Necrotizing Soft Tissue Infections: A Primary Care Review

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Patients with necrotizing soft tissue infections often present initially to family physicians. These infections must be detected and treated rapidly to prevent loss of limb or a fatal outcome. Unfortunately, necrotizing soft tissue infections have no pathognomonic signs. Patients may present with some evidence of cellulitis, vesicles, bullae, edema, crepitus, erythema, and fever. They also may complain of pain that seems out of proportion to the physical findings; as the infection progresses, their pain may decrease. Magnetic resonance imaging and laboratory findings such as acidosis, anemia, electrolyte abnormalities, coagulopathy, and an elevated white blood cell count may provide clues to the diagnosis. No single organism or combination of organisms is consistently responsible for necrotizing soft tissue infections. Most infections are polymicrobial, with both anaerobic and aerobic bacteria frequently present. Fungal infections also have been reported. Generally, bacterial and toxin-related effects converge to cause skin necrosis, shock, and multisystem organ failure. Aggressive debridement of infected tissues is critical to management. Antimicrobial therapy is important but remains secondary to the removal of diseased and necrotic tissues. (Am Fam Physician 2003;68:323-8. Copyright© 2003 American Academy of Family Physicians.)

Necrotizing soft tissue infections are a broad category of bacterial and fungal skin infections. Descriptive terms vary based on the location, depth, and extent of infection (e.g., Fournier's gangrene [necrotizing perineal infection], necrotizing fasciitis [deep subcutaneous infection]). Depending on the depth of invasion, necrotizing soft tissue infections can cause extensive local tissue destruction, tissue necrosis, systemic toxicity, and even death. Despite surgical advances and the introduction of antibiotics, reported mortality rates for necrotizing soft tissue infections range from 6 percent to as high as 76 percent.[1]

Patients with necrotizing soft tissue infections frequently present initially to primary care physicians. Because of the importance of early diagnosis and treatment, family physicians need to maintain a high index of suspicion for these infections and should be aware of possible presenting features.

Reported risk factors for necrotizing soft tissue infections include age greater than 50 years, peripheral vascular disease, diabetes mellitus, malnutrition, atherosclerosis, high comorbid index scores, obesity, and intravenous drug abuse.

Anatomic Factors and Time Course

Anatomic factors are important in explaining the facility with which necrotizing soft tissue infections cause damage.[2-5] Most bacteria and fungi can multiply within viable tissue, but fibrous attachments or "boundaries" between subcutaneous tissues and fascia (e.g., scalp, hands) can help limit the spread of infection. The natural lack of fibrous attachments in the larger areas of the body (e.g., trunk, extremities) facilitates widespread infection.[2-4]

The time course for necrotizing soft tissue infections varies. Infection can progress over days to weeks; more often, however, limb-threatening or life-threatening sequelae manifest within only a few hours after the infection begins.[2] Furthermore, seemingly limited infections may result in massive systemic effects. Many bacteria, such as group A streptococci, secrete virulence-enhancing toxins or proteins that can trigger multisystem organ

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failure and septic shock.[6] Therefore, the physician can be confronted unexpectedly with a rapidly deteriorating patient who has no overt or only minimal signs of extensive skin infection.

Risk Factors

Reported risk factors for necrotizing soft tissue infections include age greater than 50 years, peripheral vascular disease, diabetes mellitus, malnutrition, atherosclerosis, high comorbid index scores (i.e., Acute Physiology and Chronic Health Evaluation [APACHE] or Surgical Infection Stratification System), obesity, hypoalbuminemia, chronic alcoholism, and intravenous drug abuse *(Table 1)*.[1-3,7-10] Many of these risk factors reflect an immunocompromised state.

Trauma, postoperative infections, occult diverticulitis, strangulated femoral hernia with subcutaneous extravasation of infected contents, cancer, and even acupuncture have been cited as precipitating events in necrotizing soft tissue infections.[3] In addition, diabetic ketoacidosis, neutropenia, high-dose corticosteroid therapy, and burns can increase the risk of cutaneous mucormycosis-induced necrotizing skin infections.[3,7]

TABLE 1
Risk Factors for Necrotizing Soft Tissue Infections

Age greater than 50 years	Intravenous drug abuse
Atherosclerosis	Malnutrition
Burns	Obesity
Cancer or other immunocompromised state	Occult diverticulitis
Chronic alcoholism	Peripheral vascular disease
Corticosteroid use	Postoperative infection
Diabetes mellitus	Strangulated femoral hernia with content extravasation
Hypoalbuminemia	Trauma

Information from references 1 through 3 and 7 through 10.

Etiology

Although necrotizing soft tissue infections can be monomicrobial, they usually are synergistic polymicrobial infections. Investigators in one study[11] found that only 28 of 182 patients developed necrotizing skin infections from single pathogens; the other 154 patients had polymicrobial infections (average of 4.4 organisms in the original wound cultures). In this series, the majority of monomicrobial infections were caused by streptococcal isolates such as β-hemolytic streptococci (namely group A streptococci or *Streptococcus pyogenes*). Other frequently cited causes of monomicrobial necrotizing soft tissue infections include *Staphylococcus aureus* and *Clostridium perfringens*.[11]

The organisms isolated most often in polymicrobial necrotizing soft tissue infections are combinations of staphylococci (especially *Staphylococcus epidermidis* with β-hemolytic streptococci), enterococci, Enterobacteriaceae species (commonly *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*), streptococci, Bacteroides/Prevotella species, anaerobic gram-positive cocci, and Clostridium species.[11,12]

In one study,[1] 69 percent of necrotizing soft tissue infections were found to be polymicrobial, and 29 percent were caused by single pathogens. In 2 percent of infections, no organisms grew from intraoperative culture. Investigators in another study[13] found that more than 90 percent of nonclostridial polymicrobial necrotizing soft tissue infections involved β-hemolytic streptococci or coagulase-positive staphylococci; the remaining 10 percent of infections were attributed to gram-negative enteric bacteria.[13,14] Another series[15] reported that 59 percent of necrotizing soft tissue infections were polymicrobial. A review[16] of necrotizing soft tissue infections in 163 patients revealed that 71 percent of the infections were polymicrobial. In some instances, fungi have been cultured from polymicrobial infections.[11]

Perhaps the only generalization that can be made about polymicrobial necrotizing soft tissue infections is that aerobic and anaerobic organisms are frequently found in combination. Because of culture results, necrotizing soft tissue infections have previously been categorized as type I or type II infections. Type I infections are mixed infections generated by anaerobic and facultative bacteria, whereas type II infections generally are caused by group A streptococci. Staphylococci also may be found in conjunction with group A streptococci.[12]

Physical Examination

The physical examination should cover all body surfaces. This thorough approach is especially important in patients with deterioration of mental status as a result of conditions such as diabetic ketoacidosis. Sepsis from an infection must be considered in the perineum and other areas that are concealed by clothing.

Most necrotizing soft tissue infections occur in the extremities, abdomen, groin, and perineum.[2] In at least one series,[3] these infections were discovered in the extremities (53 percent of cases), perineum or buttocks (20 percent), trunk (18 percent), and head and neck (8.9 percent).

Because necrotizing skin infections begin in deep tissue planes, the epidermis may appear relatively unscathed until late in the course of infection. Therefore, it can be difficult to differentiate necrotizing soft tissue infection from nonnecrotizing infection or simple cellulitis.[17] However, some clinical clues are available *(Table 2)*.[1-3,17-20]

One group of investigators[1] noted that soft tissue edema, erythema, severe pain, temperature greater than 38°C (100.4°F), bullae, or necrosis may signify a necrotizing soft tissue infection *(Figure 1)*.[17] Other investigators[3] have found some correlation between necrotizing soft tissue infection and preexisting cellulitis (76 percent of cases) and vesicles, bullae, or necrosis (47 percent of cases). Painful skin ulcers with gangrenous margins may be a feature of mixed bacterial infections.[2] The presence of crepitus is variable. In one series,[18] crepitus was present in only 18 percent of patients with necrotizing fasciitis and was a late clinical sign. Thus, signs of soft tissue edema, erythema, ulceration, bullae, or necrosis should prompt the inclusion of necrotizing soft tissue infection in differential diagnoses.

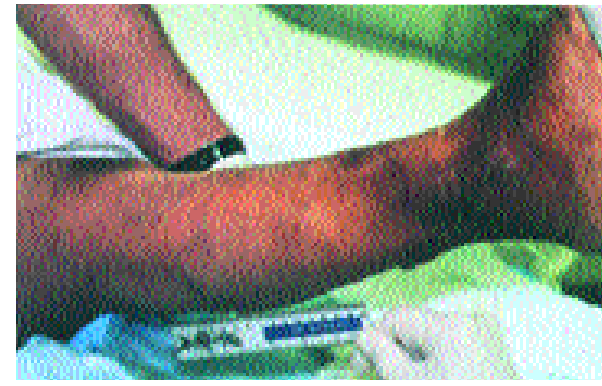

FIGURE 1. Right leg edema and erythema extending over the anterior tibia and medial malleolus in a 59-year-old woman. Violaceous bullae without evidence of obvious trauma were observed over the medial malleolus and medial calf.[17]

Complaints of pain beyond the visible limits of skin erythema or out of proportion to visible signs of skin infection also should arouse clinical suspicion for necrotizing soft tissue infection. Patients with systemic infection may be diaphoretic, febrile, and tachycardic, and they may manifest toxic delirium. In addition, they may become hypotensive and demonstrate signs of renal failure and hemolytic anemia.[2]

Because of the paucity of distinct findings, necrotizing soft tissue infections still may be missed. Bullae and skin necrosis, for example, may not be present in 66 to 70 percent of patients with occult infections.[19]

TABLE 2
Clinical Clues to the Diagnosis of Necrotizing Soft Tissue Infections

Skin	**Pain**
Erythema	Pain that extends past margin of apparent infection
Tense edema	Severe pain that appears disproportionate to physical findings
Grayish or other discolored wound drainage	Decreased pain or anesthesia at apparent site of infection
Vesicles or bullae	**General features**
Necrosis	Fever
Ulcers	Tactile temperature
Crepitus	Diaphoresis
	Tachycardia
	Toxic delirium

Information from references 1 through 3 and 17 through 20.

Diagnosis

The differential diagnosis of necrotizing soft tissue infections includes staphylococcal bacteremic skin lesions and local infections resulting from erysipelas, nonnecrotizing cellulitis, impetigo, furuncles, carbuncles, folliculitis, candidal septicemia, and insect or other bites (e.g., brown recluse spider).[2]

Physical findings are not sufficient to identify the organ-

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isms that cause these infections. For example, although clostridial myonecrosis can present with a thin, brownish discharge, a wound culture should be performed to confirm the identity of the pathogen.[21]

The gold standard for detecting necrotizing soft tissue infections is tissue biopsy obtained at the time of wound exploration and surgical debridement. During wound exploration, tissue integrity and depth of invasion also can be evaluated. The findings of fascial necrosis and myonecrosis are indicative of necrotizing infection. Loss of fascial integrity along tissue planes and frank evidence of muscle involvement are also diagnostic.[12] Note that the use of frozen sections at the time of biopsy may not always provide accurate information about the depth of tissue involvement.

Demonstration of necrotic tissue on fine-needle aspiration of infected tissue also is important in establishing the diagnosis of necrotizing soft tissue infection. In addition, other modalities have been investigated as diagnostic tests. However, with the exception of wound exploration and culture, negative results on these tests cannot exclude necrotizing skin infections.

One investigative team[3] noted a correlation between necrotizing soft tissue infections and subcutaneous air on radiographs (25 percent of cases) and white blood cell counts higher than 20,000 per mm^3 (20×10^9 per L; 49 percent of cases). However, an absence of soft tissue gas on radiographs does not exclude these infections.[17] Furthermore, neither the presence nor absence of gas on radiographs of infected sites correlates with the presence of specific pathogens.[4]

Magnetic resonance imaging (MRI) can be a helpful diagnostic adjunct because of its soft-tissue and multiplanar-imaging capabilities.[22] In these respects, MRI is superior to ultrasonography or plain-film radiography in detecting tissue inflammation and necrosis. The use of gadolinium MRI (T_2-weighted images) has been reported to yield hyperintense intramuscular and deep fascial signals and rim enhancement compatible with necrotizing soft tissue infections; however, such findings are nonspecific for these infections.[22] More investigation is needed to clarify the type of MRI findings and weighted images that can reliably distinguish necrotizing from nonnecrotizing skin infections.

Elevated polymorphonuclear leukocyte counts may reflect systemic infection. One team of investigators[1] reported that white blood cell counts higher than 16,300 per mm^3 (16.3×10^9 per L), anemia (hemoglobin level lower than 10 mg per dL [100 g per L]), hypocalcemia (corrected to a serum calcium concentration of less than 8.4 mg per dL [2.10 mmol per L]), acidosis (pH less than 7.35), crepitus, or the presence of soft tissue gas may alert physicians to the presence of necrotizing soft tissue infections.

Another investigative team[23] found that 76 percent of patients with necrotizing soft tissue infections had platelet counts below 150×10^3 per mm^3 (150×10^9 per L) or prothrombin and partial thromboplastin times more than 1.5 times higher than normal control values. Prolonged prothrombin times were associated with a higher mortality rate.

If findings such as tense skin edema, crepitus, bullae, and radiologic and laboratory abnormalities are present, they provide additional impetus to obtain urgent surgical consultation for wound exploration.[24]

Treatment

SURGICAL DEBRIDEMENT

Controlled surgical debridement of necrotic and diseased tissues remains the cornerstone of treatment and can increase survival in patients with necrotizing soft tissue infections. In one series,[18] patients who underwent surgical

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TABLE 3
Antibiotics Commonly Used to Treat Necrotizing Soft Tissue Infections

Penicillin or ampicillin plus an aminoglycoside (e.g., gentamicin [Garamycin]) and anaerobic coverage (e.g., clindamycin [Cleocin] or metronidazole [Flagyl])
Ampicillin-sulbactam (Unasyn)
Ticarcillin-clavulanate potassium (Timentin)
Piperacillin-tazobactam (Zosyn)
Imipenem-cilastatin (Primaxin)
Antipseudomonal cephalosporin (e.g., ceftazidime [Fortaz]) and clindamycin or metronidazole
Nafcillin (Unipen) plus anaerobic and gram-negative coverage
Vancomycin (Vancocin) plus anaerobic and gram-negative coverage (e.g., an aminoglycoside or aztreonam [Azactam], or a third-generation cephalosporin): used mainly in patients with penicillin allergy

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debridement more than 12 hours after hospital admission had higher amputation and mortality rates. Another investigation[25] also found higher mortality rates when diagnosis and surgical debridement were delayed. Factors noted to be critical to patient survival include prompt recognition of infection, nutritional support, surgical debridement, wound reexploration, and soft tissue coverage.[18]

With the resolution of the necrotizing infection and the establishment of granulation tissue, surgical attention can be directed toward coverage of tissue defects caused by the infectious process.[3]

ANTIBIOTIC OR ANTIFUNGAL THERAPY

Empiric antibiotic therapy can be employed until wound culture isolates are identified. Depending on the culture results, antibiotic selection can be modified. Because of likely colonization, superficial wound cultures are not helpful in determining appropriate antibiotic therapy.

Because most necrotizing soft tissue infections are polymicrobial, broad-spectrum coverage is advisable.[12] Options include combinations such as ampicillin, gentamicin (Garamycin), and clindamycin (Cleocin) or metronidazole (Flagyl).[2,3] Ampicillin-sulbactam (Unasyn), ticarcillin-clavulanate potassium (Timentin), and piperacillin-tazobactam (Zosyn) also provide adequate anaerobic and aerobic coverage. The advantages of piperacillin-tazobactam or ticarcillin-clavulanate potassium therapy include gram-negative and pseudomonal coverage.[2] Patients with necrotizing soft tissue infections also have been treated with nafcillin (Unipen) plus agents with anaerobic and gram-negative coverage.[11]

Imipenem-cilastatin (Primaxin) provides extensive broad-spectrum coverage. This combination agent is active against nosocomial gram-negative bacilli such as Enterobacter species, Citrobacter species, Acinetobacter species, *Proteus vulgaris, P. aeruginosa,* and *Serratia marcescens*.[2] Because of this coverage, imipenem-cilastatin and β-lactam and β-lactamase inhibitors have been used successfully as single agents in the treatment of necrotizing soft tissue infections.[2]

The gold standard for detecting necrotizing soft tissue infections is tissue biopsy obtained at the time of wound exploration and surgical debridement.

Broad-spectrum coverage is likely to combat the pathogens that can cause necrotizing soft tissue infections. For example, enterococci are associated with these infections. In one study,[11] however, 16 of 198 patients with necrotizing soft tissue infections received suboptimal broad-spectrum antibiotic coverage; 13 of these patients did not receive an antibiotic that was active against enterococci.

Treatment with intravenously administered amphotericin B (Abelcet) can be used with surgical debridement to control fungal skin infections.[2]

Agents commonly used to treat necrotizing soft tissue infections are listed in *Table 3*.[2,11] Treatments for gas gangrene are summarized in *Table 4*.[26]

TABLE 4
Antibiotics Commonly Used to Treat Gas Gangrene

Penicillin G: 24 million units per day in divided doses every 4 to 6 hours IV
and
Clindamycin (Cleocin): 900 mg every 8 hours IV
or
Ceftriaxone (Rocephin): 2 g every 12 hours IV
or
Erythromycin: I g every 6 hours IV (not by bolus)

IV = intravenously.

Adapted with permission from Gilbert DN, Moellering RC Jr, Sande MA. The Sanford guide to antimicrobial therapy. 32d ed. Hyde Park, Vt.: Antimicrobial Therapy, 2002:31.

WOUND REEXPLORATION

If infection progresses despite surgical debridement and the use of broad-spectrum antibiotic or antifungal therapy, surgical reexploration is necessary. The possibility of adjacent or deeper sites of occult necrosis and infection must be excluded.

OTHER TREATMENTS

Hyperbaric oxygen therapy has been a controversial adjunct in the management of necrotizing soft tissue infections. It is not recommended as a replacement for surgical debridement or intravenous antibiotic therapy.[27]

Information should be obtained about the tetanus booster status of patients with necrotizing soft tissue infections. If immunization is inadequate, appropriate tetanus prophylaxis should be administered.

The author indicates that she does not have any conflicts of interest. Sources of funding: none reported.

Figure 1 from Meltzer DL, Kabongo M. Necrotizing fasciitis: a diagnostic challenge. Am Fam Physician 1997;56:145-9.

The author thanks Alfred Tallia, M.D., M.P.H., and Niranjan V. Rao, M.D., University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, New Brunswick, N.J., for reviewing the manuscript.

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