Necrotizing fasciitis is a surgical diagnosis characterized by friability of the superficial fascia, dishwater-gray exudate, and a notable absence of pus. This and other necrotizing soft-tissue infections have multiple causes, risk factors, anatomical locations, and pathogenic mechanisms, but all such infections result in widespread tissue destruction, which may extend from the epidermis to the deep musculature.

Necrotizing infections can occur after major traumatic injuries, as well as after minor breaches of the skin or mucosa (e.g., tears, abrasions, lacerations, or insect bites), varicella infection, nonpenetrating soft-tissue injuries (e.g., muscle strain or contusion), or routine obstetrical and gynecologic procedures; they can also occur in postsurgical and immunocompromised patients (Table 1). Although necrotizing infections have common clinical features, various entities have been defined, such as progressive bacterial synergistic gangrene, synergistic necrotizing cellulitis, streptococcal gangrene, gas gangrene (clostridial myonecrosis), and nonclostridial anaerobic cellulitis. Subtle differences may distinguish one entity from another, but the clinical approaches to diagnosis and treatment are similar.

In this review, we describe the clinical and laboratory features of necrotizing fasciitis and other necrotizing soft-tissue infections. We also discuss diagnostic pitfalls and recommended treatment approaches, as well as the effect of delays in surgical intervention on mortality. (Details about pathogenic mechanisms are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)
difficult to distinguish from gas gangrene. Nonclostridial anaerobic cellulitis and synergistic necrotizing cellulitis are type I variants. Both occur in patients with diabetes and typically involve the feet, with rapid extension into the leg. Though nonnecrotizing cellulitis is common in patients with diabetes, necrotizing fasciitis should be considered in patients with systemic manifestations of sepsis, such as tachycardia, leukocytosis, acidosis, or marked hyperglycemia.

Bacterial penetration into the fascial compartments of the head and neck may result in Ludwig’s angina (i.e., infection of the submandibular fascial spaces) or Lemierre’s syndrome (thrombophlebitis of the jugular vein), with or without severe sepsis. Breach of the gastrointestinal or urethral mucosa may result in Fournier’s gangrene, which begins abruptly with severe pain and may spread rapidly from the perineal region to the anterior abdominal wall, the gluteal muscles, and in males, the genitalia. Finally, an indolent polymicrobial infection known as progressive bacterial synergistic gangrene or large phagedenic ulcer can follow surgery involving colostomy sites or wire sutures. Though large ulcerations often develop, the process does not involve the fascia.

Necrotizing fasciitis type II is a monomicrobial infection (Table 1). Among gram-positive organisms, group A streptococcus remains the most common pathogen, followed by methicillin-resistant Staphylococcus aureus (MRSA). Unlike type I infections, type II infections may occur in any age group and in persons without any underlying illness.

Other pathogens include Aeromonas hydrophila and Vibrio vulnificus. Some experts have proposed that infections with these microbes, and possibly clostridial species, be classified as necrotizing fasciitis type III. Monomicrobial necrotizing fasciitis due to gram-negative pathogens (bacteria and Escherichia coli) has also been reported, though these infections are typically seen in immunocompromised, diabetic, obese,

Table 1. Factors Conferring a Predisposition to Specific Necrotizing Soft-Tissue Infections.*

<table>
<thead>
<tr>
<th>Predisposing Factor</th>
<th>Clinical Syndrome</th>
<th>Etiologic Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major penetrating trauma: crush or deeply penetrating wound</td>
<td>Gas gangrene</td>
<td>Clostridium perfringens, C. histolyticum, or C. novyi</td>
</tr>
<tr>
<td>Minor penetrating trauma</td>
<td>NF type II</td>
<td>Aeromonas hydrophila</td>
</tr>
<tr>
<td>Freshwater laceration</td>
<td></td>
<td>Vibrio vulnificus</td>
</tr>
<tr>
<td>Saltwater laceration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor nonpenetrating trauma: muscle strain, sprain, or contusion</td>
<td>NF type II or streptococcal myonecrosis</td>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td>Mucosal breach: mucosal tear (rectal, vaginal, urethral); gastrointestinal, genitourinary or gynecologic surgery</td>
<td>NF type I</td>
<td>Mixed aerobic and anaerobic organisms</td>
</tr>
<tr>
<td>Skin breach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella lesions</td>
<td>NF type II or streptococcal myonecrosis</td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>Insect bites</td>
<td>NF type II or streptococcal myonecrosis</td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>Injection drugs</td>
<td></td>
<td>C. perfringens, C. histolyticum, C. novyi, or C. sordellii</td>
</tr>
<tr>
<td>Immunocompromised state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes with peripheral vascular disease</td>
<td>NF type I</td>
<td>Mixed aerobic and anaerobic organisms</td>
</tr>
<tr>
<td>Cirrhosis and ingestion of raw oysters</td>
<td>NF type II</td>
<td>V. vulnificus</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Gas gangrene</td>
<td>C. septicum</td>
</tr>
<tr>
<td>In women: pregnancy, childbirth, abortion (spontaneous or medically induced), gynecologic procedures or surgery</td>
<td>NF type II, streptococcal myonecrosis, or clostridial myonecrosis</td>
<td>S. pyogenes, C. perfringens, or C. sordellii</td>
</tr>
<tr>
<td>Occult factors: colonic lesions, including carcinoma</td>
<td>Spontaneous gas gangrene</td>
<td>C. septicum</td>
</tr>
</tbody>
</table>

* Gas gangrene is also known as clostridial myonecrosis.
Infections are mediated by potent bacterial exo-
necrotizing group A streptococcal and clostridial
pyogenes

lion people worldwide have invasive

A 2005 report estimated that more than 18 mil-

Infections

Invasive Group A Streptococcal Soft-Tissue

Practitioners.

A consensus among international infectious dis-

Resolution of these nomenclature issues requires

typically classified as necrotizing fasciitis type II.

Infections may occur. Very rapidly, the skin be-

Bacteremia is frequently present, and metastatic

Dysphotogenic and deep-muscle involvement is more common in

The initial lesion may appear to be only mildly

erythematous, but over a period of 24 to 72 hours,
inflammation becomes extensive, the skin turns
dusky and then purplish, and bullae appear.

Bacteremia is frequently present, and metastatic

infections may occur. Very rapidly, the skin be-

comes frankly gangrenous and undergoes exten-
sive sloughing. The patient is now perilously ill,
with a high temperature and extreme prostration.

At this stage, mortality is high, even with appro-
priate treatment.24,27

In approximately 50% of patients with group
A streptococcal necrotizing fasciitis or myone-
crosis, infection initiates deep in the soft tissues,
without a portal of entry, often at sites of non-
penetrating trauma (muscle strain or bruise).26,28,29
Initially, only fever and crescendo pain (rapid
pain escalation sufficiently severe to require
ketorolac or narcotics) may be present, and such
pain prompts patients to seek urgent medical
care. Malaise, myalgias, diarrhea, and anorexia
may also be present in the first 24 hours. Since
cutaneous manifestations are absent initially,
the infection is often misdiagnosed or the cor-
correct diagnosis is delayed,30 and as a result, the
mortality exceeds 70%.28 By the time ecchymoses
and bullae develop, tissue destruction is exten-
sive, and systemic toxicity and organ failure are
evident. Emergency surgery, including extensive
débridement or multiple amputations, is often
required to ensure survival and necessitates pro-
longed hospitalization.26,30-32 Erroneous diagnoses
include severe muscle strain and deep-vein throm-
bophlebitis; because of the associated gastro-
intestinal manifestations, food poisoning may
also be diagnosed in error. Although seeding of
the deep tissues probably occurs through tran-
sient bacteremia from the nasopharynx, reports
rarely document coexisting or antecedent symp-
tomatic pharyngitis (unpublished data). This
might be expected, given the incidence of inva-
sive disease (18 million cases) as compared with
pharyngitis (>600 million cases).22 In children,
invasive streptococcal infections have been asso-
associated with varicella zoster33-35 and influenza vi-
rus infections,36 as well as streptococcal pharyn-
gitis,37 though relatively few cases of necrotizing
fasciitis have been reported.

The toxicity of group A streptococcal necrotiz-
ing fasciitis is severe and more fulminant than
that described by Meleney in 1924.38 Ecchymoses
and bullae develop more rapidly (in 2 to 3 days)
and deep-muscle involvement is more common in
contemporary cases. The mortality is also higher.
Using only “bear claw fasciotomy” and irrigation
with Dakin’s solution (hypochlorous acid) as
treatment, Meleney reported a mortality of 20%,
as compared with a mortality of 30 to 80% in
the current era.27 Given the involvement of epider-
is, dermis, subcutaneous tissue, fascia, and mus-
cle, “necrotizing soft-tissue infection” appears
to be a more accurate term than “necrotizing
fasciitis” to describe the contemporary disease.

Nonsteroidal Antiinflammatory Drugs
and Group A Streptococcal Infection

In the 1980s, an association between the use of
nonsteroidal antiinflammatory drugs (NSAIDs)
and the development of group A streptococcal

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Organisms or spores are introduced into soft tissue. Exotoxins are released. A nonpenetrating deep-tissue injury stimulates a repair response. There is an influx of leukocytes and activation of myogenic progenitor cells.

Exotoxins cause local tissue damage. Platelet–leukocyte aggregates occlude capillaries and damage vascular endothelium. In susceptible hosts with transient bacteremia, organisms are trafficked to injury site in a vimentin-mediated process.

Exotoxins are released. Venous occlusion leads to necrosis in deep tissue. Arteries become occluded, causing necrosis in deep tissue that spreads to upper tissue layers. Bullae and ecchymoses later develop.
necrotizing fasciitis was proposed. Proponents recognized that NSAIDs can suppress critical neutrophil functions and augment the production of tumor necrosis factor α, a key mediator of septic shock. Other people argued that NSAIDs merely mask the signs and symptoms of developing infection, delaying diagnosis and treatment. Numerous clinical and epidemiologic studies have investigated, but not resolved, this issue. Experimental evidence is limited, though two studies clearly showed that non-selective NSAIDs (e.g., ketorolac and ibuprofen) accelerated the disease course and worsened outcomes. In addition, ketorolac significantly increased trafficking of circulating group A streptococci to strain-injured muscles in mice.

**NECROTIZING CLOSTRIDIAL INFECTIONS**

Gas gangrene (clostridial myonecrosis) is an acute invasion of healthy living tissue that occurs spontaneously or as a result of traumatic injury. Recurrent gas gangrene, occurring several decades after the primary infection, has also been described.

Deeply penetrating injuries that compromise the blood supply create an anaerobic environment that is ideal for spore germination and bacterial proliferation. Such trauma accounts for approximately 70% of cases of gas gangrene. Other predisposing conditions are bowel and biliary tract surgery, intramuscular epinephrine injection, retained placenta, prolonged rupture of the membranes, and intrauterine fetal death. *Clostridium perfringens* causes approximately 80% of such infections; other pathogens include *C. septicum*, *C. novyi*, and *C. histolyticum*.

Data regarding contamination versus active infection of traumatic wounds come from studies performed during World Wars I and II. In 1915, Fleming documented that 60.4% of war wounds were contaminated with clostridia. Yet MacLennan found that active infection (gas gangrene or “anaerobic cellulitis”) occurred in fewer than 10 patients per 1000 wounded. In 1941, Qvist suggested that anaerobic cellulitis required only débridement of tissue that was damaged by trauma itself, whereas in gas gangrene, amputation was necessary to control rapid invasion of healthy tissue and thus ensure survival — a premise that guides clinical practice today.

Spontaneous (nontraumatic) gas gangrene is commonly caused by *C. septicum*, which is more aerotolerant than other clostridial pathogens. Most infections occur in patients with gastrointestinal portals of entry such as adenocarcinoma or in those with congenital or cyclic neutropenia. *C. sordellii* infections can affect women after natural childbirth, as well as after abortion or other gynecologic procedures. Such infections can also develop in men, women, and children after traumatic injuries and surgical procedures or illicit-drug injection. Common sites include the skin, muscle, uterus, and perineum. Systemic signs include an absence of fever, profound hypotension, diffuse capillary leak, hemoconcentration...
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2258

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gas in the tissues of patients with gas gangrene or necrotizing fasciitis type I. Imaging evidence of gas in the tissues, or the presence of crepitus, should prompt immediate surgical consultation. A finding of swelling alone may not be useful in patients who have had a traumatic injury or have undergone surgery or childbirth, since swelling cannot be used to distinguish between infection, trauma, and inflammation. MRI may show thickening and hyperintensity of intermuscular fascia on T2-weighted images, findings that are sensitive but not entirely specific for necrotizing fasciitis.

A study of enhanced CT in patients with documented necrotizing fasciitis as compared with those who had other musculoskeletal infections suggested that the absence of fascial enhancement was specific for necrotizing fasciitis.60

### Tissue Biopsy, Histologic Tests, and Gram’s Staining

Gram’s staining of surgically obtained material is crucial for determining the cause of infection and guiding empirical treatment. Percutaneous biopsy and examination of a frozen section has
been proposed to aid in the diagnosis of necrotizing infection.61,62 However, this technique is subject to sampling error and is not a good substitute for open surgical inspection and biopsy. Group A streptococcal necrotizing infection is characterized histologically by the destruction of muscle tissue, a paucity of infiltrating phagocytes, and large numbers of gram-positive cocci at the site (Fig. 3). The histologic findings are similar for gas gangrene, though with more evidence of edema, gas formation, or both.

SURROGATE MARKERS FOR EARLY DIAGNOSIS OF NECROTIZING FASCITIS

A C-reactive protein level of more than 200 mg per liter,63 a modestly increased white-cell count with a marked left shift,64 and an elevated serum creatinine level in the absence of hypotension are suggestive of severe group A streptococcal infection. Marked leukemoid reactions (50 to 150,000 white cells per cubic millimeter) and profound hemoconcentration are characteristic of C. sordellii infection. A white-cell count of more than 15,400 per cubic millimeter plus a serum sodium level of less than 135 mmol per liter distinguishes necrotizing fascitis in general from nonnecrotizing soft-tissue infections, with a negative predictive value of 99% but a positive predictive value of only 26%.64 Elevated levels of serum creatine phosphokinase or serum aspartate aminotransferase suggest deep infection involving muscle or fascia (as opposed to cellulitis).

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) scoring system uses the total white-cell count and hemoglobin, sodium, glucose, creatinine, and C-reactive protein levels to distinguish between mild soft-tissue infections and necrotizing fascitis.55,66 For adults with LRINEC scores of 5.8 or higher (on a scale of 0 to 13, with higher scores indicating a greater likelihood of necrotizing soft-tissue infection), the positive predictive value for necrotizing fascitis ranged from 57 to 92% in three studies,5,65,67 with negative predictive values of 86% and 96% in two studies.65,68 The disparities may be attributable, in part, to the fact that the specificity of the LRINEC score is greatest for severe disease.9 In a study involving children with necrotizing fasciitis, the median LRINEC score was only 3.7.69

SURGICAL INTERVENTION

For patients with aggressive soft-tissue infection or those with mild infection plus evidence of systemic toxicity, prompt surgical exploration is extremely important8,32,70 for three reasons: to determine the extent of infection, to assess the need for débridement or amputation, and to obtain specimens for Gram’s staining and culture. When infection is near the vital structures of the neck, surgical intervention may be necessary to prevent airway obstruction. Reinspection of the surgical site within 24 hours after surgery is recommended.8,70 Inspection and débridement should be continued every 1 to 2 days until necrotic tissue is no longer present.5,32,62,70-72 Negative-pressure devices have shown promise in facilitating closure and healing of these complex wounds in small series of patients.73-75

There is universal agreement that early surgical débridement is crucial in managing these complex cases. But how early is early? Pinpointing the critical time for surgical intervention on the basis of published data is problematic, since the starting point for measuring the time to surgery varies among studies, particularly retrospective analyses, with some studies using the time from establishment of a definitive diagno-

Figure 3. Histopathological Features of Group A Streptococcal Necrotizing Fasciitis and Myonecrosis.

Routine hematoxylin and eosin staining of a muscle specimen from a patient who died from cryptogenic group A streptococcal infection shows the classic features of this infection: widespread tissue destruction, lack of a tissue inflammatory response, and large numbers of bacteria in the tissues.
sis, some using the time from initial recognition of the infection, and others using the time from hospital admission. Studies at tertiary care hospitals typically report the shortest times to surgery, probably because the diagnosis was made elsewhere, before admission to the study hospital. We agree with Bandyopadhyay and colleagues that the definition of the time to surgery should be standardized.

Nevertheless, survival is significantly increased among patients taken to surgery within 24 hours after admission as compared with those in whom surgery is delayed for more than 24 hours. Survival is further increased with earlier surgical intervention (e.g., within 6 hours), supporting the notion that the earlier surgery is performed, the better the outcome.

**PHARMACOLOGIC TREATMENT**

**Polymicrobial Necrotizing Infections**

For mixed aerobic and anaerobic infections of the head and neck, abdomen, perineum, or gynecologic organs, definitive treatment should be based on Gram’s staining, culture, and sensitivity information. Because of antibiotic resistance in gram-positive microbes and among the Enterobacteriaceae, broader antibiotic coverage may be necessary, particularly if the patient has recently been hospitalized or treated with antibiotics. Treatment should also be guided by local antibiograms, since the emergence of resistance is geographically determined and specific. The Infectious Diseases Society of America (IDSA) publishes guidelines for the treatment of skin and soft-tissue infections. The current guidelines recommend vancomycin or linezolid plus one of the following therapies: piperacillin–tazobactam, a carbapenem, or ceftriaxone–metronidazole. Additional information on specific and alternative treatments is also provided in the IDSA guidelines. Studies are under way to evaluate ceftazidime–avibactam for highly resistant gram-negative microbes.

**Group A Streptococcal Infections**

Treatment with clindamycin in combination with penicillin for 10 to 14 days is recommended for group A streptococcal infection. Clindamycin monotherapy should be considered only after antibiotic susceptibility has been determined, since both constitutive and inducible resistance in group A streptococcus have increased, to 15% in the United States and to 95.5% in China. Treatment failures have been reported in cases of clindamycin resistance. In a study of experimental myonecrosis due to group A streptococcus with resistance to erythromycin and clindamycin, tedizolid, a second-generation oxazolidinone antibiotic, was highly efficacious and superior to linezolid.

**Other Necrotizing Fasciitis Type II Infections**

Current guidelines recommend that A. hydrophila infections be treated with doxycycline plus either ciprofloxacin or ceftriaxone. A combination of doxycycline plus either ceftriaxone or cefotaxime is recommended for V. vulnificus infections. For MRSA infections, vancomycin, linezolid, daptomycin, or ceftaroline is likely to be effective, though such treatment has not been adequately studied.

**Traumatic or Spontaneous Gas Gangrene**

Treatment with penicillin plus clindamycin for 10 to 14 days is recommended for traumatic or spontaneous gas gangrene. The recommendation of penicillin is based on in vitro sensitivity data. The recommendation of clindamycin is based on data showing that it is more effective than penicillin in animal models of gas gangrene caused by C. perfringens; clinical trials of clindamycin have not been performed.

**CARE OF CRITICALLY ILL PATIENTS**

Guidelines for the care of critically ill patients have recently been published. However, problems specifically associated with necrotizing infections are of concern, as noted below.

**Capillary Leak Syndrome**

Circulating bacterial toxins and host mediators cause diffuse endothelial damage. Intravenous fluid requirements may be extremely high (10 to 12 liters of normal saline per day). However, profound hypoalbuminemia (0.5 to 1 g per deciliter) is also common, and replacement with colloid (albumin) may therefore be necessary to maintain oncotic pressure.

**Intravascular Hemolysis**

Bacterial hemolysins cause striking and rapid reductions in the hematocrit in the absence of
disseminated intravascular coagulopathy. Thus, the hematocrit may be a better indicator of the need for transfusion than the hemoglobin level.

**Cardiomyopathy**

Global hypokinesia, as indicated by echocardiography and cardiac output, is seen in some patients with streptococcal toxic shock syndrome. Among survivors, this cardiomyopathy is reversible, fully resolving in 3 to 24 months after infection. Some patients have survived with the use of cardiac-assist devices. Management is difficult, since use of vasopressors increases afterload, resulting in decreased peripheral perfusion and reduced cardiac output. Symmetric gangrene resulting in loss of one to four extremities has been described. Careful monitoring and maintenance of mean arterial pressure so that it does not exceed 65 mm Hg in patients with this infection seem prudent, though no clinical studies have been performed to support this recommendation.

**ADJUNCTIVE MEASURES**

**Hyperbaric Oxygen**

A review of 57 studies performed between 1997 and 2003 concluded that hyperbaric oxygen is not useful for the treatment of necrotizing fasciitis, a finding that is similar to the results of other studies. In contrast, a significant survival benefit of hyperbaric oxygen in necrotizing fasciitis was documented in recent studies from the United States and Australia. Other studies have also suggested a beneficial role of hyperbaric oxygen in the treatment of gas gangrene, though experimental studies showed no benefit. Recently, a study has been initiated to evaluate the effect of hyperbaric oxygen on inflammatory and vasoactive biomarkers in necrotizing infections. Meanwhile, its benefits remain controversial. Surgical débridement, which is essential for the treatment of necrotizing fasciitis, should not be delayed in order to pursue hyperbaric oxygen treatment.

**Intravenous Immune Globulin**

The rationale for using intravenous immune globulin (IVIG) in patients with necrotizing fasciitis is based on its ability to neutralize extracellular toxins that mediate pathogenesis. Clinical studies suggesting that there are benefits to IVIG have had serious limitations, including differences in surgical intervention or clindamycin use between the group that received IVIG and the group that did not, lack of power due to the small sample size, low mortality in the group that did not receive IVIG, and differences in the incidence of necrotizing fasciitis between the two study groups. Furthermore, both the quantity and quality of neutralizing antitoxin antibodies vary from batch to batch of IVIG. In view of these limitations and the lack of data from definitive double-blind, controlled studies, the IDSA does not recommend IVIG for necrotizing group A streptococcal infections. Other investigators are in agreement. In a well-controlled 2017 study involving 4127 patients with necrotizing fasciitis and streptococcal toxic shock syndrome in 130 hospitals in the United States, IVIG had no effect on mortality or length of hospital stay. Thus, though IVIG has its advocates, a consensus supporting its use has not been reached.

**Other Measures**

A phase 2 trial of a new inhibitor of bacterial superantigens showed no significant benefit with respect to survival, number of surgical débridements, or serum cytokine levels.

**SUMMARY**

Necrotizing soft-tissue infections share many clinical and pathological features, and all such infections result in extensive tissue destruction. No single clinical laboratory test or group of tests can adequately replace surgical inspection for diagnosis of these infections. Early diagnosis, prompt surgical intervention, and appropriate antibiotic treatment are essential to reduce mortality and improve outcomes.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.
Necrotizing soft-tissue infections


38. Lesko SM. The safety of ibuprofen
Necrotizing soft-tissue infections


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