Necrotizing Soft-Tissue Infections
NEJM December 2017. Dennis L. Stevens, Ph.D., M.D., and Amy E. Bryant, Ph.D

Definition
• Necrotizing fasciitis is a surgical diagnosis characterized by friability of the superficial fascia, dishwater-gray exudate, and a notable absence of pus, resulting in widespread tissue destruction, which may extend from the epidermis to the deep musculature.
• Can occur after major traumatic injury or minor breaches of the skin (abrasion, insect bite, varicella infn, nonpenetrating soft-tissue injury, routine ob-gyn procedures.
• Although necrotizing infections have common clinical features, various clinical entities have been defined including progressive bacterial synergistic gangrene, synergistic necrotizing cellulitis, streptococcal gangrene, gas gangrene (clostridial myonecrosis), and nonclostridial anaerobic cellulitis.

Epidemiology
• Necrotizing fasciitis types I and II are distinguished largely by whether the cause is polymicrobial (type I) or monomicrobial (type II).
• Type I infection is polymicrobial, both aerobic and anaerobic organisms, usually elderly/comorbidity. Necrotizing cellulitis seen in diabetic foot infections, nonnecrotizing cellulitis also common in DM foot infn, but think necrotizing when signs of sepsis, tachy, leukocytosis, acidosis, marked hyperglycemia.
• Bacterial penetration into the fascial compartments of the head and neck may result in Lemierre’s syndrome (thrombophlebitis of the IJ) or Ludwig’s angina (submandibular fascial planes).
• Fournier’s gangrene- breach of the GI or urethral mucosa, abrupt severe pain and rapid spread from the perineal region to the abdominal wall, gluteal muscles, male genitalia.
• Type II necrotizing fasciitis is monomicrobial. Group A strep is most common, also MRSA, may occur in any age group and in healthy infections. Group A Strep necrotizing infection due to exotoxin.

<table>
<thead>
<tr>
<th>Predisposing Factor</th>
<th>Clinical Syndrome</th>
<th>Etiologic Agent</th>
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<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>
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<td>Minor penetrating trauma</td>
<td>NF type II</td>
<td>Aeromonas hydrophila</td>
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<td>Freshwater laceration</td>
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<td>Vibrio vulnificus</td>
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<td>Saltwater laceration</td>
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<tr>
<td>Minor nonpenetrating trauma: muscle strain, sprain, or contusion</td>
<td>NF type II or streptococcal myonecrosis</td>
<td>Streptococcus pyogenes</td>
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<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>
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<td>Skin breach</td>
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<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>Gas gangrene</td>
<td>C. perfringens, C. histolyticum, C. novyi, or C. sordellii</td>
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<td>Immunocompromised state</td>
<td></td>
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<tr>
<td>Diabetes with peripheral vascular disease</td>
<td>NF type I</td>
<td>Mixed aerobic and anaerobic organisms</td>
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<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>
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<tr>
<td>Occult factors: colonic lesions, including carcinoma</td>
<td>Spontaneous gas gangrene</td>
<td>C. septicum</td>
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* Gas gangrene is also known as clostridial myonecrosis.
Invasive Group A Strep Soft-Tissue Infections

- Two distinct clinical presentations have been described (50% each): infection with a defined portal of bacterial entry and infection that arises spontaneously in the deep tissue, without an overt wound or lesion.
- S. pyogenes gains entry to the deep tissues through superficial cutaneous lesions (chickenpox vesicles, insect bites, or lacerations), after breaches of skin or mucosal integrity (due to drug injections, surgical incisions, or childbirth), or after penetrating trauma.
- 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 becomes frankly gangrenous and undergoes extensive sloughing. The patient is now perilously ill, with a high temperature and extreme prostration. At this stage, mortality is high, even with appropriate treatment.
- In approximately 50% of patients with group A streptococcal necrotizing fasciitis or myonecrosis, infection initiates deep in the soft tissues, without a portal of entry, **often at sites of non-penetrating trauma (muscle strain or bruise)**.
- 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 correct **diagnosis is delayed**, and as a result, the **mortality exceeds 70%**.
- Seeding of the deep tissues probably occurs through transient bacteremia from the nasopharynx.
- 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.

Necrotizing Clostridial Infections

- Gas gangrene (clostridial myonecrosis) occurs spontaneously or as a result of trauma.
- Deeply penetrating injuries that compromise the blood supply create an anaerobic environment that is ideal for spore germination and bacterial proliferation.
- 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.
- Spontaneous (nontraumatic) gas gangrene is commonly caused by C. septicum, which is more aerotolerant than other clostridial pathogens.
- Systemic signs include an absence of fever, profound hypotension, diffuse capillary leak, hemoconcentration (Hct 50-80%), marked leukemoid reaction (white-cell count, 50,000 to 150,000 per cubic millimeter).
- Mortality is 70 to 100%, and death occurs within 2 to 4 days after hospital admission.

**Diagnosis**

**Clinical Findings**

- Classic manifestations of necrotizing fasciitis include soft-tissue edema (in 75% of cases), erythema (72%), severe pain (72%), tenderness (68%), fever (60%), and skin bullae or necrosis (38%).
- **Factors that differentiated necrotizing fasciitis from cellulitis were recent surgery, pain out of proportion to clinical signs, hypotension, skin necrosis, and hemorrhagic bullae.**
In patients with cryptogenic group A streptococcal infection (i.e., infection with no portal of entry), crescendo pain is the most important clinical clue for such infection, and its onset typically occurs well before shock or organ dysfunction is manifested.

However, crescendo pain may be absent or attenuated in patients who are receiving analgesic agents, including NSAIDS; in patients who have undergone surgery, childbirth, or trauma, the pain may be incorrectly attributed to normal postoperative soreness, typical post-partum discomfort, or the trauma itself, respectively, rather than to acute infection.

Pain may also be absent in patients with altered mental status or those with diabetes-related neuropathy.

Thus, all patients presenting with a sudden onset of severe pain in an extremity, with or without an obvious portal of bacterial entry or the presence of fever, should be evaluated for severe soft-tissue infection on an emergency basis.

### Table 2. Pitfalls in the Diagnosis of Necrotizing Soft-Tissue Infection.

<table>
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<tr>
<th>Pitfall</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>Absence of fever</td>
<td>Fever is often absent in patients with necrotizing soft-tissue infections because of NSAIDs that are self-administered or prescribed in the emergency department or in postsurgical settings. Fever is also absent in patients with necrotizing infection due to C. sordellii.</td>
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<tr>
<td>Absence of cutaneous manifestations</td>
<td>Patients with spontaneous or cryptogenic necrotizing infections (i.e., infections without an obvious bacterial portal of entry) that begin in the deep soft tissues often do not have cutaneous signs of infection until late in the course of the disease.</td>
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<tr>
<td>Attributing severe pain to injury or procedure</td>
<td>Severe pain is a key finding in patients with necrotizing infections. However, when such infections develop after surgery or parturition, pain may be erroneously attributed to the procedure itself. Similarly, perineal pain may be attributed to hemorrhoids, epididymitis, or vaginal or rectal trauma. Severe pain associated with spontaneous or cryptogenic infections is often wrongly attributed to muscle strain or venous thrombosis. If pain is out of proportion to the suspected cause or requires opioids or ketorolac for management, a developing necrotizing infection should be considered. Pain may be absent because of the use of narcotics or NSAIDs or because of neuropathy in patients with diabetes.</td>
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<tr>
<td>Nonspecific imaging tests</td>
<td>In patients with necrotizing infections, radiographs may show only edema, with no evidence of gas in the deep tissue. Since this finding is consistent with noninfectious causes (e.g., soft-tissue injury and postsurgical and postpartum conditions), it may confound the diagnosis.</td>
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<tr>
<td>Attributing systemic manifestations to other causes</td>
<td>Nausea, vomiting, and diarrhea may be early manifestations of toxemia from group A streptococcal infection, though they are often wrongly attributed to food poisoning or viral illness.</td>
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### Imaging Tests

- Radiographs, CT scans or MRIs will show soft-tissue swelling in patients with group A streptococcal infection and will show gas in the tissues of patients with gas gangrene or necrotizing fasciitis type I.
- Per UPTODATE (Oct 2020), CT is most accurate for necrotizing soft tissue infection (NSTI). Key finding is gas which is seen in clostridial and polymicrobial (Type 1) infections. CT better than MRI which can be overly sensitive.

### Surrogate Markers

- The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) scoring system uses a scale from 0-13 with scores below 5.8 showing negative predictive value of 86-96%.
- In children with NSTI, the median score of LRINEC was only 3.7

### TREATMENT

#### Surgical Intervention

- For patients with aggressive soft-tissue infection or those with mild infection plus evidence of systemic toxicity, prompt surgical exploration is extremely important for three reasons:
  - 1) determine the extent of infection,
2) assess the need for débridement or amputation
3) 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.
- Inspection and débridement continued every 1 to 2 days until necrotic tissue is no longer present.
- Universal agreement that early surgical débridement is crucial in managing these complex cases.
- Survival is significantly increased among patients taken to surgery within 24 hours after admission.
- 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 NSTI- IDSA says Vanco + (Zosyn or Rocephin /Flagyl).
- Group A Strep- Clinda + Penicillin.
- Traumatic or spontaneous Gas Gangrene- PCN+Clinda.

Care of Critically Ill Patients
- Capillary Leak Syndrome may require extremely high IV fluid requirements (10-12L of NS/day).
- Profound hypoalbuminemia is also common which may require Albumin replacement.
- Reversible cardiomyopathy is seen in some patients with Strep toxic shock.

Hyperbaric Oxygen
- Mixed results, recent studies show some benefit.

Intravenous Immune Globulin
- Article said evidence was inconclusive but UPTODATE Oct 2020 says a 2018 metaanalysis published after this article showed significant mortality improvement with IVIG.