcompletely hemolyze the medium, producing a greenish discoloration around their colonies. ß-hemolytic streptococci are identified by the distinct zone of hemolysis or clearing they produce around their colonies on blood agar. Organisms included in this group are *S.pyogenes* and *S.agalactiae*. Finally, those are δ–hemolytic do not produce a zone of hemolysis and are known as the non-hemolytic streptococci. This group includes the enterococci. Using the Lancefield method, the ß-hemolytic streptococci are then further sub-classified based upon antigenic differences in the cell wall carbohydrates.[5] The most commonly referred to are group A streptococci or GAS (*S.pyogenes*), group B streptococci (*S.agalactiae*), and group D streptococci (the *enterococci*). Virulence factors of the streptococci include the M-proteins and the streptococcal pyrogenic exotoxins A, B, and C. The M-protein is located on the cell wall of S.pyogenes, and is believed to make the streptococci more virulent by conferring them an ability to resist phagocytosis. There are more than 80 antigenically different sub-types of the M-protein, therefore type-specific antibodies directed against specific M-proteins following infection confer host resistence to GAS of that M-protein type. The streptococci also variably express pyrogenic exotoxins A, B, and C, which are secreted proteins otherwise known as "superantigens". This name is derived from the fact that these "superantigens" possess the ability to non-specifically stimulate a large number of T-cells, approximately 100 to 1000-fold more, in contrast to only specific anti-streptococcal T-cell activation. T-cell activation results in cytokinne release, which in normal amounts play an integral role in the body's ability to fight infection. However, the massive cytokine release resulting from non-specific "superantigen" stimulation of T-cells leads to an overwhelming inflammatory response, ultimately leading to tissue damage, multiple organ failure, the sepsis syndrome and death.[4,6,7]

Table 1 - Proposed case definition for streptococcal toxic shock syndrome.*

I. Isolation of Group A streptococci (S pyogenes)

A. From a normally sterile site
B. From a non-sterile site

II. Clinical signs of severity

A. Hypotension: systolic blood pressure ≤90 mm-Hg, and

B. More than 2 of the following signs:

1. Renal impairment: creatinine >177 umol/L
2. Coagulopathy: platelets <100,000/mm3 or diseminated intravascular coagulation
3. Liver involvement: ALT, AST, or total bilirubin >2 x upper limit normal for age
4. Adult respiratory distress syndrome
5. Generalized erythematous macular rash (may desquamate)
6. Soft tissue necrosis, including necrotizing fasciitis, myositis, or gangrene

*definite case: fulfills criteria IA and II (A & B)
probable case: fulfills criteria IB and II (A & B);
ALT - Alanine aminotransferase; AST - Aspartate aminotransferase

Risk factors. Necrotizing fasciitis can affect any individual, even the very young and previously healthy person. There has been a higher incidence observed however, in persons over the age of 65 and those with significant associated illness such as diabetes, alcohol abuse, malnutrition, chronic cardiac disease and peripheral vascular disease. Generally, there is a history of a portal of entry: an abrasion or laceration, insect bite, chronic skin condition, intravenous injection site, or a surgical incision.[1-3] Non-steroidal anti-inflammatory drug (NSAID) use has also been associated with the incidence of necrotizing fasciitis. It is unclear however, whether this is merely an association or there is an actual cause and effect relationship between these drugs and necrotizing fasciitis. There have been reports of early necrotizing fasciitis being mis-diagnosed as a musculoskeletal disorder and mistakenly treated with NSAID's. This led to the amelioration of pain and signs of inflammation, with a subsequent delay in diagnosis until signs of shock and tissue necrosis were present.[8]

Clinical presentation. On initial presentation, the clinical signs of necrotizing fasciitis are non-specific, and therefore easily missed. The disease may affect any part of the body, but most often involves the extremeties.[3] The patient may look and subjectively feel unwell. They may present with a diffuse erythematous swelling of the affected area,

accompanied by fevers, chills, and rigors. Pain that is out of proportion to the findings on physical exam may be the only clue that necrotizing fasciitis is present. As the infection progresses bullae develop, first filled with clear fluid and may rapidly take on a maroon or violaceous color.[2] Inflammation spreads quickly along the fasical planes, ultimately leading to necrosis and liquefaction of the overlying tissue. As tissue destruction progresses, ischemia with infarction of the superficial cutaneous nerves takes place, and the pain the patient originally felt dissipates. At this point, approximately 50% of patients may have developed full-blown streptococcal toxic shock syndrome (STSS), defined as isolation of GAS from a normally sterile site accompanied by hypotension and multiple organ system failure. Table 1[9] summarizes the diagnostic criteria for STSS. This syndrome carries a high case-fatality rate, between 30-80%.[9,10] Laboratory findings in necrotizing fasciitis may include leucocytosis with left shift and an elevated creatinine kinase. A gram stain of the affected tissue may demonstrate gram positive cocci in chains and culture of this material may yield GAS or other organisms. Bacteremia is frequently present. To assist in determining the depth and extent of soft tissue involvement, computed axial tomography or magnetic resonance imaging may be helpful. However, surgical management should not be delayed in favor of these, as only surgical assessment can determine the state of the fascia. Subcutaneous emphysema on plain radiographs may be demonstrated in polymicrobial necrotizing fasciitis, although this will not be seen in infection caused by GAS as these are non gas-forming organisms.

Diagnosis. There is no one pathognomonic feature that can aid in diagnosis of necrotizing fasciitis, therefore it is critical to have a high index of suspicion. In the post surgical patient, signs of sepsis, wound dehiscence, and a foul smelling clear to grey-colored discharge at the operative site may be suggestive of a Type 1 polymicrobial necrotizing fasciitis. Surgical exploration is indicated to establish the status of the wound and fascia. In GAS necrotizing fasciitis, initially subjective pain out of proportion to the physical findings is characteristic, because early fasciitis mostly involves the subcutaneous tissues and overlying skin is often normal. As tissue injury progresses anesthesia may ensure, but these findings are not pathognomonic. On history, the patient may report an antecedent minor injury, and concurrent flu-like illness with fever and chills. Once the diagnosis of necrotizing fasciitis is considered, delays in surgical exploration of the suspected site must be avoided. At the time of surgical investigation, if upon probing the fascia it does not provide any resistance, a diagnosis of necrotizing fasciitis can be established.[3] Fresh frozen section analysis of devitalized tissue can aid in confirming this diagnosis. To help guide the most appropriate antimicrobial therapy, tissue must be obtained for gram stain and anaerobic and aerobic cultures. As well, at the time of initial presentation, it is important to obtain a complete blood count, coagulation parameters, electrolytes, biochemistry measuring renal and hepatic function, blood cultures, and cultures from any obviously affected site.

Treatment. For both types of necrotizing fasciitis, early recognition and treatment is critical to decrease the substantial morbidity and mortality associated with this condition. This includes initiating aggressive fluid resuscitation, obtaining the appropriate serum investigations and cultures, beginning empiric antimicrobial therapy, and early surgical intervention with debridement of all devitalized tissue. At surgery, it is crucial that a radical debridement of all devitalized tissue be initiated with the goal being to reach healthy bleeding tissue. Unfortunately, this does not guarantee all affected tissue has been removed, and in many cases a "second-look surgery" is necessary to ensure the fasciitis has not progressed.

A proportion of patients with GAS necrotizing fasciitis will have shock, with hypotension and evidence of end-organ damage. These patients require urgent stabilization and are best cared for in an intensive care setting. Here they can be aggressively resuscitated with fluids and supported with inotropes, as well as undergoing invasive hemodynamic monitoring and assisted ventilation if needed.

When contemplating the diagnosis of GAS necrotizing fasciitis, it is prudent to begin empiric antimicrobial therapy consisting of parenteral penicillin G (4 million units every 6 hours) and parenteral clindamycin (600mg every 8 hours). If concern exists that there may be a polymicrobial infection including gram negative organisms, consider the addition of an aminoglycoside or a 3rd generation cephalosporin with the doses adjusted for renal function. Clindamycin was more effective than penicillin in reducing mortality in the mouse models of streptococcal myositis. This likely follows from the fact that clindamycin acts as an inhibitor of protein synthesis, and thus may decrease the synthesis of streptococcal M protein and pyrogenic exotoxins.[11-13] The streptococci, however, remain exquisitely sensitive to penicillin, and thus penicillin combined with clindamycin may be of added benefit.[10] Again, it is important to remember that antimicrobial therapy alone is not sufficient treatment for any type of necrotizing fasciitis. Surgery is absolutely necessary to explore and debride any devitalized tissue. Delay in surgical exploration leads to poor patient outcome as the infection may progress to such an extent that complete surgical excision is impossible, in particular if infection spreads to the abdomen, thorax, neck or face.

"Second-look" procedures are often necessary to ensure all devitalized tissue has been excised.

There are 2 adjuncts to the treatment of necrotizing fasciitis: intravenously administered immunoglobulin (IVIG) for patients suffering from streptococcal toxic shock syndrome[7,14] and hyperbaric oxygen.[15] Data from observational studies suggests they have a role, especially IVIG, although double blind randomized controlled studies have not been performed to evaluate the efficacy of these treatments. Intravenously administered immunoglobulin is believed to block overzealous T-cell activation, although the exact mechanism is not understood. It is thought that IVIG either blocks specific receptor sites on the T-cells or bind to and neutralize the "superantigens". Doses ranging from 400mg/kg/day to 2g/kg/day for one to 5 days have been used, but the most efficacious dosing and frequency of administration have not been determined. The current recommended dose of IVIG is a single dose of 2g/kg with a repeat dose at 48 hours if the patient remains unstable.[7,16] The use of hyperbaric oxygen is controversial as there is conflicting data supporting it's use. It may be attempted if available, but it must not delay or replace conventional therapy.

Infection control and public health issues. Infection control precautions for cases of necrotizing fasciitis include good hand washing, standard wound precautions, and isolation only if potentially infectious secretions cannot otherwise be controlled. When a patient with necrotizing fasciitis is admitted to hospital, the infection control staff should be notified so the most recent recommendations regarding patient management can be obtained and implemented. Household members of the index case with invasive GAS disease have an increased risk of almost 200 times compared to the general population of invasive GAS disease. However, the need for antimicrobial prophylaxis for contacts of cases is not well established. Generally, close household contacts of persons with invasive GAS disease are advised to receive prophylaxis with a suitable anti-streptococcal agent such as penicillin, amoxicillin, erythromycin, cephalexin, or clindamycin for a 10 day period. A close contact is defined as having the following relationship to the index case: someone with whom >4 hours per day or 20 hours per week of contact is had, who shares sleeping arrangements, or has direct mucous membrane contact with oral or nasal secretions within 7 days of illness. Throat cultures are not indicated because negative cultures do not negate the indication for chemoprophylaxis.[16] The health care provider should consult the local health authorities for the most recent recommendations concerning antimicrobial chemoprophylaxis. It is also the responsibility of the health care team and the local health authorities to accurately inform and reassure the public whenever a case of invasive GAS disease occurs in light of the often inaccurate and exaggerated media attention this illness receives.

In conclusion, necrotizing fasciitis remains a rare, although devastating disease if not recognized early and treated appropriately. Early diagnosis requires physician awareness of presenting and a high index of suspicion. As well, due to the negative media attention this illness receives, the physician must allay the fears and answer questions his patients have about this disease.

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