Necrotizing soft tissue infections

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INTRODUCTION

Necrotizing soft tissue infections (NSTIs) include necrotizing forms of fasciitis, myositis, and cellulitis [1-4]. These infections are characterized clinically by fulminant tissue destruction, systemic signs of toxicity, and high mortality. Accurate diagnosis and appropriate treatment must include early surgical intervention and antibiotic therapy.

Several different names have been used to describe the various forms of necrotizing infections; this is related in part to naming based on clinical features rather than surgical or pathologic findings. The degree of suspicion should be high since the clinical presentation is variable and prompt intervention is critical. The lay press has referred to organisms that cause NSTI as "flesh-eating bacteria."

Necrotizing fasciitis, myositis, and cellulitis will be reviewed here. Clostridial infection and pyomyositis are discussed separately. (See "Clostridial myonecrosis" and "Primary pyomyositis".)

Surgical management of NSTI is discussed separately. (See "Surgical management of necrotizing soft tissue infections".)

CONDITIONS, MICROBIOLOGY, AND EPIDEMIOLOGY

NSTI can include involvement of the epidermis, dermis, subcutaneous tissue, fascia, and muscle [1]. Necrotizing infection may be categorized based on microbiology and presence or absence of gas in the tissues (table 1).

Distinguishing necrotizing fasciitis from necrotizing myositis may be difficult as skeletal muscle and fascia are involved in both syndromes [5-7]. Necrotizing myositis primarily involves skeletal muscle, whereas necrotizing fasciitis primarily involves fascia.

Necrotizing fasciitis — Necrotizing fasciitis is an infection of the deep soft tissues that results in progressive destruction of the muscle fascia and overlying subcutaneous fat. Infection typically spreads along the muscle fascia due to its relatively poor blood supply; muscle tissue is frequently spared because of its generous blood supply [8]. Development of anesthesia may precede the appearance of skin necrosis and provide a clue to the presence of necrotizing fasciitis [9]. Initially, the overlying tissue can appear unaffected; therefore, necrotizing fasciitis is difficult to diagnose without direct visualization of the fascia.

Necrotizing fasciitis may be divided into two microbiologic categories: polymicrobial (type I) and monomicrobial infection (type II) [10-12]:

- Polymicrobial (type I) necrotizing infection is caused by aerobic and anaerobic bacteria.

  Typically, at least one anaerobic species (most commonly *Bacteroides*, *Clostridium*, or *Peptostreptococcus*) is isolated in combination with Enterobacteriaceae (eg, *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Proteus*) and one or more facultative anaerobic streptococci (other than group A *Streptococcus* [GAS]) [13-15]. Obligate aerobes (such as *Pseudomonas aeruginosa*) are rarely components of such mixed infections. Uncommonly, fungi (predominately *Candida* species) are recovered in polymicrobial (type I) necrotizing infection [16].

  Fournier gangrene is caused by facultative organisms (*E. coli*, *Klebsiella*, enterococci) along with anaerobes (*Bacteroides*, *Fusobacterium*, *Clostridium*, anaerobic or microaerophilic streptococci) [17]. (See 'Involved sites' below.)

  Necrotizing infection of the head and neck is usually caused by mouth anaerobes (such as Fusobacteria, anaerobic streptococci, *Bacteroides*, and spirochetes). (See 'Involved sites' below.)

  Other terms for polymicrobial (type I) infection include synergistic necrotizing cellulitis and progressive bacterial synergistic gangrene.

- Monomicrobial (type II) necrotizing infection is usually caused by GAS or other beta-hemolytic streptococci. Infection may also occur as a result of *Staphylococcus aureus* [18,19]. Infection with no clear portal of entry occurs in about half of cases; in such circumstances, the pathogenesis of infection likely consists of hematogenous translocation of GAS from the throat (asymptomatic or symptomatic pharyngitis) to a site of blunt trauma or muscle strain [1,7].

  M protein is an important virulence determinant of GAS. Necrotizing infection caused by GAS strains with M types 1 and 3 is associated with streptococcal toxic shock syndrome in about 50 percent of cases [20-22]. GAS strains of these and other serotypes can produce pyrogenic exotoxins, which induce cytokine production, likely contributing to shock, tissue destruction, and organ failure [6,23,24]. (See "Group A streptococcus: Virulence factors and pathogenic mechanisms" and "Invasive group A streptococcal infection and toxic shock syndrome: Epidemiology, clinical manifestations, and diagnosis".)

  Numerous other pathogens can cause monomicrobial (type II) necrotizing infection less frequently; *Vibrio vulnificus* and *Aeromonas hydrophila* deserve special comment. Infections due to these pathogens typically occur in the setting of traumatic injury associated with sea water or fresh water, respectively. Other risk factors for necrotizing infection due to *V. vulnificus* include cirrhosis and ingestion of contaminated oysters [25]. (See "Vibrio vulnificus infection".)

The incidence of necrotizing fasciitis ranges from 0.3 to 15 cases per 100,000 population [1,26]:

- Polymicrobial (type I) necrotizing fasciitis (caused by aerobic and anaerobic bacteria) usually occurs in older adults and/or in individuals with underlying comorbidities. The most important predisposing factor is diabetes, especially with associated peripheral vascular disease. (See 'Risk factors' below.)

- Monomicrobial (type II) necrotizing fasciitis (most commonly caused by GAS) may occur in any age group and in individuals with no underlying comorbidities [15]. In the United States, there are an estimated 3.5 cases of invasive GAS infections per 100,000 persons; necrotizing infections make up approximately 6 percent of these cases [27].

Necrotizing myositis — Necrotizing myositis is an infection of skeletal muscle typically caused by GAS (and other beta-hemolytic streptococci). It may be preceded by skin abrasions, blunt trauma, or heavy exercise [5,28-32]. Necrotizing myositis is rare. One report noted 21 cases documented between 1900 and 1985; another review of over 20,000 autopsies noted 4 cases [28,29].

Clostridial myonecrosis (gas gangrene) is discussed separately. (See "Clostridial myonecrosis".)

Necrotizing cellulitis — Necrotizing cellulitis is typically caused by anaerobic pathogens and may be divided into two types: clostridial (usually caused by *Clostridium perfringens*; less frequently *Clostridium septicum*) and nonclostridial (caused by polymicrobial infection).

In both types, crepitus is observed in the skin, but there is sparing of fascia and deep muscles. Pain, swelling, and systemic toxicity are not prominent features, and the relative mildness helps distinguish cellulitis from clostridial myonecrosis (gas gangrene) in the immunocompetent host. (See "Clostridial myonecrosis".)

RISK FACTORS

Necrotizing infection can occur among healthy individuals with no past medical history or clear portal of entry in any age group [15].

Risk factors for NSTI include [1,13,18,33-37]:

- Major penetrating trauma
- Minor laceration or blunt trauma (muscle strain, sprain, or contusion)
- Skin breach (varicella lesion, insect bite, injection drug use)
- Recent surgery (including colonic, urologic, and gynecologic procedures as well as neonatal circumcision)
- Mucosal breach (hemorrhoids, rectal fissures, episiotomy)
- Immunosuppression (diabetes, cirrhosis, neutropenia, HIV infection)
- Malignancy
- Obesity
- Alcoholism
- In women: pregnancy, childbirth, pregnancy loss, gynecologic procedures

Diabetes is a particularly important risk factor for necrotizing infection involving the lower extremities, perineum, and head and neck region [14,15]. In addition, use of sodium-glucose cotransporter 2 inhibitors (agents used for treatment of adults with type 2 diabetes) has been associated with NSTI of the perineum (Fournier gangrene) [38]. (See "Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus", section on 'Genitourinary tract'.)

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) may be associated with development or progression of streptococcal necrotizing infection; data are conflicting [1,19,39-41]. Regardless

of their role in pathogenesis, NSAIDs may mask signs and symptoms of inflammation in patients with NSTI, which may be associated with a delay in diagnosis.

CLINICAL MANIFESTATIONS

Typical findings — NSTI can include involvement of the epidermis, dermis, subcutaneous tissue, fascia, and muscle [1]. Necrotizing infection most commonly involves the extremities (lower extremity more commonly than upper extremity), particularly in patients with diabetes and/or peripheral vascular disease. Necrotizing infection usually presents acutely (over hours); rarely, it may present subacutely (over days). Rapid progression to extensive destruction can occur, leading to systemic toxicity, limb loss, and/or death [6,7,22]. Therefore, early recognition of necrotizing infection is critical.

Clinical manifestations of necrotizing infection include [1,2,4,7,42,43]:

- Erythema (without sharp margins; 72 percent)
- Edema that extends beyond the visible erythema (75 percent)
- Severe pain (out of proportion to exam findings in some cases; 72 percent)
- Fever (60 percent)
- Crepitus (50 percent)
- Skin bullae, necrosis, or ecchymosis (38 percent)

Fever (102 to 105°F), tachycardia, and systemic toxicity may be observed. Hypotension may be present initially or develop with progressive infection. Other symptoms include malaise, myalgias, diarrhea, and anorexia.

The subcutaneous tissue may be firm and indurated, such that the underlying muscle groups cannot be palpated distinctly [2,4]. Marked edema may produce a compartment syndrome with complicating myonecrosis requiring fasciotomy. Lymphangitis and lymphadenitis are infrequent. (See "Acute compartment syndrome of the extremities".)

The process progresses rapidly over several days, with changes in skin color from red-purple to patches of blue-gray. Within three to five days after onset, skin breakdown with bullae (containing thick pink or purple fluid) and frank cutaneous gangrene can be seen.

In the setting of surgical wound infection, NSTI is characterized by copious drainage, dusky and friable subcutaneous tissue, and pale, devitalized fascia.

In the setting of necrotizing fasciitis, diminished sensation to pain develops in the involved area, due to thrombosis of small blood vessels and destruction of superficial nerves in the

subcutaneous tissue. This may precede the appearance of skin necrosis and provide a clue to the presence of necrotizing fasciitis [9]. Subcutaneous gas is often present in the polymicrobial (type I) form of necrotizing fasciitis, particularly in patients with diabetes [15].

Involved sites — Necrotizing fasciitis most commonly involves the extremities, as discussed in the preceding section. Other presentations include necrotizing fasciitis of the perineum (Fournier gangrene), head and neck region, and neonatal infection:

- **Perineum (Fournier gangrene)** – Necrotizing fasciitis of the perineum, known as Fournier gangrene, can occur as a result of a breach in the integrity of the gastrointestinal or urethral mucosa [44,45]. Fournier gangrene is a form of polymicrobial (type I) infection. Fournier gangrene typically begins abruptly with severe pain and may spread rapidly to the anterior abdominal wall and the gluteal muscles. Men are more commonly affected than women. Involvement in men may include the scrotum and penis (picture 1); involvement in women may include involvement of the labia.

- **Head and neck region** – Necrotizing fasciitis of the head and neck can result from a breach in oropharynx mucous membrane integrity following surgery or instrumentation or in the setting of odontogenic infection [46].

  In one study including 45 patients with cervical necrotizing fasciitis, most were attributable to mixed aerobic and anaerobic bacteria. The majority of cases were of dental origin (78 percent); the remaining cases were of pharyngeal origin or occurred after surgery or trauma [47]. Fasciitis spread to the face (22 percent), lower neck (56 percent), and mediastinum (40 percent). In a separate study, 28 percent of patients with necrotizing fasciitis of the head and neck developed mediastinitis; factors that contributed to mediastinal involvement included prior corticosteroid use, infection by gas-producing microbes, and a pharyngeal focus of infection [48]. Cervical (head and neck) necrotizing fasciitis is usually a polymicrobial (type I) infection. However, monomicrobial (type II) infection due to group A *Streptococcus* (GAS) can also occur. (See 'Conditions, microbiology, and epidemiology' above.)

  Other conditions that can occur in the setting of necrotizing infection involving the head and neck region include Ludwig's angina (submandibular space infection) and Lemierre syndrome (septic thrombophlebitis of the jugular vein). (See "Ludwig angina" and "Lemierre syndrome: Septic thrombophlebitis of the internal jugular vein".)

- **Neonatal infection** – Most cases of necrotizing fasciitis in neonates present with abdominal or perineal involvement and are often due to beta-hemolytic streptococci.

Polymicrobial infection occurs less often. Associated conditions include omphalitis, balanitis (related to circumcision), and hernia repair [49-53].

Laboratory findings — Laboratory findings are generally nonspecific. Abnormalities may include leukocytosis with left shift, acidosis, coagulopathy, hyponatremia, elevated inflammatory markers (C-reactive protein and/or erythrocyte sedimentation rate), and elevations in serum creatinine, lactate, creatine kinase (CK), and aspartate aminotransferase (AST) concentrations [1,6,54-57]. Elevations in serum CK or AST concentrations suggest deep infection involving muscle or fascia (as opposed to cellulitis) [1].

NSTI cannot be predicted reliably using laboratory parameters, particularly in the setting of early infection. A tool called the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score has been described; it is based on laboratory indicators including white cell count, hemoglobin, sodium, glucose, creatinine, and C-reactive protein [58,59]. The tool has demonstrated variable sensitivity; it should not be used to rule out NSTI [58,60-62].

Blood cultures are positive in approximately 60 percent of patients with monomicrobial (type II) necrotizing fasciitis (eg, due to GAS or other beta-hemolytic streptococci) and are routinely positive in patients with necrotizing myositis [30]. The yield of blood cultures is lower among patients with polymicrobial (type I) necrotizing fasciitis; in one series, it was 20 percent [15]. In addition, blood culture results may not reflect all organisms involved [63]. (See 'Conditions, microbiology, and epidemiology' above.)

DIAGNOSIS

General approach — NSTI should be suspected in patients with soft tissue infection (erythema, edema, warmth) and signs of systemic illness (fever, hemodynamic instability) in association with crepitus, rapid progression of clinical manifestations, and/or severe pain (out of proportion to skin findings in some cases) (algorithm 1). Early recognition of necrotizing infection is critical; rapid progression to extensive destruction can occur, leading to systemic toxicity, limb loss, and/or death [6,7,22].

The diagnosis of necrotizing infection is established via surgical exploration of the soft tissues in the operating room, with physical examination of the skin, subcutaneous tissue, fascial planes, and muscle [1]. Surgical exploration is required to establish the presence of necrotizing infection, evaluate the scope of involvement, and to debride devitalized tissue. Surgical exploration should **not** be delayed when there is clinical suspicion for a necrotizing infection

while awaiting results of radiographic imaging, culture results, or other diagnostic information. (See "Surgical management of necrotizing soft tissue infections".)

Intraoperative specimens should be sent for Gram stain and culture (in addition to histology) (table 1).

Radiographic imaging studies can be useful to help determine whether necrotizing infection is present but should not delay surgical intervention when there is crepitus on examination or rapid progression of clinical manifestations [6]. (See 'Radiographic imaging' below.)

Blood cultures (two sets) should be obtained prior to administration of antimicrobial therapy. Reasonable serum laboratory testing includes complete blood count with differential, chemistries, liver function tests, creatinine concentration, coagulation studies, creatine kinase concentration, lactate concentration, and inflammatory markers (C-reactive protein and/or erythrocyte sedimentation rate). (See 'Laboratory findings' above.)

Clinical factors that may make diagnosis of NSTI difficult include [1]:

- Absence of fever – Fever may be absent; in some cases, this may be due to use of nonsteroidal anti-inflammatory drugs.
- Absence of cutaneous manifestations – Patients presenting with no obvious portal of entry may present with infection that began deep in the soft tissues; superficial signs of infection may not appear until late in the course of disease.
- Attribution of severe pain to alternative cause – Pain may be erroneously attributed to recent surgery or other known condition.
- Nonspecific imaging tests – Radiographic imaging may demonstrate edema with no gas in the deep tissue; these findings may be attributed to noninfectious causes, thereby confounding the diagnosis.
- Attributing systemic manifestations to other causes – Gastrointestinal symptoms (nausea, vomiting, diarrhea) may be early manifestations of toxemia due to group A streptococcal infection but may be wrongly attributed to other conditions.

Surgical exploration and debridement — Surgical exploration is the **only** way to establish the diagnosis of necrotizing infection. Findings on direct examination include swollen and dull-gray appearance of the fascia, thin exudate without clear purulence, and easy separation of tissue planes by blunt dissection (picture 2) [2,4].

Surgery should be performed at the center where the patient presented, provided an appropriately trained surgeon is available (rather than delaying care for transfer). Early debridement is associated with better outcomes; survival is significantly increased among patients taken to surgery within 24 hours after admission compared with those in whom surgery is delayed, and survival is further increased with earlier surgical intervention (eg, within six hours) [43,64,65].

Intraoperative specimens should be sent for Gram stain and culture (table 1).

Tissue biopsy may be obtained but is not required to establish the diagnosis of necrotizing infection. Characteristic pathologic features of necrotizing fasciitis include extensive tissue destruction, thrombosis of blood vessels, abundant bacteria spreading along fascial planes, and infiltration of acute inflammatory cells [66]. Characteristic pathologic features of necrotizing myositis include degeneration and necrosis of skeletal muscle fibers, infiltration of granulocytes, and numerous bacteria in areas of muscle necrosis (picture 3).

Issues related to surgical management of NSTIs are discussed further separately. (See "Surgical management of necrotizing soft tissue infections".)

Radiographic imaging — Radiographic imaging can be useful to help determine whether necrotizing infection is present but should not delay surgical intervention when there is crepitus on examination or rapid progression of clinical manifestations [6].

The best initial radiographic imaging exam is computed tomography (CT) scan (image 1 and image 2). The most useful finding is presence of gas in soft tissues, which is seen most frequently in the setting of clostridial infection or polymicrobial (type I) necrotizing fasciitis (table 1); this finding is highly specific for NSTI and should prompt immediate surgical intervention [13,67,68]. Other radiographic findings may include fluid collections, absence or heterogeneity of tissue enhancement with intravenous contrast, and inflammatory changes beneath the fascia [69].

Magnetic resonance imaging (MRI) is not as useful as CT for detection of gas in soft tissues. In addition, MRI can be overly sensitive; it tends to overestimate deep tissue involvement and therefore cannot be used to reliably distinguish between necrotizing cellulitis and deeper infection [70].

Ultrasound may be used for detection of localized abscesses and gas in tissues but has not been well studied in necrotizing fasciitis.

Frequently, imaging studies demonstrate soft tissue swelling; this finding is not specific since it is not possible to distinguish between swelling caused by infection, trauma, surgery, or inflammation. Therefore, in such cases, the diagnosis of necrotizing infection can be established only by surgical exploration.

DIFFERENTIAL DIAGNOSIS

Conditions included in the differential diagnosis include:

- Cellulitis – Cellulitis presents with skin erythema, edema, and warmth. Fever may be present, but cellulitis is generally not associated with hemodynamic instability or exquisite tenderness. Elevations in serum CK or AST concentrations suggest deep infection involving muscle or fascia (as opposed to cellulitis). (See "Cellulitis and skin abscess: Epidemiology, microbiology, clinical manifestations, and diagnosis".)

- Pyoderma gangrenosum – Pyoderma gangrenosum may be difficult to distinguish from necrotizing fasciitis [63,71-74]. Distinguishing features are summarized in the table (table 2). The distinction is important because inappropriate surgical debridement of pyoderma gangrenosum can cause extension of the lesion, and inappropriate administration of immunosuppressive therapy may worsen necrotizing fasciitis. (See "Pyoderma gangrenosum: Pathogenesis, clinical features, and diagnosis".)

- Gas gangrene (clostridial myonecrosis) – Gas gangrene (clostridial myonecrosis) is an acute invasion of healthy tissue that occurs spontaneously or as a result of traumatic injury. Both gas gangrene and polymicrobial (type I) NSTI are associated with gas in the tissues. In gas gangrene, the Gram stain typically demonstrates gram-positive rods, while, in polymicrobial necrotizing fasciitis, the Gram stain typically demonstrates mixed aerobes and anaerobes (table 1). The distinction is important in that management of clostridial myonecrosis may require amputation, whereas management of necrotizing fasciitis requires debridement (but limb salvage may be possible). (See "Clostridial myonecrosis".)

- Pyomyositis – Pyomyositis may be confused with necrotizing myositis. These conditions differ in that pyomyositis is characterized by abscess formation in skeletal muscle, while necrotizing myositis is characterized by gangrenous necrosis. These are distinguished by clinical and radiographic features. Pyomyositis is usually caused by *S. aureus* and is generally associated with less systemic toxicity than necrotizing myositis. (See "Primary pyomyositis".)

- Deep venous thrombosis – Deep venous thrombosis (DVT) is characterized by extremity swelling, pain, and warmth; the pain is less extreme than in the setting of necrotizing infection. Fever may be present in DVT but is more common in the setting of soft tissue infection. (See "Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity".)

TREATMENT

Clinical approach — Treatment of necrotizing infection consists of early and aggressive surgical exploration and debridement of necrotic tissue, together with broad-spectrum empiric antibiotic therapy and hemodynamic support. Administration of antibiotic therapy in the absence of debridement is associated with a mortality rate approaching 100 percent [13].

Surgical debridement — NSTI is a surgical emergency. Radiographic imaging studies should not delay surgical intervention when there is crepitus on examination or rapid progression of clinical manifestations.

The goal of operative management is to perform aggressive debridement of all necrotic tissue until healthy, viable (bleeding) tissue is reached. Inspection and debridement in the operating room should be continued every one to two days until necrotic tissue is no longer present [42]. For severe necrotizing infection involving the extremities, amputation may be needed to control the infection [13].

Issues related to surgical debridement and reconstruction procedures are discussed further separately. (See "Surgical management of necrotizing soft tissue infections".)

Antibiotic therapy — In general, empiric treatment of necrotizing infection should consist of broad-spectrum antimicrobial therapy, including activity against gram-positive, gram-negative, and anaerobic organisms [13]. Antibiotic therapy should be initiated promptly after obtaining blood cultures (algorithm 1).

Acceptable empiric antibiotic regimens include [2,4]:

- A carbapenem:
  - Imipenem (adults: 1 g IV every 6 to 8 hours)
  - Meropenem (adults: 1 g IV every 8 hours; children and neonates with a postnatal age >7 days: 20 mg/kg per dose every eight hours),

- Ertapenem (adults: 1 g IV every 24 hours)]

or

- Piperacillin-tazobactam (adults: 3.375 g every 6 hours or 4.5 g every 8 hours; children and neonates with a postnatal age >7 days: 75 mg/kg per dose of the piperacillin component, not to exceed to a maximum of 3 g, every 6 hours)

PLUS

- An agent with activity against methicillin-resistant *S. aureus* (MRSA; such as vancomycin or daptomycin) (table 3). In neonates and children, vancomycin (15 mg/kg/dose every six to eight hours) is the usual empiric antibiotic for MRSA; the six-hour dosing interval is employed for sicker children.

PLUS

- Clindamycin, for its antitoxin and other effects against toxin-elaborating strains of beta-hemolytic streptococci and *S. aureus* (600 to 900 mg intravenously [IV] every eight hours in adults; 40 mg/kg per day divided every eight hours in children and neonates) [7,75-80] (see "Invasive group A streptococcal infection and toxic shock syndrome: Treatment and prevention", section on 'General principles'). For patients with NSTI due to beta-hemolytic streptococci or *S. aureus* that are resistant to clindamycin, linezolid or tedizolid can be used (linezolid, adults and children ≥12 years: 600 mg IV every 12 hours; children <12 years of age: 10 mg/kg IV every eight hours [maximum 600 mg/dose]) or tedizolid (adults: 200 mg IV every 24 hours; not US Food and Drug Administration [FDA] approved for use in children). (See "Invasive group A streptococcal infection and toxic shock syndrome: Treatment and prevention", section on 'General principles' and "Staphylococcal toxic shock syndrome", section on 'Antibiotic therapy'.)

For patients who have particular exposures that may suggest infections with specific organisms, such as trauma in fresh water (*Aeromonas*) or sea water (*V. vulnificus*), it is appropriate to ensure that empiric therapy includes antimicrobial agents with activity against such organisms. (See "Aeromonas infections", section on 'Therapy' and "Vibrio vulnificus infection", section on 'Treatment' and "Soft tissue infections following water exposure".)

Due to concerns for multidrug resistance among some Enterobacteriaceae and lack of consistent availability, ampicillin-sulbactam and ticarcillin-clavulanate, respectively, are no longer recommended. Patients with hypersensitivity to carbapenems or piperacillin-tazobactam may be treated with either an aminoglycoside or a fluoroquinolone, plus metronidazole.

Antibiotic treatment should be tailored to Gram stain, culture, and sensitivity results when available [2,4]:

- Group A streptococcal (GAS) or other beta-hemolytic streptococcal infection – Penicillin (4 million units IV every four hours in adults >60 kg with normal renal function or 300,000 units/kg per day divided every six hours in children) **plus** clindamycin (600 to 900 mg IV every eight hours in adults or 40 mg/kg per day divided every eight hours in neonates and children) [7].

  Combination therapy with penicillin and clindamycin should be continued until patients are clinically and hemodynamically stable for at least 48 to 72 hours; thereafter, penicillin monotherapy may be administered.

- Clostridial infection – Penicillin plus clindamycin (dosing as above). (See "Clostridial myonecrosis".)

- *Aeromonas hydrophila* – (See "Aeromonas infections".)

- *Vibrio vulnificus* – (See "Vibrio vulnificus infection".)

- Polymicrobial infection – Vancomycin (table 3) plus a beta-lactam-beta-lactamase inhibitor.

Antibiotics should be continued until no further debridement is needed and the patient's hemodynamic status has normalized; this duration often consists of at least two weeks of treatment and must be tailored to individual patient circumstances [81].

Hemodynamic support — Hemodynamic instability may require aggressive supportive care with fluids and vasopressors. Intravenous fluid requirements may be high, and albumin replacement may be required in the setting of capillary leak syndrome associated with streptococcal toxic shock syndrome (TSS) [1]. (See "Invasive group A streptococcal infection and toxic shock syndrome: Epidemiology, clinical manifestations, and diagnosis" and "Evaluation and management of suspected sepsis and septic shock in adults".)

Intravenous immune globulin — We favor administration of intravenous immune globulin (IVIG) for patients with NSTI in the setting of streptococcal TSS. This approach is supported by a 2018 meta-analysis including five studies of patients with streptococcal TSS treated with clindamycin (one randomized and four nonrandomized), in which use of IVIG was associated with a significant reduction in 30-day mortality (33.7 to 15.7 percent) [82]. Similarly, in a subsequent prospective observational study of patients with NSTI due to GAS, use of IVIG was associated with reduced 90-day mortality [83]. Prior data from retrospective studies and

statistically underpowered prospective trials have been inconclusive on the efficacy of IVIG for NSTI [84-86]. The combination of clindamycin and IVIG is likely efficacious by reducing circulating toxins produced by GAS [82].

Issues related to use of IVIG in the setting of streptococcal TSS are discussed separately. (See "Invasive group A streptococcal infection and toxic shock syndrome: Treatment and prevention", section on 'Intravenous immune globulin'.)

Perioperative care — Issues related to perioperative care and use of hyperbaric oxygen are discussed separately. (See "Surgical management of necrotizing soft tissue infections" and "Hyperbaric oxygen therapy", section on 'Infection'.)

PREVENTION

Close contacts of a patient with necrotizing infection due to group A *Streptococcus* (GAS) can become colonized with a virulent strain [87,88]. The likelihood of a secondary case of necrotizing fasciitis or toxic shock syndrome is very low but higher than for the general population [89,90].

Postexposure prophylaxis — The role of postexposure prophylaxis in reducing the likelihood of a secondary GAS infection is uncertain [91]. We suggest prophylaxis for highly susceptible individuals (such as immunocompromised individuals or patients with recent surgery) who are close contacts of a patient with necrotizing infection due to GAS. We use penicillin (250 mg orally 4 times daily) for 10 days in such patients. Alternative regimens have been suggested [92], however, the optimal antibiotic prophylaxis remains undefined.

Regardless of whether a close contact receives postexposure prophylaxis or not, it is imperative that they be educated about the signs and symptoms of invasive GAS infections and to seek immediate medical care if these clinical features develop within 30 days of diagnosis in the index case.

Evidence supporting use of postexposure prophylaxis is limited due in part to the relative rarity of necrotizing GAS infection, and it has not been studied in prospective, randomized trials. Nevertheless, we favor this approach because of the potential severity of the infection.

Issues related to prophylaxis for contacts are discussed further separately. (See "Invasive group A streptococcal infection and toxic shock syndrome: Treatment and prevention", section on 'Prophylaxis for contacts'.)

Infection control — In addition to standard precautions, patients with invasive GAS infection associated with soft tissue involvement warrant droplet precautions and contact precautions [93]. Droplet and contact precautions may be discontinued after the first 24 hours of antimicrobial therapy.

OUTCOME

Necrotizing infection is associated with considerable mortality, even with optimal therapy [83]. Observational studies have reported the following mortality rates:

- Polymicrobial (type I) necrotizing fasciitis – 21 percent [15]
  - Fournier gangrene – 22 to 40 percent [44,45,94]
  - Cervical necrotizing fasciitis – 22 percent [47]
  - Neonatal necrotizing fasciitis – 59 percent [49]
- Monomicrobial (type II) necrotizing fasciitis – 14 to 34 percent [6,20,21]

Factors associated with increased mortality include [15,21,95,96]:

- White blood cell count >30,000/microL; band neutrophils >10 percent
- Serum creatinine >2.0 mg/dL (177 mmol/L)
- Age >60 years
- Streptococcal toxic shock syndrome
- Clostridial infection
- Delay in surgery for more than 24 hours
- Infection involving the head, neck, thorax, or abdomen

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Skin and soft tissue infections".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading

level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Gangrene (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definitions** – Necrotizing soft tissue infections (NSTIs) include necrotizing forms of fasciitis, myositis, and cellulitis. They may be categorized based on microbiology and presence or absence of gas in the tissues (table 1).
  - **Necrotizing fasciitis** – Necrotizing fasciitis is an infection of the deep soft tissues that results in progressive destruction of the muscle fascia and overlying subcutaneous fat. Infection may be polymicrobial (type I) or monomicrobial (type II) (see 'Necrotizing fasciitis' above):
    - Polymicrobial (type I) necrotizing infection is caused by aerobic and anaerobic bacteria. It usually occurs in older adults and/or in individuals with underlying comorbidities including diabetes.
    - Monomicrobial (type II) necrotizing infection is most commonly caused by group A *Streptococcus* (GAS) (and other beta-hemolytic streptococci). It may occur in any age group and in individuals with no underlying comorbidities.
  - **Necrotizing myositis** – Necrotizing myositis is a rare, serious infection of skeletal muscle typically caused by GAS (and other beta-hemolytic streptococci). (See 'Necrotizing myositis' above.)
  - **Necrotizing cellulitis** – Necrotizing cellulitis is typically caused by anaerobic pathogens and may be divided into two types: clostridial (usually caused by *Clostridium perfringens*) and nonclostridial (caused by polymicrobial infection). Unlike necrotizing fasciitis and

myositis, necrotizing cellulitis is a mild illness in the immunocompetent host. (See 'Necrotizing cellulitis' above.)

- **Risk factors** – Risk factors associated with NSTI include skin or mucosal breach, traumatic wounds, and diabetes or other immunosuppressing conditions. (See 'Risk factors' above.)

- **Clinical manifestations** – Clinical manifestations of NSTI include erythema, edema extending beyond the visible erythema, severe pain (out of proportion to exam findings in some cases), fever, crepitus, and skin bullae, necrosis, or ecchymosis. Systemic toxicity may be observed. Necrotizing infection most commonly involves the extremities (lower extremity more commonly than upper extremity) and usually presents acutely. Other presentations of necrotizing fasciitis include involvement of the perineum (Fournier gangrene), head and neck region, and neonatal infection. (See 'Clinical manifestations' above.)

- **Diagnosis** – NSTI should be suspected in patients with soft tissue infection (erythema, edema, warmth) and signs of systemic illness (fever, hemodynamic instability) in association with crepitus, rapid progression of clinical manifestations, and/or severe pain (out of proportion to skin findings in some cases) (algorithm 1).

  - **Definitive diagnosis** – The diagnosis of necrotizing infection is established via surgical exploration of the soft tissues in the operating room, with physical examination of the skin, subcutaneous tissue, fascial planes, and muscle. (See 'Diagnosis' above.)

  - **Role of imaging** – Radiographic imaging studies can be useful to help determine whether necrotizing infection is present **but should not delay surgical intervention** when there is crepitus on examination or rapid progression of clinical manifestations. The best initial radiographic imaging exam is computed tomography scan. Presence of gas in the tissues (seen most frequently in the setting of polymicrobial [type I] necrotizing fasciitis or clostridial infection) is highly specific for NSTI and should prompt immediate surgical intervention. (See 'Radiographic imaging' above.)

- **Treatment** – Treatment of necrotizing infection consists of early and aggressive surgical exploration and debridement of necrotic tissue, together with broad-spectrum empiric antibiotic therapy and hemodynamic support. (See 'Treatment' above.)

  In general, empiric antibiotic treatment of necrotizing infection should consist of broad-spectrum antimicrobial therapy, including activity against gram-positive, gram-negative, and anaerobic organisms. Acceptable empiric antibiotic regimens include the following (see 'Antibiotic therapy' above):

- A carbapenem or piperacillin-tazobactam **plus**
- An agent with activity against methicillin-resistant *Staphylococcus aureus* **plus**
- Clindamycin (for its antitoxin effects against toxin-elaborating strains of beta-hemolytic streptococci and *S. aureus*)

Antibiotic treatment should be tailored to Gram stain, culture, and sensitivity results when available.

For patients with NSTI and toxic shock syndrome due to beta-hemolytic streptococci, we suggest adding intravenous immune globulin (**Grade 2C**). (See 'Intravenous immune globulin' above.)

Issues related to surgical management of NSTI and hemodynamic support are discussed separately (See "Surgical management of necrotizing soft tissue infections" and "Evaluation and management of suspected sepsis and septic shock in adults".)

- **Management of close contacts** – For highly susceptible individuals (such as immunocompromised individuals or patients with recent surgery) who are close contacts of a patient with necrotizing infection due to GAS, we suggest postexposure prophylaxis with oral penicillin (**Grade 2C**). (See 'Prevention' above.)

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Topic 7662 Version 64.0

GRAPHICS

Approach to microbiologic diagnosis of necrotizing infections

Presence of gas in soft tissue (on radiographic imaging)*
Polymicrobial (gram-positive cocci, gram-positive rods, gram-negative cocci, and gram-negative rods)
Necrotizing fasciitis type I (polymicrobial)
Necrotizing cellulitis: Nonclostridial anaerobic (crepitant) cellulitis
Gram-positive rods
Acute clinical presentation
▪ Clostridial myonecrosis (gas gangrene)
• *C. perfringens* – Traumatic
• *C. septicum* – Spontaneous
• *C. sordellii* – Gynecologic
Indolent clinical presentation
▪ Clostridial (anaerobic) cellulitis
• *C. perfringens* – More common
• *C. septicum* – Less common
Absence of gas in soft tissue (on radiographic imaging)*
Gram-positive cocci
Necrotizing fasciitis type II (monomicrobial)
▪ Group A *Streptococcus* or other beta-hemolytic streptococci
▪ *Staphylococcus aureus* (methicillin-sensitive [MSSA] or methicillin-resistant [MRSA])
Necrotizing myositis due to group A *Streptococcus* or other beta-hemolytic streptococci
Gram-negative rods
Aeromonas species – Freshwater exposure
Vibrio species – Saltwater exposure

* Radiographic imaging can be useful to help determine if necrotizing infection is present but should not delay surgical intervention when there is crepitus on examination or rapid progression of clinical

manifestations. The most useful radiographic finding is presence of gas in soft tissues; computed tomography is the most sensitive radiographic modality for detection of this finding.

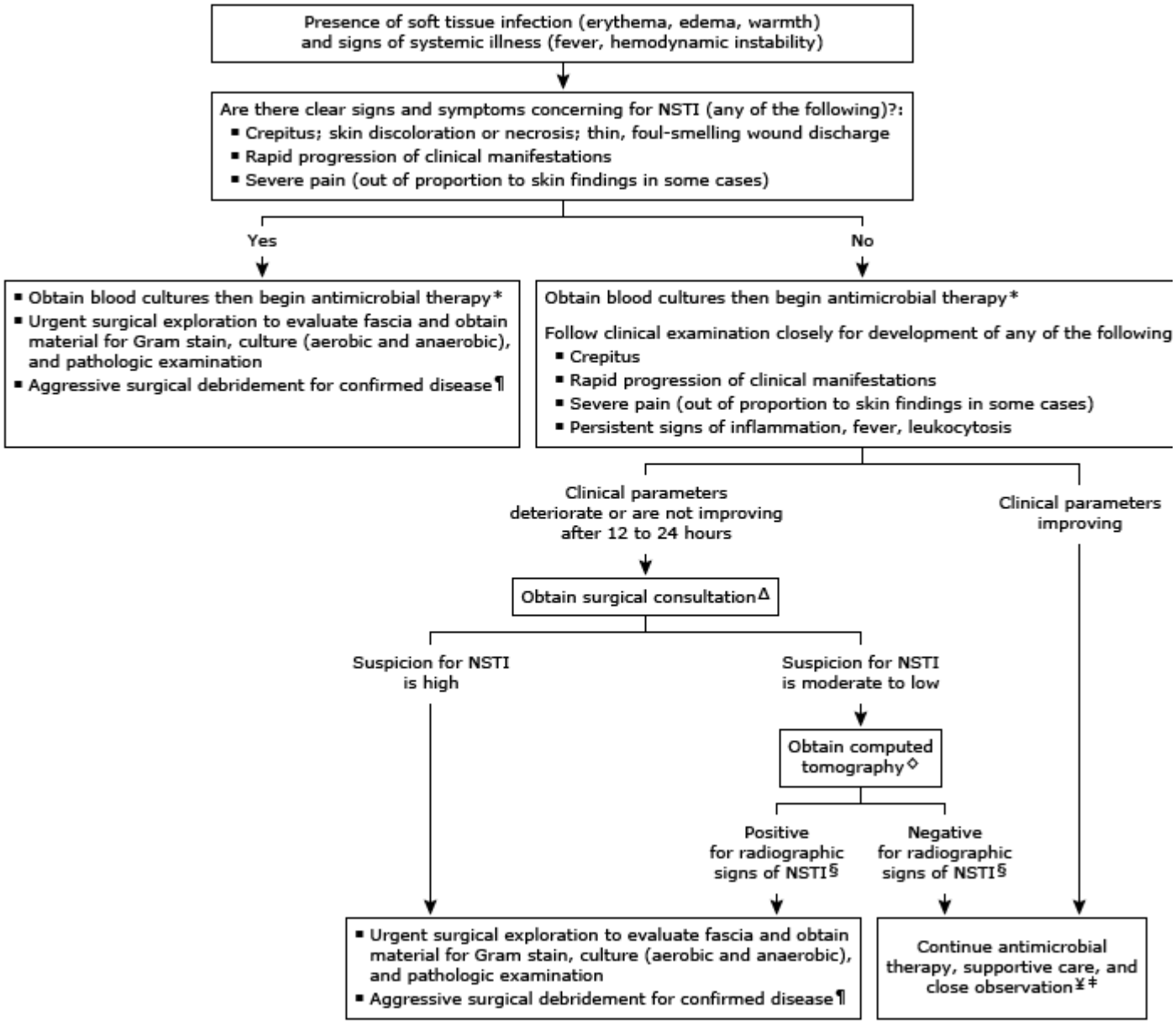
Graphic 116305 Version 2.0

Fournier's gangrene in a patient with diabetes

Necrotizing fasciitis of the perineum (Fournier's gangrene) can involve the scrotum. The infection can begin abruptly with severe pain and may spread rapidly.

Graphic 58093 Version 1.0

Approach to evaluation and initial management of possible necrotizing soft tissue infection



NSTI: necrotizing soft tissue infection; MRI: magnetic resonance imaging.

* Refer to UpToDate text for discussion of approach to empiric antimicrobial therapy. Supportive management may require fluid resuscitation, hemodynamic support, and management of comorbid conditions. Supportive management is adjusted according to clinical features over time.

¶ Intraoperative findings include extensive soft tissue destruction with fascia that is not adherent to adjoining layers. Soft tissue involvement often extends beyond margins based solely on external appearance. Thrombosis of the underlying dermal capillary network is apparent and precedes overt skin necrosis; incision through involved areas will not bleed normally.

Δ Decisions regarding whether to pursue surgical intervention and the appropriate timeframe should be tailored to individual clinical circumstances, with consideration of patient's immune status and other comorbidities.

◇ The first-line imaging study depends on the anatomic location, clinical condition of the patient, availability of technology, and expertise at interpretation. Other imaging modalities include MRI and ultrasound.

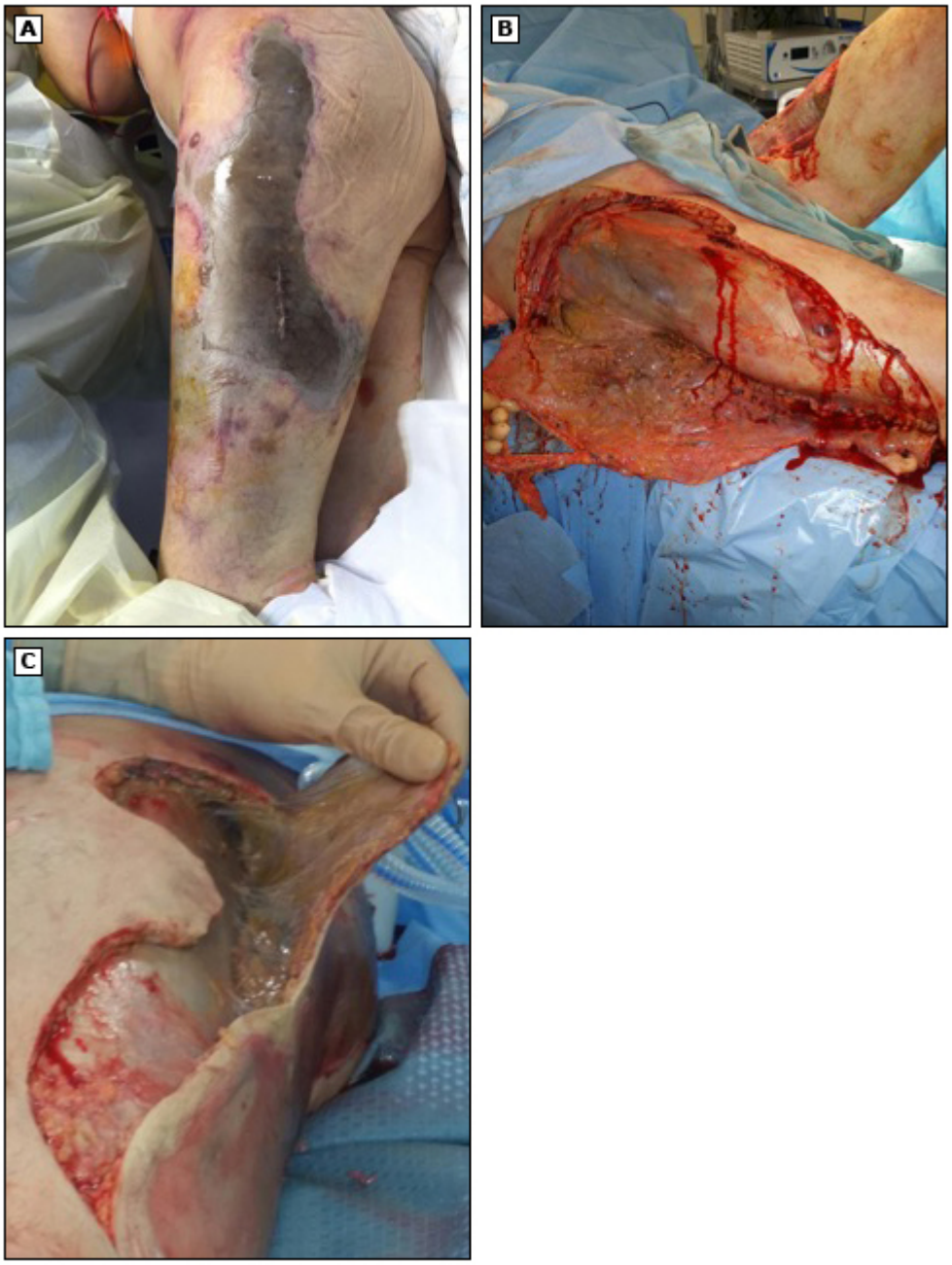
§ Imaging findings of NSTI include gas in the soft tissues, fluid collections, absence or heterogeneity of tissue enhancement with intravenous contrast, and inflammatory changes beneath the fascia.

¥ Alternative diagnoses include other soft tissue infections (including cellulitis or abscess) and inflammatory skin conditions. Refer to the UpToDate text for further discussion.

‡ If clinical concern for NSTI persists, MRI or limited surgical exploration with fascial biopsy may be pursued.

Graphic 116424 Version 1.0

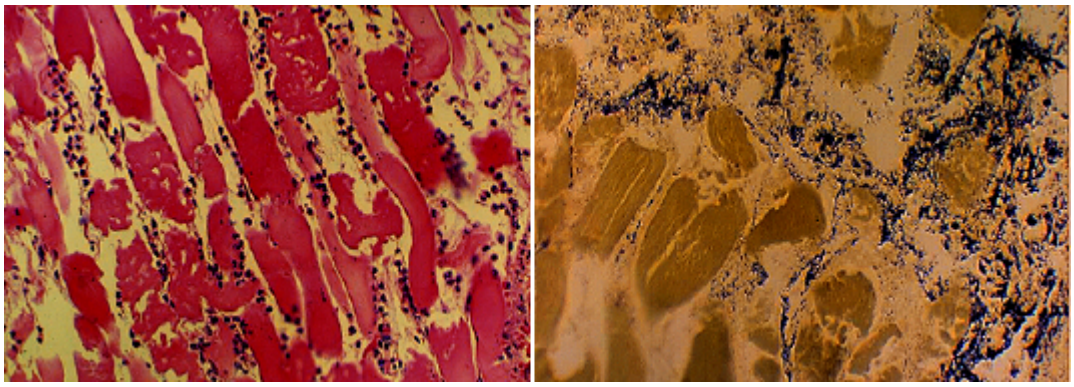
Bilateral thigh necrotizing soft tissue infection



The pictures illustrate a case of necrotizing soft tissue infection that presented as increasing confusion over a few days in a 72-year-old with diabetes but no history of dementia. The patient presented late with tenderness and skin changes of the bilateral thighs (A, left thigh). During surgical exploration and debridement (B, C) the characteristic appearance of necrotic skin, underlying fascia, and dish-water fluid drainage can be seen.

Graphic 109141 Version 1.0

Spontaneous gangrenous myositis

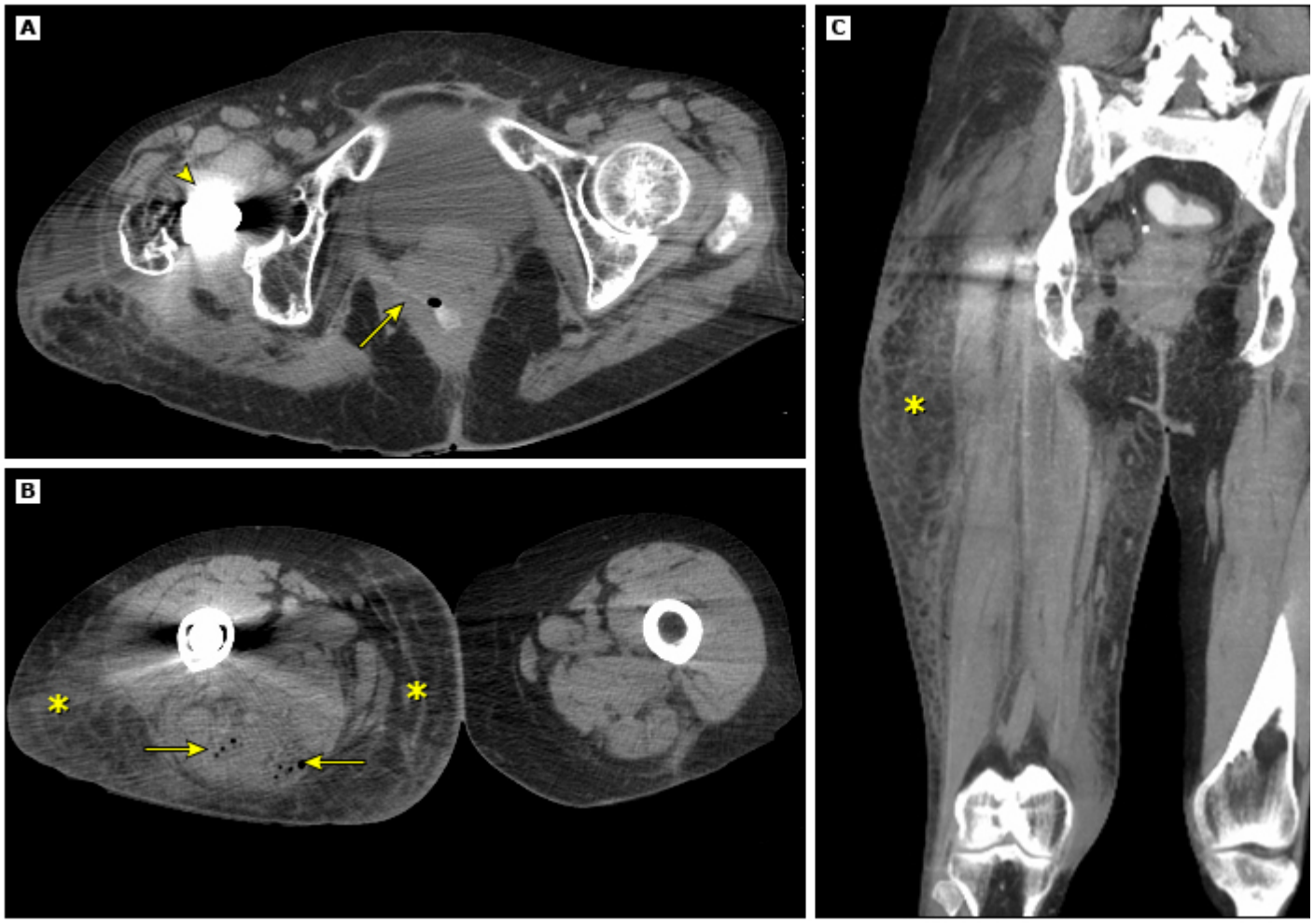


Muscle biopsy from a patient with spontaneous gangrenous myositis due to *Streptococcus pyogenes* (group A *Streptococcus*). Left panel: Necrotic muscle fibers with numerous infiltrating leukocytes. Right panel: Gram stain shows gram-positive bacteria in an area of muscle necrosis.

Courtesy of Larry M Baddour, MD.

Graphic 53989 Version 3.0

Necrotizing fasciitis on CT

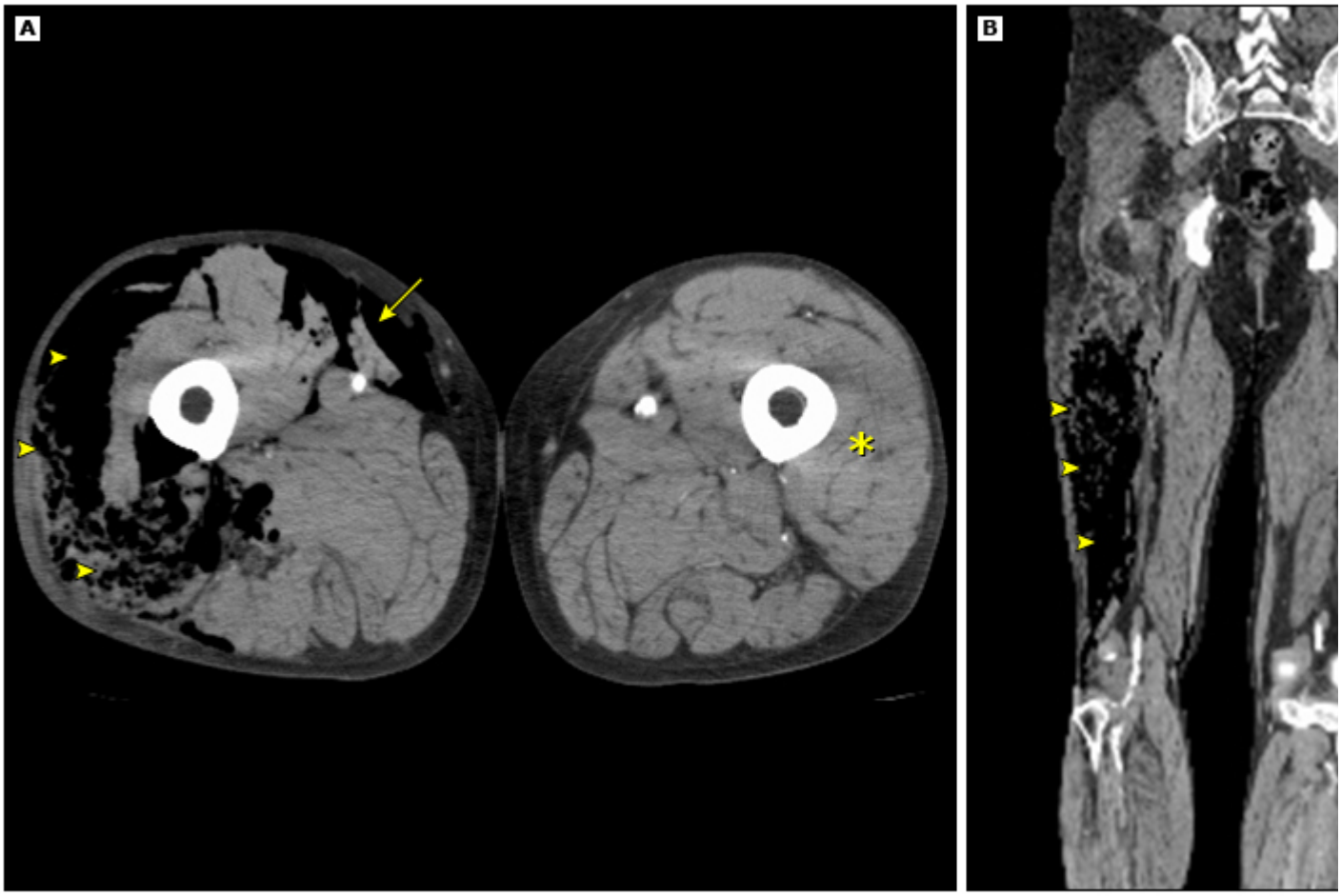


An axial CT scan through the lower pelvis (A) in a patient with Crohn's disease and a right hip replacement (arrowhead) shows a fistulous tract (arrow) from the rectum to the soft tissues of the right hip. Image B shows bubbles of gas in the swollen hamstring muscles (arrows) and circumferential edema of the thigh (asterisks) compared with the normal-sized left thigh. Image C is a coronal reconstruction of the thighs and exemplifies the difference in size caused by inflammatory edema (asterisk). Image D is a sagittal reconstruction and shows gas bubbles throughout the hamstring musculature (arrows).

CT: computed tomography.

Graphic 97786 Version 3.0

Necrotizing myositis on CT



An axial CT scan through the mid thighs (A) shows necrosis of the right vastus lateralis muscle (arrowheads) with spread to the medial aspect of the thigh (arrow). The normal left vastus lateralis (asterisk) is shown in contrast. Image B is a coronal reconstruction and shows the cranio-caudal extent of the necrosis (arrowheads).

CT: computed tomography.

Graphic 101588 Version 2.0

Clinical features of necrotizing fasciitis and pyoderma gangrenosum

Necrotizing fasciitis	Pyoderma gangrenosum
No association with inflammatory bowel disease	Strong link with inflammatory bowel disease
Rapid progression	Slower progression within days
Can resemble cellulitis in early stage	Does not resemble cellulitis
Violaceous ulcer edge not a typical feature	Violaceous ulcer edge is typical
Septic picture can develop	Unlikely to develop sepsis
Likely to require intensive care	Unlikely to require intensive care
Responds to surgery	Worsens with surgery
Lack of resistance to blunt dissection of fascial planes	Fascial planes have normal resistance to dissection
Worsens with immunosuppressive therapy	Responds to immunosuppressive therapy
Should respond to antibiotics and surgery	No response to antibiotics and worsens with surgery
Usually positive blood and tissue cultures	Usually negative blood and tissue cultures

Adapted with permission from: Bisarya K, Azzopardi S, Lye G, Drew PJ. Necrotizing fasciitis versus pyoderma gangrenosum: Securing the correct diagnosis! A case report and literature review. Eplasty 2011; 11:e24.

Graphic 115267 Version 1.0

Parenteral antimicrobial therapy for treatment of skin and soft tissue infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) in adults

Drug	Adult dose
Antibiotics of choice*	
Vancomycin¶	15 to 20 mg/kg/dose every 8 to 12 hours
Daptomycin△	4 to 6 mg/kg IV once daily
Alternative agents	
Short-acting agents with parenteral or oral dosing	
Linezolid	600 mg IV (or orally) twice daily
Tedizolid	200 mg IV (or orally) once daily
Delafloxacin	300 mg IV twice daily (or 450 mg orally twice daily)
Omadacycline◇	100 mg IV once daily (or 300 mg orally once daily)
Short-acting agent with parenteral dosing§	
Ceftaroline	600 mg IV every 12 hours
Telavancin	10 mg/kg once daily
Long-acting agents with parenteral dosing	
Dalbavancin	Single-dose regimen: 1500 mg once Two-dose regimen: Initial dose 1000 mg, followed by 500 mg dose one week later
Oritavancin	1200 mg IV as a single dose

MRSA: methicillin-resistant *S. aureus*; IV: intravenously; AUC: area under the 24-hour time-concentration curve.

* In areas outside the United States where teicoplanin is available, some use it as the drug of choice for initial therapy of gram-positive pathogens, while others favor its use for patients with intolerance to vancomycin.

¶ For severely ill patients, a vancomycin loading dose (20 to 35 mg/kg) is appropriate[1]; within this range, we use a higher dose for critically ill patients. The loading dose is based on actual body weight, rounded to the nearest 250 mg increment and not exceeding 3000 mg. The initial maintenance dose and interval are determined by nomogram (typically 15 to 20 mg/kg every 8 to 12 hours for most patients with normal renal function). Subsequent dose and interval adjustments are based on AUC-guided or trough-guided serum concentration monitoring. Refer to the UpToDate topic on vancomycin dosing for sample nomogram and discussion of vancomycin monitoring.

Δ Dosing of daptomycin for treatment of skin and soft tissue infection is 4 to 6 mg/kg IV once daily; dosing for treatment of bacteremia is at least 6 mg/kg IV once daily. (Refer to the UpToDate topic on treatment of MRSA bacteremia for further discussion.)

◇ A loading dose may be used: 200 mg IV over 60 minutes OR 100 mg IV over 30 minutes twice.

§ Ceftobiprole has broad-spectrum activity against gram-positive and gram-negative organisms and is available in some countries outside the United States.

Data from: Lui C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011; 52:285.

Reference:

1. *Rybak MJ, Le J, Lodise TP, et al. Therapeutic Monitoring of Vancomycin for Serious Methicillin-Resistant Staphylococcus Aureus Infections: A Revised Consensus Guideline and Review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2020; 77:835.*

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