# Necrotizing Soft Tissue Infection

# 113

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**Learning Goals**

- Be able to identify the early and late signs and symptoms of NSTI.
- Understand the different pathophysiology of each of the four classes of NSTI.
- Be able to choose appropriate antimicrobial therapy based on the causative organism.

## 113.1 Introduction

Necrotizing soft tissue infections are quite rare. Most practicing physicians will see one case of NSTI during their career, making it a challenge for most physicians to be able to recognize the early signs and symptoms of this disease and act promptly. On average, there are only 500–1500 cases of NSTI reported each year, with an incidence of 0.4 per 100,000 individuals in the United States, as reported by the Centers for Disease Control and Prevention. NSTI tends to occur at higher rates in patients with advanced age, obesity, diabetes, alcoholism, immunosuppression, and other chronic conditions. However, it is important to note that up to 20% of cases occur in patients without any predisposing conditions or risk factors. Additionally, there are geographical and regional differences in etiology and microbiology at the national and regional levels [1].

## 113.2 Etiology

NSTIs are caused when bacteria penetrate the skin's protective barrier and enter the subcutaneous space. The low blood supply to this area creates a hypoxic environment with little immunologic response, which is an ideal environment for bacteria to rapidly multiply. The most common situations in which bacteria are able to penetrate the skin are through traumatic wounds, incisions, diabetic foot ulcers, decubitus ulcers, the perineum, and a perforated viscus. NSTI can occur at any site on the body, but the most common locations are the perineum, genitalia, abdomen, and extremities. One factor that has contributed to making NSTIs difficult to diagnose is that many NSTIs have had different names over time based on location. Examples of this are Fournier's gangrene, necrotizing fasciitis, clostridial myonecrosis, synergistic necrotizing cellulitis, and gas gangrene.

Morgan Collom has died before the publication of this book.

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## 113.3 Classification

Necrotizing soft tissue infections are classified into four different types based on the pathogen of origin. This classification system was first described by Giuliano and colleagues [2]. Type I infections are polymicrobial infections, type II are monomicrobial infections, type III are marine infections and type IV are fungal infections.

### 113.3.1 Type I Infections

The most common NSTIs are the type I class of infections, which are polymicrobial and represent approximately 75% of all NSTIs. Hence, initial treatment should begin with broad-spectrum antibiotic treatment. On average, four organisms are cultured from a single infection. These polymicrobial infections are often comprised of gram-positive cocci, gram-negative rods, and anaerobes. From these, the most common gram-positive organisms are *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Enterococcus species*. The most common gram-negative rod isolate is *Escherichia coli*. Lastly, the most common isolated anaerobes have been *Bacteroides* and *Peptostreptococcus* [2].

Type I infections also tend to occur in older patients with more medical comorbidities. These infections are more commonly located in the perineum and have occurred as a result of a perforated viscus, diabetic foot ulcers, or decubitus ulcers. Polymicrobial infections are less lethal than some monomicrobial infections but can still cause extensive local damage.

### 113.3.2 Type II Infections

Type II NSTIs tend to be much more aggressive and virulent than the more common polymicrobial infections. They often present much more acutely with a higher potential for local aggressive spread. Signs of systemic toxicity, as well as toxic shock, are more likely. Type II infections tend to occur in younger, healthier patients with a history of trauma, IV drug use, or surgery. The most likely pathogens in this group include group A β-hemolytic streptococci (GAS), *Clostridium* species, and community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA).

The species most frequently associated with type II NSTIs is *Streptococcus pyogenes* [1]. These rapidly progressive NSTIs are associated with a high mortality rate [3–6]. Pathogenic strains produce multiple exotoxins and virulence factors, causing life-threatening infections in otherwise healthy individuals [3, 4, 7]. The exotoxins commonly released include hemolysins, fibrinolysins, hyaluronidases, antiphagocytic M proteins, leukocidins, and streptolysins O and S. These exotoxins cause damage by preventing phagocytosis and bacterial clearance, damaging neutrophils, and breaking down hyaluronic acid and other connective tissues.

Clostridium infections (gas gangrene) are quite rare and are typically associated with traumatic wounds, puncture wounds, and IV drug use. These infections can quickly progress from injury to systemic toxicity and death in just a few hours. Many *Clostridia* species are endemic to the soil; however, with the rise of IV drug use, there has also been a rise in the prevalence of *Clostridia* species isolated from this patient population [8]. There are two main exotoxins that are responsible for the rapid destructive spread and systemic toxicity associated with these infections, which are α-toxin and θ-toxin. Clostridium reproduces every 8 min, which produces α-toxin (phosphorylase C) and θ-toxin (perfringolysin). Early on, these toxins are potent platelet agonists, which can lead to platelet aggregation, thrombus formation, and ultimately ischemia. As the toxins are absorbed locally, they can cause neutrophil dysfunction and death. As the infection progresses and the toxins are absorbed systemically, they can cause intravascular hemolysis, increase vascular permeability, and directly inhibit myocardial contractility.

Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) NSTIs are

on the rise. CA-MRSA infections tend to affect healthy patients outside of the hospital. They are common in prisoners, contact sports team members, military personnel, IV drug users, institutional residents, and individuals who attend child and adult daycare. The main virulence factor that CA-MRSA produces is a coagulase that causes tissue destruction and invasion. In addition, it has the ability to produce Panton-Valentine leucocidin, which is a white blood cell and dermonecrotic toxin.

### 113.3.3 Type III Infections

Type III NSTI infections are caused by gram-negative marine organisms such as *Vibrio vulnificus* and *Aeromonas* species. *Vibrio vulnificus* is the most common and is found predominantly in warm coastal waters, including the southern United States [9–11]. Infection can occur through an open wound or a break in the skin while being exposed to seawater or seafood harboring the bacteria. Less commonly, the infection is acquired through the ingestion of colonized oysters, which results in hematogenous spread in patients with cirrhosis. Type III infections tend to follow a similar progression as type II infections. They can present with hemorrhagic bullae, ecchymosis, and cellulitis [11]. However, significant systemic toxicity, including multiorgan failure and cardiovascular collapse, can occur rapidly and early.

### 113.3.4 Type IV Infections

Fungal NSTIs are the rarest of all NSTIs and also carry a high mortality rate. There are only a handful of reported cases. It appears that the risks of systemic fungal infections are similar to the risks associated with fungal NSTIs, which include primary immunosuppression, poorly controlled diabetes, obesity and chronic alcoholism. The most common isolated fungus from a polymicrobial NSTI is *Candida* spp., while the most common monomicrobial fungal NSTI is due to mucormycosis [12].

## 113.4 Diagnosis

### 113.4.1 History

A thorough history and physical examination are the most critical components in establishing a diagnosis of NSTI as the diagnosis is heavily reliant on clinical gestalt rather than diagnostic testing. A clinical diagnosis of NSTI continues to remain a challenge for most physicians due to the rarity of the disease as well as the early symptoms mimicking much more common conditions such as cellulitis and erysipelas. There are several comorbidities that may predispose a patient to develop an NSTI, which include obesity, diabetes, liver and kidney failure, alcoholism, immunosuppression, and vasculopathy. However, up to a fifth of patients with NSTI lack a single comorbidity. The source of the injury is often ambiguous as well. Only a small proportion of patients will present with a history of trauma, IV drug use, surgical incision, or a puncture wound. The majority of patients without a clear source of injury usually present with an infected perineum, diabetic foot ulcer, decubitus ulcer, or seeding in the soft tissue from a perforated viscus. It seems the most important component of a patient's history and physical exam is the chronology of the disease. The signs and symptoms of NSTI progress much more rapidly compared to those of cellulitis or an abscess.

### 113.4.2 Clinical Characteristics

There are no pathognomonic symptoms for NST's and clinical presentation can vary depending on the microbiological pathogen, anatomical location, and depth of infection. Early in the disease process, the most common symptoms are erythema, warmth, tenderness, swelling, skin hypersensitivity, pain out of proportion to the exam, and pain beyond the margin of erythema and fever. The majority of these symptoms are nonspecific and common in many other conditions, making early diagnosis difficult. The two most important early symptoms, which should alert the physician

of a possible NSTI, are pain out of proportion to the exam and tenderness beyond the area of erythema. Both of these symptoms may point to a rapidly progressive infection that has spread deep into the subcutaneous tissue and muscles while only causing early skin changes. As the infection progresses, later symptoms can develop, which include bullae, violaceous erythema, necrotic tissue, crepitus, cutaneous anesthesia, and shock. Once these later signs and symptoms develop, the prognosis is poor.

### 113.4.3 Diagnostic Tools

There is no specific diagnostic study that can confirm or rule out an NSTI. A diagnosis must be based on clinical suspicion with the assistance of a few diagnostic studies when appropriate. When clinical suspicion is high for NSTI, delay in diagnostic studies should be avoided as the time to treatment is critical.

### 113.4.4 Laboratory

Laboratory values tend to be nonspecific and can only help aid in diagnosis. In patients with NSTI, it is not uncommon to see leukocytosis, leukopenia, or bandemia. Other common lab abnormalities can include elevations in creatinine, BUN, lactic acid, creatine phosphokinase, hyponatremia, and coagulopathy. A study by Wall and colleagues found that a WBC count >15,400 cells/mm$^3$ or a serum sodium level <135 mmol/L had a negative predictive value of 99% and a sensitivity of 90%. These lab values lack specificity and only have a positive predictive value of 26%, which can rule out NSTI, but not confirm it [13, 14].

Currently, the most widely adopted diagnostic tool is the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC), established by Wong and colleagues [15] (Table 113.1). LRINEC is a set of six independent variables, with each variable given a specific number toward a final score. These final scores are broken down into three categories: low risk, intermediate risk, and high risk (Table 113.2). Scores greater than 6 correspond to a PPV of 92% and an NPV of 96%. LRINEC scores are to be used as an adjunct to help risk stratify patients with suspected NSTI. Although this score is widely used, it has never been validated.

**Table 113.1** LRINEC score system

| *LRINEC variable* | *Value* | *Score* |
|---|---|---|
| WBC (cells/mm$^3$) | <15<br>15–25<br>>25 | 0<br>1<br>2 |
| Sodium (mmol/L) | >135<br><135 | 0<br>2 |
| Creatinine (mg/dL) | <1.6<br>>1.6 | 0<br>2 |
| Hemoglobin (g/dL) | >13.5<br>11–13.5<br><11 | 0<br>1<br>2 |
| Glucose (mg/dL) | <180<br>>180 | 0<br>1 |
| C-reactive protein (mg/L) | <150<br>>150 | 0<br>4 |
| *Sum of points* | *Risk category* | *Necrotizing fasciitis probability* |
| <5 | Low | <50% |
| 6–7 | Intermediate | 50–75% |
| >8 | High | >75% |

[15]

New data looking at biomarkers showed that Ficolin-2, a pattern recognition molecule, could be used to predict short-term mortality (<28 days). Hansen et al. concluded that a low Ficolin-2 level on admission (<1.9 μg/mL) was independently associated with higher short-term mortality [17]. Another biomarker, Pentraxin-3 (PTX-3), is a marker of inflammation similar to CRP. Elevation in the levels of PTX-3 was shown to correlate with increased disease severity and mortality in a prospective study by Hansen et al. [18]. This study was not able to establish an independent association of morbidity and mortality but shows a potential role in the future pending further analysis.

### 113.4.5 Imaging

Due to the rapid lethality of NSTI, imaging studies should be utilized cautiously and not delay the time to treatment. If imaging can be obtained quickly in a stable patient, a plain radiograph is the gold standard, followed by computed tomog-

**Table 113.2** Antimicrobial therapy options for NSTI

| Agent | Dose | Remarks |
|---|---|---|
| *Classic empiric agents* | | |
| Vancomycin (MRSA) | 15 mg/kg IV q12h | Often more readily available and lower in cost |
| Penicillin (gram-positive) | 2–4 MU IV q4–6h | |
| Gentamicin (gram-negative) | 5–7 mg/kg IV q24h | |
| Clindamycin | 600–900 mg IV q8h | |
| *Other empiric agents* | | |
| Tigecycline | 100 mg IV then 50 mg IV q12h | MRSA, gram-positive, gram-negative, anaerobic |
| Clindamycin | 600–900 mg IV q8h | |
| Ceftaroline | 600 mg q12h | MRSA, gram-positive, gram-negative, anaerobic |
| Metronidazole | 500 mg IV q6–8h | |
| Clindamycin | 600–900 mg IV q8h | |
| Vancomycin | 15 mg/kg IV q12h | |
| Clindamycin | 600–900 mg IV q8h | |
| PLUS one of the following: | | |
| Imipenem/cilastatin | 1 g IV q6–8h | |
| Meropenem | 1 g IV q8h | |
| Ertapenem | 1 g IV q24h | |
| Cefotaxime | 2 g IV q6h | |
| Vancomycin | 15 mg/kg IV q12h | |
| Clindamycin | 600–900 mg IV q8h | |
| Metronidazole | 500 mg IV q6–8h | |
| PLUS one of the following: | | |
| Piperacillin/tazobactam | 3.375 g IV q6h | |
| Ciprofloxacin | 400 mg IV q12h | |

| Pathogen specific | | |
|---|---|---|
| Agent | Dose | Remarks |
| *Group A Streptococcal* | | |
| Penicillin<br>+<br>Clindamycin | 2–4 MU IV q4–6h<br>600–900 mg IV q8h | In severe cases, PCN should be combined with clindamycin or macrolide to avoid treatment failure |
| *Clostridial* | | |
| Penicillin<br>+<br>Clindamycin | 2–4 MU IV q4–6h<br>600–900 mg IV q8h | In severe cases, PCN should be combined with clindamycin to avoid treatment failures and neutralize toxins |
| *CA-MRSA* | | |
| Vancomycin<br>Linezolid<br>Daptomycin<br>Ceftaroline<br>Quinupristin/<br>Dalfopristin | 15 mg/kg IV q12h<br>600 mg IV q12h<br>4 mg/kg IV q24h<br>600 mg IV q12h<br>7.5 mg/kg IV q8h | Agent of choice, Risk AKI<br>Inhibit toxin production<br>Second choice, bactericidal<br>Bactericidal MRSA and VISA<br>Effective against VRSA |
| *Vibrio* | | |
| Cefotaxime<br>+<br>Minocycline | 2 g IV q6h<br>200 mg IV then<br>100 mg IV q12h | Combination most effective |

[16]

raphy per current recommendations from the American College of Radiology. A plain radiograph may demonstrate subcutaneous emphysema or air tracking in the soft tissue. This finding is highly specific for a clostridial NSTI, but not sensitive for any of the remaining types of NSTI.

Computed tomography is only slightly more sensitive than a plain radiograph, but is nonspecific and may demonstrate air tracking, fascial separation, fascial thickening, and possible deep abscess formation. Ultrasound and magnetic resonance imaging have no role [19].

### 113.4.6 Macroscopic/Microscopic

Macroscopic diagnosis is typically performed intraoperatively. Common macroscopic findings of an NSTI are weeping of "dishwater" or hemorrhagic fluid from facial planes, a lack of bleeding, noncontractile muscle, grey necrotic tissue, and a positive "finger test." This test is positive when the surgeon is able to use his finger to dissect through tissue that is normally strong and adherent. Macroscopic findings are helpful in guiding the extent of the excision and debridement. To achieve a microscopic diagnosis, a biopsy must be taken of the deep fascia and muscle. Ideally, the biopsy specimen should reveal liquefaction necrosis, thrombosed blood vessels, and PMN infiltrates. Microscopic diagnosis is impractical and typically unnecessary as macroscopic findings are generally considered adequate for diagnosis.

**Differential Diagnosis**
- Complicated soft tissue infection
- Non-necrotizing cellulitis
- Abscess

## 113.5 Medical Treatment

### 113.5.1 Antibiotic Therapy

Broad-spectrum antimicrobial therapy should begin immediately after NSTI is suspected. Most NSTI are polymicrobial, and empiric antibiotic therapy should cover gram-positive, gram-negative, anaerobes, and MRSA, considering local microbiological susceptibility [20, 21].

Even NSTIs that are commonly monomicrobial (e.g., extremity infections due to trauma or IV drug use) should be treated broadly until proper identification of the pathogen is achieved through cultures and sensitivities. In addition, the adjuvant uses of an antimicrobial with ribosomal synthesis inhibitory properties (e.g., clindamycin, linezolid) should be considered to reduce the production of certain toxins (e.g., alpha-toxin, super antigen M protein).

Table 113.2 summarizes the recommendations for empiric therapy as well as pathogen-specific therapy.

#### 113.5.1.1 Duration

Empiric antibiotic treatment should be continued until cultures and sensitivities can guide the de-escalation of antibiotic coverage. Discontinuation of antibiotic therapy can be considered once the patient is hemodynamically stable, the WBC has normalized, and all debridement has been completed. In general, a shorter course (e.g., <7 days) of antibiotics is adequate and has similar clinical outcomes compared to a more prolonged course [22].

### 113.5.2 Surgical Treatment

The mainstay treatment for NSTI is immediate and adequate surgical debridement of all devitalized and necrotic tissue (Fig. 113.1). Multiple studies have concluded that there is a seven- to ninefold increase in mortality if surgical debridement is delayed or inadequate [23]. The adequacy of debridement is difficult to define, therefore making this determination subjective and dependent on each surgeon's experience and judgement.

One expected pitfall is not making the incision wide enough. Surgeons who lack experience treating NSTI tend to make incisions that are too small. Although excessively wide and aggressive incisions and debridement can have their own set of complications, patients with incisions and debridement that are too small tend to have a worse outcome. It is recommended that the initial incision extends outside the area of initial induration and cellulitis. This incision should be carried down through the subcutaneous tissue until the deeper muscle layers are reached. Thorough exploration of the tissue and fascial planes must occur to guide the extent of debridement. All necrotic and devitalized tissue must be excised. As previously mentioned, this tissue is often necrotic in color and is easily dissected with a positive "finger test." Murky grey or "dirty dishwater" fluid may be encountered from the fascial planes as well. Excision should be carried out until healthy tissue is reached. This healthy tissue should exhibit brisk bleeding, and the muscle should show visible contractility upon stimula-

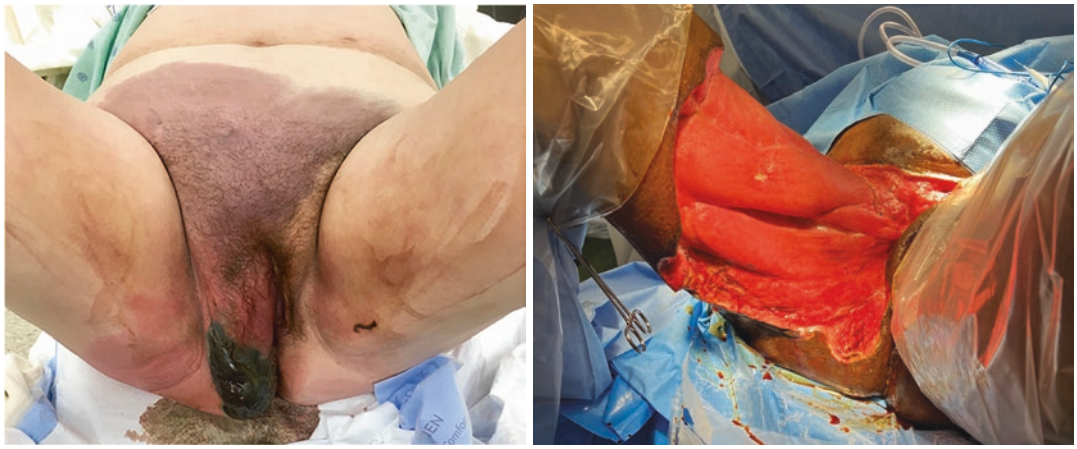

**Fig. 113.1** Perineal necrotizing soft tissue infection prior to debridment procedures. Treatment of patient with aggressive excision and debridement [33, 34]

tion with electrocautery. It is also important to send the tissue to microbiology for Gram stain and culture to help guide and de-escalate aggressive initial antibiotic therapy.

Frequent reevaluation is a mainstay of therapy. It is usual practice to return to the operating room within 24 h of the initial debridement. This recommendation is based on several retrospective reviews [23–25]. Recently, a prospective study was conducted by Okoye et al. comparing the timing of repeat debridement and its effects on the morbidity and mortality of patients [26]. This multivalent analysis of 64 patients with NSTI determined that patients who underwent early repeat debridement had significantly better morbidity and mortality compared to the group that underwent delayed debridement. A retrospective cohort study by Chang et al. supported these findings. Their study showed that patients with an LRINEC score >8 who had a primary amputation had a mortality benefit compared to those who had a delayed amputation [27].

Wound care after surgical debridement has traditionally been done with the use of wet-to-dry dressings to facilitate mechanical debridement. While this method of wound care is still adequate, the use of negative pressure wound therapy systems has become increasingly common. The use of negative pressure wound systems has demonstrated advantages to traditional wound therapy with decreased length of stay and decreased time to heal [28, 29]. It is also easier for patients to manage, with the dressing change occurring every 3–4 days rather than changing the wet-to-dry dressings one to two times a day. Skin grafting and reconstructive procedures can be performed once the patient has been stabilized and the infection has been fully treated.

#### 113.5.2.1 Support

The last aspect of treatment is intense physiologic support. Close hemodynamic monitoring in an intensive care unit with the use of invasive monitoring (e.g., arterial and central venous lines) is highly recommended. Many of these patients will require aggressive fluid resuscitation and ionotropic support. Blood products should also be made readily available. Serial laboratory values should be taken to monitor blood glucose, renal function, and electrolyte shifts. Lastly, early enteral nutritional support is recommended as patients are in a high catabolic state and have high caloric and protein requirements.

### 113.5.3 Adjunctive Therapy

#### 113.5.3.1 Hyperbaric Oxygen

Hyperbaric oxygen may be used as an adjunct to therapy but should never replace or delay surgical and antimicrobial therapies. HBO theoretically works by increasing the supply of oxygen to the wound, which should promote healing and inhibit bacterial growth. However, there is no high-level evidence to support the use of HBO in the treatment of NSTI.

### 113.5.4 IVIG

What does IVIG stand for? The goal of IVIG therapy is to decrease the circulating amount of bacterial exotoxin, which is responsible for causing systemic toxicity. IVIG accomplishes this by binding to the bacterial exotoxin. The use of IVIG in the treatment of streptococcal toxic shock syndrome has revealed improved outcomes, according to Linnér and colleagues [30]. However, the use of IVIG in the treatment of streptococcal TSS in patients with NSTI has not been able to show any statistically significant survival benefit. This was further echoed by the INSTINCT trial by Madsen et al. in 2017. This blinded randomized controlled trial involving patients in the ICU with NSTI was unable to find any difference in the physical component summary between the group that received IVIG and the group that received the placebo [31].

## 113.6 Prognosis

There have only been modest improvements in mortality since 1871, with an average mortality rate of 25%. Disfigurement and disability are common complications due to the extensive surgical debridement that must occur to control infection. Plastic surgery and reconstructive surgeries following the resolution of the infection may be necessary to lessen this disfigurement [32].

Patients who underwent extensive debridement of one or more of their limbs may develop contractures during the healing process. Complications such as pneumonia, urinary tract infections, catheter-related bloodstream infections, and secondary soft tissue infections are common. During debridement of Fournier's gangrene, more specific complications can occur, which include impotence, decreased sperm count, and motility. Fecal incontinence may occur when debridement involves the perianal or perirectal region, making it a difficult location to heal with constant fecal contamination. Diverting loop colostomy is often performed in these specific situations to allow for non-contaminated wound care and adequate wound healing.

**Dos and Don'ts**

- Do not postpone lifesaving treatment.
- When NSTI is suspected, start broad-spectrum antibiotics immediately.
- Do not delay wide surgical debridement of all devitalized skin and soft tissue.
- Delay is associated with a seven- to ninefold increased risk of mortality if surgical debridement is delayed or inadequate.
- Do return to the operating room within 24 h for re-evaluation of the adequacy of debridement.

**Take-Home Messages**

- NSTI are usually polymicrobial.
- Early diagnosis remains difficult.
- The mortality rate remains at 25%.
- Initial antibiotic therapy should always be broad-spectrum with aggressive de-escalation.
- Early surgical treatment is a mainstay of therapy.

**Questions**

1. A 23-year-old male with a history of intravenous drug use presents to the emergency department with a tender, erythematous, swollen left arm with a small amount of drainage. He is mildly tachycardic. Which of the following imaging studies would be the least helpful in making a diagnosis of NSTI?
   A. MRI
   B. CT
   C. Ultrasound
   D. Plain XR
2. A 45-year-old obese female with a history of diabetes presents to the ED with complaints of swelling, pain, and foul-smelling drainage from her groin. Her heart rate is 125 bpm. She is febrile at

39 °C and slightly hypotensive at 90/50. What is this patient's LRINEC score based on the lab values below? What is her associated risk?

Sodium: 128 mEq/L. Glucose: 170 mg/dL. Creatinine: 1.3 mg/dL. WBC count: 17,000/mm$^3$. Hemoglobin: 10.5 g/dL. C-reactive protein: 152

3. A 58-year-old male is POD #1 from an exploratory laparotomy. On examination, his wound is very tender, indurated, and has begun to weep slightly. You suspect a possible NSTI. What organism is most likely the cause of infection?
   A. *CA-MRSA*
   B. *Streptococcus pyogenes*
   C. *Clostridium perfringens*
   D. *Escherichia coli*
4. Which of the following is NOT a risk factor for the development of NSTI?
   A. IV drug use
   B. Diabetes
   C. Obesity
   D. Alcoholism
   E. None of the above
5. Match the organism to the correct antibiotic regimen.
   1. *Clostridium* species A. Doxycycline, cefotaxime
   2. CA-MRSA B. Vancomycin, penicillin, gentamicin, clindamycin
   3. *Vibrio* species C. Penicillin, clindamycin
   4. Polymicrobial D. Linezolid

Answers

1. C.
2. 10. High Risk.
3. B.
4. E.
5. 1: C; 2: D; 3: A; 4: B.

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## Further Reading

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