REVIEW

CME CREDIT

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GROUP A STREPTOCOCCAL NECROTIZING FASCIITIS

Diagnosing and treating the "flesh-eating bacteria syndrome"

ABSTRACT

Over the past decade the incidence of necrotizing fasciitis due to group A streptococci has increased. Appropriate management of this life-threatening infection requires rapid recognition, immediate antibiotic therapy, and expeditious surgical debridement or excision.

KEY POINTS

Suspect necrotizing fasciitis rather than cellulitis if there is severe pain (sometimes followed by anesthesia), inflammation, and necrosis that spread rapidly, bullous formation, toxic shock syndrome, or an elevated creatine kinase level.

Fever with unexplained severe musculoskeletal pain are important clues to imminent necrotizing fasciitis.

Infection often follows a penetrating or blunt traumatic injury to the site involved, but may occur without any preceding noticeable injury. Other predisposing factors include varicella, chronic skin conditions, and previous surgery.

Patients with group A streptococcal necrotizing fasciitis require expeditious surgical management. Multiple debridements are usually required.

Appropriate antimicrobial therapy can include a beta-lactam agent plus clindamycin.

THE PAST 10 YEARS have seen increasing reports of a disturbing type of subcutaneous infection: necrotizing fasciitis, caused by group A streptococci. Appearing suddenly, sometimes in previously healthy victims with no history of a wound or injury, these infections can progress within hours to necrosis of an entire limb, often culminating in amputation or death. The lay media quickly named this disease "the flesh-eating bacteria syndrome."

Fortunately, necrotizing fasciitis is uncommon. But when it occurs, it demands fast action to save the patient's life. This review discusses recent perspectives on the pathophysiology, clinical manifestations, and therapy of necrotizing fasciitis caused by group A streptococci.

MICROBIOLOGY OF NECROTIZING FASCIITIS

Necrotizing fasciitis is an uncommon soft-tissue infection characterized by rapidly spreading inflammation and subsequent necrosis of the muscle fascia and overlying skin. It is usually grouped under the larger classification of necrotizing soft tissue infections, which are differentiated by the anatomical extent of involvement and include clostridial cellulitis, synergistic necrotizing cellulitis, and gas gangrene (myonecrosis).[1,2] In necrotizing fasciitis, the infection and inflammation are usually limited in depth to the top of the muscle fascia.

Cases of necrotizing fasciitis can be classified into two types[3]: type 1, polymicrobial infections with mixed anaerobic and aerobic organisms; and type 2, with *Streptococcus pyogenes* as the predominant pathogen. Until recently most reviews focused on type 1 infec-

tions, often in association with underlying conditions such as diabetes mellitus. However, in the last decade, type 2 infections have increased in incidence.[4,5]

Streptococcus pyogenes the primary culprit

Streptococcus pyogenes is a member of the group A beta-hemolytic streptococci (so called because they react with Lancefield group A antisera), and accounts for almost all group A streptococcal strains; others include the hemolytic strains *S anginosus* and *S equisimilis* and nonhemolytic strains such as *S salivarius*.[6] For this presentation, "group A streptococci" refers to *S pyogenes* only.

S pyogenes is ubiquitous and is found both in humans and in animals. It is one of the most common human pathogens and can cause a number of diseases: pharyngitis, pyoderma, scarlet fever, cellulitis, toxic shock syndrome, necrotizing skin infections, and postinfectious sequelae such as rheumatic fever and acute glomerulonephritis. When accompanied by shock, organ failure, bacteremia, necrotizing fasciitis, and death, these infections are called the streptococcal toxic shock syndrome.[7]

These infections, particularly scarlet fever, have fluctuated in incidence and severity in the past (see "Necrotizing fasciitis in history," this page). Invasive group A streptococcal infections declined dramatically from the early 20th century until the mid-1980s, when they started to reemerge [9,10] (see "Why are invasive group A streptococcal infections increasing?").

NECROTIZING FASCIITIS IN HISTORY

Two hundred years ago the germ theory of disease did not yet exist, and the term "necrotizing fasciitis" would not be coined until the 1950s. Yet, there is evidence that this disease existed. Loudon[8] reviewed historic documents and concluded that diseases once known as "malignant ulcer," "hospital gangrene," and "phagedena" were probably streptococcal necrotizing fasciitis, and that these horribly virulent conditions were well known in the armed forces during the Napoleonic Wars, the Crimean War, and in the Confederate Army in the American Civil War.

Thomas Trotter, an 18th century British naval physician, wrote:

"In the summer of 1799, the malignant ulcer made its appearance on board the *Temeraire*...Every wound, abrasion of the cuticle, blistered part, scald, or burn, passed rapidly through the various stages of inflammation, gangrene and sphacelus [sloughing, mortification]...some suffered large exfoliations of bone."

Surgeon John Hennen wrote of an outbreak in an army hospital during the Napoleonic wars:

"The whole hospital was overrun with gangrene...the face of the sufferer assumed a ghastly, anxious appearance...the slightest change of posture, or the most delicate examination of the sore, put [the patient] to torture...The bravest soldier betrayed the greatest imaginable impatience of pain and depression of spirits. Men who had borne amputation without a groan, shrank at the washing of the sores...sinking into sullen despair...the limb became horribly foetid...[it was] one of the most subtle and destructive poisons that ever infested an hospital, attacking equally the most robust and the most debilitated, and, if unchecked by medical aid, proceeding invariable to a fatal termination."

During the Crimean War, Florence Nightingale wrote: "80 cases of hospital gangrene [were] recorded in one month at Scutari (and many, many more passed unrecorded)."

By the early 20th century, necrotizing fasciitis seems to have nearly disappeared, but recent reports indicate it is again on the rise.

EPIDEMIOLOGY OF NECROTIZING FASCIITIS

Cases tend to be sporadic. In the largest population surveillance study of this disease, Kaul et al[23] reported the incidence as 0.40 cases per 100,000 population in 1995. Mortality rates have ranged from 20% to 40%.[7,23,24] Secondary cases are rare, but have been reported among family members with intimate contact and also among medical personnel caring for patients.[15,20] Large outbreaks have not occurred because the vast majority of the population has acquired immunity to one or more of the streptococcal virulence factors.

This disease can occur at any age, often in young, previously healthy patients.[9,24] However, Kaul et al[23] observed a higher incidence in patients older than 65 years and in patients with underlying diseases such as diabetes, alcohol abuse, chronic cardiac disease, or peripheral vascular disease.

CLINICAL PRESENTATION

Infection often follows a penetrating or blunt traumatic injury to the site involved, but may occur without any preceding noticeable injury. Other predisposing factors include varicella, chronic skin conditions (decubitus or ischemic ulcers, psoriasis), and previous surgery.

The most common primary site is the extremities. Among our patients, the upper extremity has been most commonly involved. However, Kaul et al[23] found the lower extremities were the most common primary site (53% of cases), followed by the upper extremity (29%), trunk (9%), groin or perineum (8%), and face (1%). Cases involving the lower extremity or the perineum and groin are often caused by a polymicrobial aerobic-anaerobic infection, which may include group A streptococci—an important fact when considering initial empiric antimicrobial therapy.

The sequence of infection

Necrotizing fasciitis usually follows a set sequence.

Diffuse erythema and swelling, exquisite tenderness and pain are the first signs and symptoms. Lymphangitis and lymphadenitis are infrequently observed.

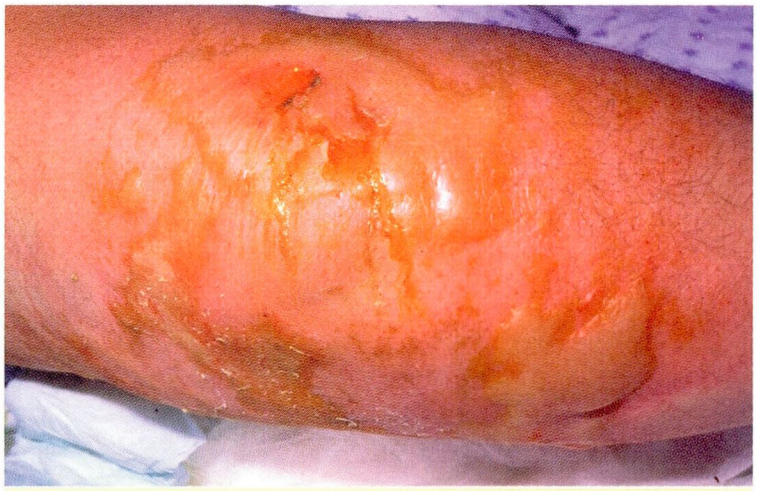

FIGURE 1. Necrotizing cellulitis and fasciitis of the elbow of a previously healthy 32-year-old woman who presented with streptococcal toxic shock syndrome.

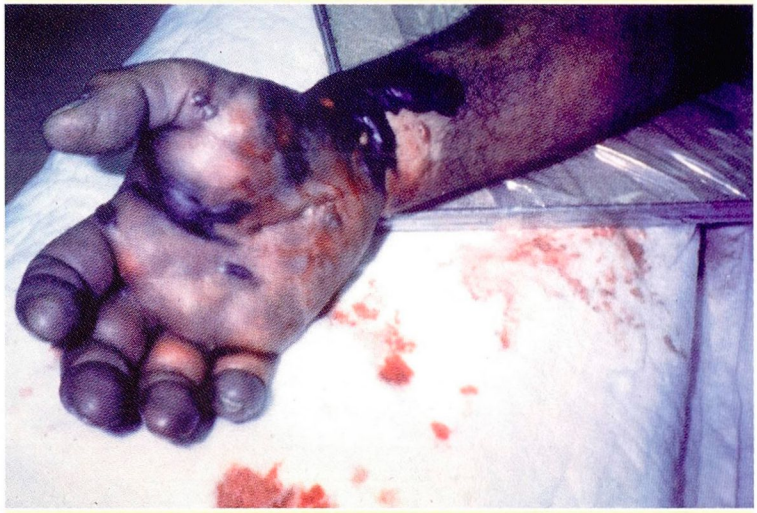

FIGURE 2. Hand and forearm of a 73-year-old man with group A streptococcal necrotizing fasciitis and myonecrosis. This patient was home eating dinner 6 hours prior to this photograph, illustrating the rapid onset of severe and extensive disease. Amputation of the entire upper extremity was performed.

Bullae filled with clear fluid follow next. Commonly, these bullous lesions rapidly become maroon or violaceous (FIGURES 1 AND 2) and are followed by:

Frank cutaneous gangrene that evolves rapidly, and an extension of inflammation

WHY ARE INVASIVE GROUP A STREPTOCOCCAL INFECTIONS INCREASING?

Extensive study of group A streptococcal infections, conducted over the past 75 years, has revealed a number of substances produced by strains of this organism that may increase its virulence. However, a firm understanding of the complex pathophysiology of these infections remains unclear. Investigators have increased their efforts to uncover virulence factors both old and new that may be responsible for the perceived resurgence of severe disease.

FACTORS IN THE ORGANISM

Group A streptococci produce a number of surface components and extracellular products that are believed to play important roles in infection, such as M-proteins, hyaluronic acid capsules, pyrogenic exotoxins, and others. This multiplicity of possible virulence factors has prevented investigators from conclusively implicating any single one of them as the reason for invasive infection.

M-protein is believed to make streptococci more invasive by conferring an ability to resist phagocytosis.[11] Conversely, type-specific antibodies directed against specific M-proteins following infection confer host resistance to group A streptococci of that M-type. A major shift in the distribution of M-protein types was observed in the early 1980s, with an increasing frequency of M1 and M3 serotypes.[12] Although types M1 and M3 were found more often in invasive fatal infections than were other M serotypes, other M serotypes including M6, M12, M18, M28 as well as many M nontypable strains have also been recovered.[4,13–15]

Superantigens. Initial studies of M1 and M3 isolates from invasive cases implicated streptococcal pyrogenic exotoxins (SPEs), formerly known as erythrogenic or scarlet fever toxins. In these studies, SPE-A appeared to play a major role in severe disease. A higher percentage of streptococcal isolates from cases of invasive disease produced SPE-A than did strains from less severe cases.[16,17]

SPE-A, SPE-B, and SPE-C belong to a group of proteins termed "superantigens."[18] Superantigens, in general, activate a much larger proportion of T cells than do conventional peptide antigens in some individuals, resulting in the production of various cytokines. These cytokines in turn are believed to be responsible for the manifestations of streptococcal toxic shock syndrome and necrotizing fasciitis.

SPE-A and SPE-B induce mononuclear cells to produce cytokines (eg, tumor necrosis factor, interleukin-1B, interleukin-6), which can mediate the fever, shock, and tissue injury observed with streptococcal toxic shock syndrome and necrotizing fasciitis.[4,19] SPE-producing strains of group A streptococci were prevalent in the early part of this century but had essentially disappeared after 1940. Decreased host immunity to these exotoxins is one possible explanation for the reemergence of severe disease. Two newly described exotoxins, streptococcal "superantigen" and mitogenic factor, are also

along fascial planes.[2] In some patients, necrosis progresses less quickly; Kaul et al[23] described a subset of patients with diabetes or peripheral vascular disease or both, in whom chronic underlying ischemia may have contributed to soft tissue necrosis and in whom the progression of necrosis was less rapid.

Overlying skin anesthesia provides a clue that the process is necrotizing fasciitis and not simple cellulitis. As tissue necrosis progresses the pain may disappear, as thrombosis of small blood vessels leads to destruction of the superficial nerves located in the underlying subcutaneous tissues. Local skin anesthesia may antedate the appearance of skin necrosis.

Toxic shock syndrome

Toxic shock syndrome is linked to necrotizing

capable of inducing a variety of cytokines and may also play a role in pathogenicity.

LACK OF IMMUNITY IN THE HOST

A complex interaction between streptococcal virulence factors and the immune or nonimmune host ultimately determines the clinical syndrome and outcome of streptococcal infection. The amount of virulence factors produced and the interaction of these factors with an immune or nonimmune host determine the severity of illness.

Recent evidence suggests that clonal expansion of more virulent strains of group A streptococci may not be responsible for the recent increase in severe cases; rather, lack of acquired immunity in susceptible individuals may be to blame. Acquired immunity to one or more streptococcal virulence factors by most of the population has probably prevented large outbreaks of invasive disease.

From 1994 to 1996, we observed a number of cases of streptococcal toxic shock syndrome and necrotizing fasciitis in northeastern Ohio that were caused by group A streptococcal serogroup M3. Invasive M3 isolates seen in the Akron area demonstrated the same DNA banding profile by pulsed-field gel electrophoresis.[20] A survey of group A streptococci recovered from blood and wound specimens from both invasive and noninvasive cases during the same period showed that although this distinct M3 clone was isolated from approximately 30% of the specimens tested, only a few patients had invasive disease.[21] These and other observations underscore the role of the host in determining the severity of streptococcal infection.

NSAID USE MAY PROMOTE NECROTIZING FASCIITIS

Our own experience and that of others suggests that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has a positive association with the progression of invasive group A streptococcal infection, including necrotizing fasciitis.[22] Stevens[22] found that in several cases, pain was erroneously attributed to phlebitis, muscle strain, bursitis, or arthritis. Many of these patients received NSAIDs but no antibiotics, and the disease progressed even though the NSAIDs reduced the signs and symptoms of inflammation. In many cases, group A streptococcal necrotizing fasciitis was not diagnosed until signs of shock or tissue gangrene were apparent.

There is a biochemical rationale that could support an association with NSAIDs.[22] Although NSAIDs are often used to relieve pain and reduce fever, they also alter granulocyte function. In addition, they enhance production of tumor necrosis factor, probably by preventing feedback inhibitors by prostaglandin E2. Thus, NSAIDs may predispose to group A streptococcal necrotizing fasciitis by inhibiting granulocyte function, augmenting cytokine production, and attenuating the cardinal manifestations of inflammation in a patient with group A streptococcal cellulitis.

fasciitis. Approximately 50% of patients with streptococcal toxic shock syndrome have necrotizing fasciitis.[25] Conversely, in most case series, approximately 50% of cases of group A streptococcal necrotizing fasciitis were associated with toxic shock syndrome.[23,24] TABLE 1 lists the criteria for diagnosing both conditions, devised by a committee of clinicians, epidemiologists, and microbiologists.[7]

Laboratory findings

Leukocytosis is usually present.

Gram stain smears from aspirates or debrided tissue often reveal gram-positive cocci.[24] In contrast, in our experience a Gram stain is rarely positive in most cases of nonnecrotizing cellulitis.

An elevated serum creatine kinase level is often a clue to the presence of necrotizing

TABLE 1

Case definitions of streptococcal toxic shock syndrome* and necrotizing fasciitis

Streptococcal toxic shock syndrome, definite case
- Group A *Streptococcus* isolated from a normally sterile site
  - AND
- Hypotension
  - AND
- At least two of the following:
  - Renal impairment
  - Coagulopathy
  - Liver abnormalities
  - Acute respiratory distress syndrome
  - Extensive tissue necrosis (ie, necrotizing fasciitis)
  - Erythematous rash

Streptococcal toxic shock syndrome, probable case
- As above, but group A *Streptococcus* is isolated from a nonsterile body site

Necrotizing fasciitis, definite case
- Necrosis of soft tissues with involvement of the fascia
  - AND
- Serious systemic disease, including one or more of the following:
  - Death
  - Shock (systolic blood pressure < 90 mm Hg)
  - Disseminated intravascular coagulopathy
  - Respiratory, hepatic, or renal failure
  - AND
- Isolation of group A *Streptococcus* from a normally sterile body site

Necrotizing fasciitis, suspected case
- Necrosis and serious systemic disease (as above)
  - AND EITHER
- Serologic confirmation of group A streptococcal infection by a fourfold rise against streptolysin O or DNAase B
  - OR
- Histologic confirmation of Gram-positive cocci in a necrotic soft tissue infection

*Any group A streptococcal infection associated with early onset of shock and organ failure.

SOURCE: FROM STEVENS DL. INVASIVE GROUP A STREPTOCOCCAL INFECTIONS: THE PAST, PRESENT AND FUTURE. PEDIATR INFECT DIS J 1994; 13:561–566.

TABLE 2

Clues that suggest necrotizing fasciitis rather than cellulitis

- Pain (severe, followed by anesthesia)
- Rapidly spreading swelling and inflammation
- Bullae
- Necrosis (later appearance)
- Toxic shock syndrome
- Elevated creatine kinase level
- Predisposing factors: varicella, use of nonsteroidal anti-inflammatory drugs

fasciitis or myositis.

Bacteremia. Blood cultures are frequently positive. Kaul et al[23] found that bacteremia predicted increased mortality; however, bacteremia is not a clinically useful marker because it can only be detected 24 to 48 hours after presentation. Similarly, the presence of group A streptococcal bacteremia does not reliably distinguish necrotizing fasciitis from cellulitis, since bacteremia is also found in association with non-necrotizing cellulitis. Further, other pathogens can cause necrotizing fasciitis, including *Clostridia* species, mixed aerobes and anaerobes, staphylococci, *Vibrio vulnificus* (salt water injury), *Aeromonas hydrophilia* (fresh water injury), *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Yersinia enterocolitica*.

Differential diagnosis: Necrotizing fasciitis vs cellulitis

Although the diagnosis of necrotizing fasciitis may be clear-cut at the later stage of disease (extensive necrosis), it is often difficult to differentiate from cellulitis at presentation. Since cellulitis can be treated with antimicrobial agents without surgical management, whereas necrotizing fasciitis requires timely surgical debridement and excision of tissue in addition to the use of antimicrobial agents, this distinction is important.

Clinical characteristics that should direct one to consider group A streptococcal necrotizing fasciitis are listed in TABLE 2. Bullae may be observed in cellulitis without fasciitis (FIGURE 3). Fever with unexplained severe musculoskeletal pain is an important clue to imminent necrotizing fasciitis. Another indication of necrotizing disease: a hemostat introduced through a limited incision will pass easily along a plane just superficial to the deep fascia in the involved area.

Other conditions that may mimic the early manifestations of necrotizing fasciitis include trauma with hematoma (although

fever and leukocytosis are usually absent), phlebitis, bursitis, and arthritis.

Imaging studies

Computed tomography, magnetic resonance imaging, and routine soft tissue roentgenograms may be helpful in demonstrating the involvement of subcutaneous tissue beyond the visibly involved cutaneous abnormality. However, these studies should not delay surgical evaluation if necrotizing fasciitis is suspected. Rather, they should serve to expedite and direct surgical intervention. Furthermore, since gas is not present in group A streptococcal necrotizing fasciitis (in contrast to that caused by mixed aerobic-anaerobic or clostridial infection), the findings of imaging studies are often nonspecific.

PROMPT THERAPY IS VITAL

Streptococcal necrotizing fasciitis must be recognized early and treated quickly (TABLE 3). Kaul et al[23] reported that the mortality rate approached 100% if appropriate surgical intervention was not performed. Although necrotizing cutaneous infections are generally classified into specific entities (ie, necrotizing fasciitis, *Clostridium* myonecrosis) on the basis of selected clinical characteristics and etiology, the initial clinical manifestations are usually not distinctive. Regardless of the etiology, the primary therapy is emergent surgery and treatment with antibiotics active against streptococci, *Clostridium* species, and mixed aerobes and anaerobes.

Surgical therapy

The goals of surgery are threefold: to remove all necrotic tissues by urgent radical debridement, to preserve as much viable skin as possible, and to maintain hemostasis. Amputation may be necessary to remove all nonviable tissues. A "second-look" procedure may be necessary within 12 to 24 hours to reculture and further remove all necrotic and infected materials that may have been missed. Multiple debridements may be necessary (FIGURE 4): McHenry et al[26] reported a case series of 65 patients with necrotizing fasciitis, each of whom needed an average of 33 operative debridements, and several of whom needed amputations to control the infection.

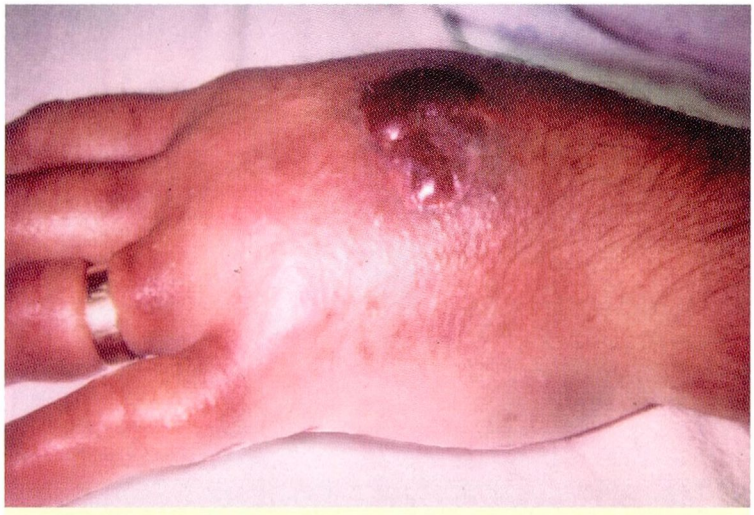

FIGURE 3. Bullous cellulitis without necrotizing fasciitis in a 60-year-old man.

TABLE 3

General principles in the care of patients with necrotizing fasciitis

Patients with necrotizing fasciitis or myonecrosis who do not undergo exploration and debridement will surely die

Devitalized tissue, including muscle, fascia, and skin must be removed

Appropriate surgical debridement in certain locations of the body—head, neck, thorax, abdomen—may be virtually impossible

Multiple debridements over the course of several weeks are usually necessary

Extensive reconstructive surgery is generally necessary

Some corollaries to these principles

Adequate debridement can rarely be performed in one step

Skin overlying necrotic fascia may remain viable, and if it appears to be so at the time of initial debridement, it may be spared for a second look during follow-up debridement

Patients with established necrotizing fasciitis are frequently poor surgical risks, with high surgical mortality and morbidity; nonetheless, failure to perform the operation will result in virtually 100% mortality

If primary care physicians are concerned that a deeper infection might be present, surgical evaluation is warranted

SOURCE: ADAPTED FROM STEVENS, DL. NECROTIZING FASCIITIS: DON'T WAIT TO MAKE A DIAGNOSIS. INFECTIONS IN MEDICINE 1997; 14: 684–688.

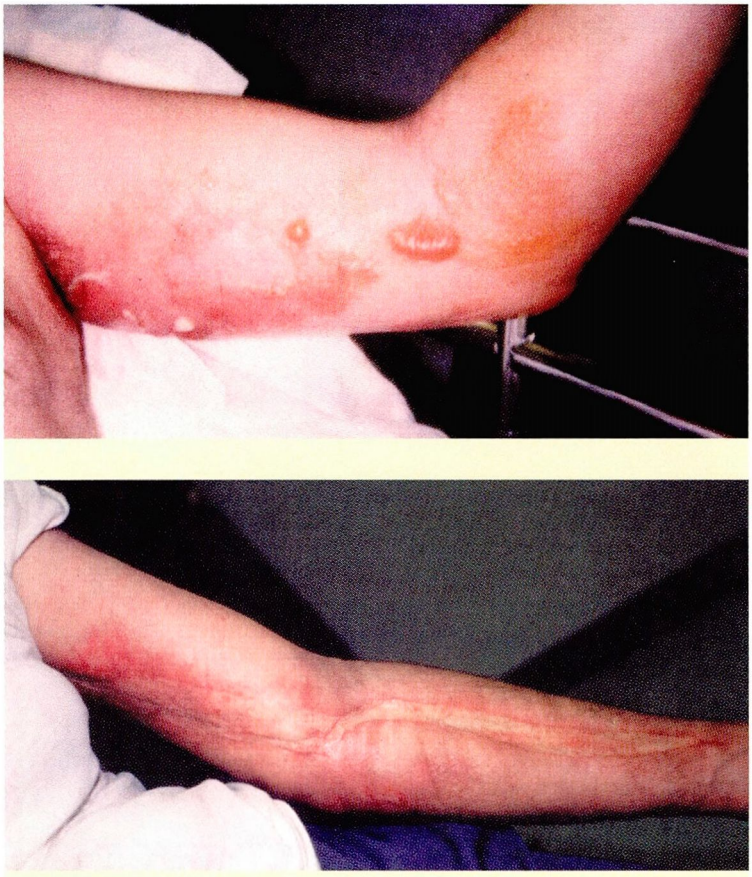

FIGURE 4. Top, necrotizing fasciitis in a 67-year-old man. Bottom, same patient after six operative procedures—fasciotomies and debridements.

TABLE 4

Recommended therapy for necrotizing fasciitis

- Surgical debridement, amputation
- Antimicrobial therapy
  - One of the following:
    - Piperacillin-tazobactam
    - Ticarcillin-clavulanate
    - Imipenem-cilastatin
  - Plus:
    - Clindamycin (penicillin may not be effective)
  - For penicillin-allergic patients:
    - Clindamycin plus ciprofloxacin
- Tetanus toxoid
- Intravenous immunoglobulin (for severe cases)
- Hyperbaric oxygen (controversial)

Empiric antimicrobial therapy

It is difficult to determine the etiology on the basis of the clinical presentation; therefore, empiric antibiotic therapy should be started as soon as this disease is suspected. The antimicrobial agents chosen should have activity against *Streptococcus*, *Clostridium*, and mixed aerobic-anaerobic organisms. A combination of a beta-lactam plus a beta-lactamase inhibitor such as ticarcillin-clavulanate, piperacillin-tazobactam, or a carbapenem should provide the adequate spectrum.

Penicillin is not effective in the presence of a large inoculum of bacteria.[27,28] Further, Stevens et al[29] demonstrated that streptococci do not express penicillin-binding protein on their membranes during the stationary phase, ie, when they are not dividing.

Clindamycin, in contrast, has shown greater efficacy in experimental fulminant streptococcal infection.[27,29] Clindamycin, unlike the beta-lactams, inhibits protein synthesis and is not affected by the inoculum size or the stage of bacterial growth.[25] In addition, clindamycin suppresses bacterial toxin synthesis and enhances phagocytosis of streptococci.[30,31]

Recommendations. We recommend initial therapy with a combination of a beta-lactam, a beta-lactamase inhibitor, and clindamycin until the etiology is known (TABLE 4). Tetanus prophylaxis should be considered in patients who are not up to date with immunization.

Other therapies

Hyperbaric oxygen is still debated as a therapy for this disease.[2,32] Surgery and antimicrobial therapy should not be postponed while a patient receives this therapy.[33,34]

Intravenous immunoglobulin has been shown to have some beneficial effect in toxic shock syndrome.[35–37] This effect may be due to its ability to neutralize superantigen.[38] (Patients with lethal infections lack neutralizing antibodies to one or several toxins.[39,40])

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