Necrotizing Soft Tissue Infections

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Necrotizing soft tissue infections (NSTIs) are a group of rare but fulminant complicated skin and soft tissue infection. The United States (US) Food and Drug Administration differentiates complicated from uncomplicated skin and soft tissue infections based on several criteria including the need for surgical intervention [1]. These infections are typically characterized by advancing tissue necrosis and are known colloquially as being caused by "flesh-eating bacteria." Other terms that are used to describe NSTIs include: gas gangrene, streptococcal gangrene, gangrenous cellulitis, necrotizing cellulitis or erysipelas, bacterial synergistic gangrene, Meleney ulcer or gangrene, and Clostridial myonecrosis. NSTIs of the perineum are referred to as Fournier's gangrene. Although NSTI is often used synonymously to mean necrotizing fasciitis, coined by Dr. Wilson in 1952, NSTIs have now come to represent a spectrum of diseases that range from necrotizing cellulitis to myonecrosis (Fig. 40.1).

Epidemiology

Incidence

The incidence of NSTIs in the USA has been increasing since the 1980s [2, 3]. Whether the increase represents a true rise in the number of infections or simply better identification and reporting of NSTIs is unclear. The incidence ranges from 3800 to 5800 cases annually [4]. Furthermore, the gross incidence of NSTIs more than doubled between 1999 and 2007, and the population-adjusted incidence rate has increased by 91 % [5]. Although NSTIs are still considered rare, it is estimated that clinicians, regardless of specialty, will encounter at least one NSTI patient in their lifetime [6].

Classification

There are several methods for describing NSTIs, although there is no standard classification system. NSTIs can be described by their depth of invasion (Fig. 40.1); necrotizing fasciitis is characterized by pathological findings at the level of the subcutaneous fat (i.e., thrombosed vessels) and deep fascia (i.e., necrosis). NSTIs can also be classified by their anatomic location (i.e., Fournier's gangrene for NSTIs of the perineum).

Another method for describing NSTIs is based on their microbiology: Type I, II, and III. Type I NSTIs are the most common type, accounting for 55–75 % of infections. They are polymicrobial and include organisms such as gram-positive cocci, gram-negative bacilli, and anaerobes. They have been associated with multiple predisposing factors including surgical procedures, diabetes, and peripheral vascular disease. Type II NSTIs are caused by Group A beta-hemolytic *Streptococci* with or without *Staphylococcus aureus*. These infections are less common than Type I infections and can occur in young, healthy individuals. Type III NSTIs have been attributed to *Vibrio* species by some authors and to *Clostridium* species by other authors.

An alternative classification system was proposed by Bakleh et al. based on histopathologic findings [7]. They proposed three stages based on combinations of inflammatory response and gram-stain results. Grades of the inflammatory response were characterized by the degree of neutrophilic infiltration and presence of necrosis or microabscesses. The histopathologic stages correlated with mortality, although only unadjusted analyses were performed due to small sample size.

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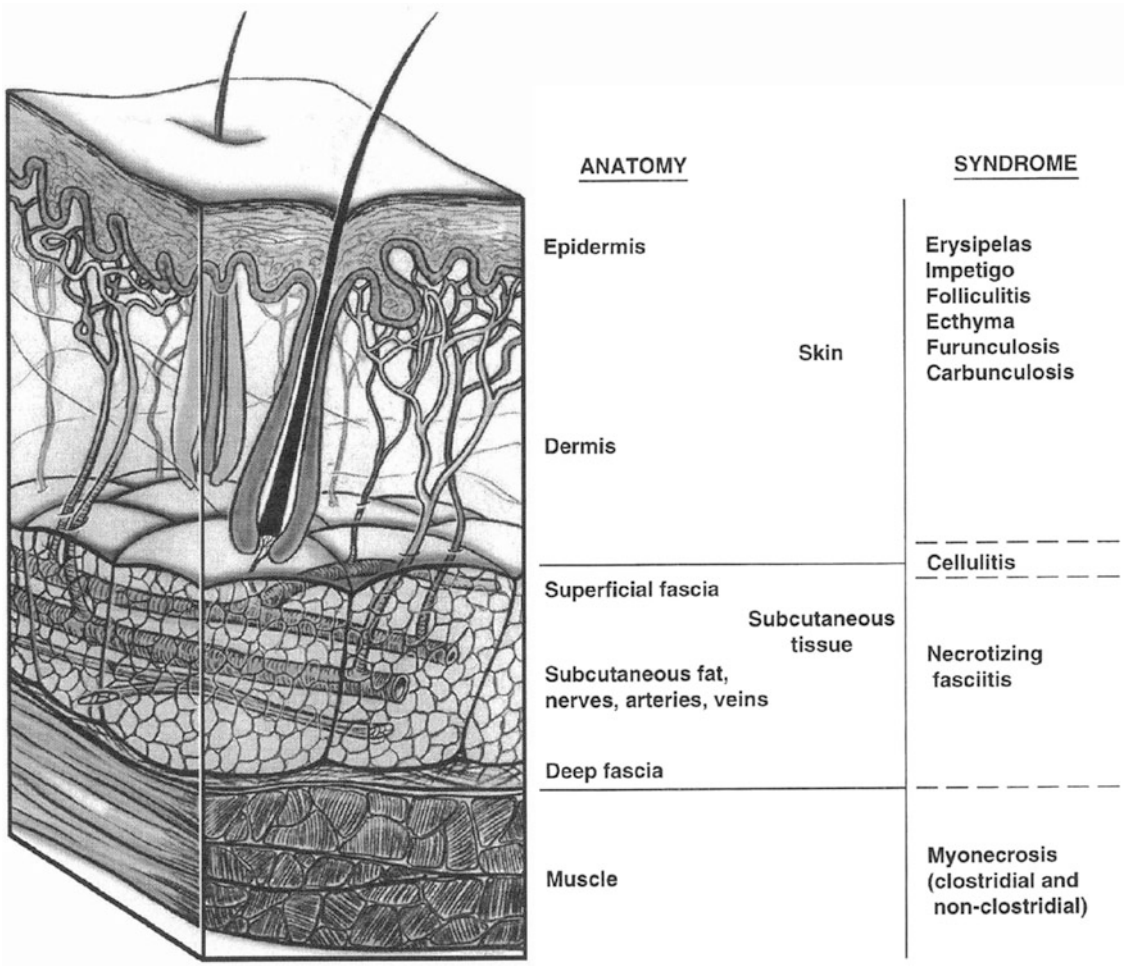

Fig. 40.1 Anatomy of skin and soft tissue and infectious processes associated with each layer. Reproduced with permission from the American College of Chest Physicians. (From Green R, Dafoe D, Raffin T. Necrotizing fasciitis. *Chest*. 1996;110:219–229, with permission)

Risk Factors

Although there are multiple risk factors, NSTIs often develop in young, healthy hosts. Comorbidities that have been associated with NSTIs include diabetes mellitus, peripheral vascular disease, obesity, chronic renal failure, cirrhosis, heart disease, acquired immunodeficiency syndrome (AIDS), and immunosuppression. Injection drug use and alcoholism are associated with NSTIs as well. Infections may develop as a result of insect bites, abscesses, recent trauma, or surgery [2, 8].

Microbiology

As previously described, NSTIs may be polymicrobial or monomicrobial depending upon the patient's comorbidities, risk factors, and clinical setting. Cultures may identify gram-positive and gram-negative bacteria, aerobic and anaerobic bacteria, and fungi. Historically, monomicrobial NSTIs were attributed to *Group A Streptococcus* (GAS), *Clostridium* species, and *Vibrio* species, but as described as follows, any number of microorganisms may cause monomicrobial NSTIs. Table 40.1 details many of the virulence factors of the causative organisms of NSTIs.

The two most common gram-positive cocci isolated from patients with NSTIs are *Staphylococci* and *Streptococci* [1, 9]. *S. aureus* is the most common pathogen present in serious soft tissue infections in North America, Latin America, and Europe [10]. Over time, its virulence and resistance has changed; there has been a concomitant decrease in infections caused by methicillin-sensitive *Staphylococcus aureus* (MSSA) and an increase in infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) [11]. Furthermore, there has been an increase in the prevalence of community-acquired MRSA (CA-MRSA), which was first described in the 1990s [10]. Initially CA-MRSA infections were primarily present only in specific sub-populations such as prisoners or sports participants, but now CA-MRSA is on its way to becoming the predominant strain of MRSA in hospitals [12]

Table 40.1 Causative microorganisms of NSTIs and their virulence factors

Microorganism	Virulence factors
Gram-positive bacteria	
CA-MRSA	Panton-Valentine Leukocidin gene, encoding a potent exotoxin
GAS (*S. pyogenes)*	M protein, superantigens, degradative enzymes, associated with Streptococcal Toxic Shock Syndrome
Gram-negative bacteria	
Klebsiella spp.	Carbapenemase, K1 genotype with increased ability to spread hematogenously resulting in distant abscesses
Aeromonas	Potent exotoxins
Fungi	
Aspergillus	Mycotoxins
Cryptococcus spp.	Polysaccharide capsule, superoxide dismutase, proteases

and is increasingly identified in patients with NSTIs [13]. In 2005, Miller et al. described 14 patients with NSTIs and positive cultures for CA-MRSA, 12 of who had monomicrobial infections [13]. These patients had risk factors such as diabetes and hepatitis, history of injection drug use, homelessness, and prior MRSA infection. All of the infections were due to the USA300 clone and had similar genotypes including the presence of the Panton-Valentine leukocidin (pvl) gene, which encodes an exotoxin that causes leukocyte destruction. There is a suggestion that mortality may not be as high in patients with CA-MRSA, but because of its increasing prevalence, empiric coverage should be started in patients with suspected NSTIs [13–16].

Streptococcus pyogenes is a type of Group A beta-hemolytic *Streptococcus* (GAS) that can cause a spectrum of diseases from bacterial pharyngitis to necrotizing fasciitis and myositis to toxic shock syndrome. In a European population-based study, the crude rate of *S. pyogenes* infection was 2.79 per 100,000 population [17]. Eight percent (308 patients) of all of the cases were diagnosed with necrotizing fasciitis, of which 50 % were associated with toxic shock syndrome (TSS). Streptococcal TSS has been reported to be an independent predictor of mortality [18]. Risk factors for GAS infections include comorbidities such as liver disease or underlying malignancy and behaviors such as injection drug use, but these infections can also occur in healthy immunocompetent patients [19]. GAS NSTIs have a predisposition for the lower extremities and tend to spread rapidly.

Several gram-negative rods have been associated with NSTIs, including *Klebsiella* species, *Enterobacter* species, *Pseudomonas* and *Aeromonas*, *Vibrio* species, *Acinetobacter* species, *Eikenella corrodens*, and *Citrobacter freundii* [1, 9]. Liver disease is a risk factor for NSTIs caused by gram-negative rods, particularly *Vibrio*, *Klebsiella*, and *Aeromonas* [20]. Furthermore, these gram-negative rod NSTIs appear to have a higher prevalence in Asian countries [18]. *Vibrio* infections occur in immunocompromised hosts such as those with cirrhosis, diabetes mellitus, adrenal insufficiency, and chronic renal insufficiency; they are associated with contact with seawater or ingestion of raw seafood [20–22]. These infections may have an atypical presentation; increased level of suspicion should occur in these patients, particularly when hemorrhagic bullae are present given an increased associated mortality. *Klebsiella* NSTIs are also more common in Asia, but have been reported as nosocomial infections in patients with underlying malignancy as well as after liver transplantation in the Western hemisphere [23, 24]. *Klebsiella* NSTIs, specifically the virulent K1 genotype, manifest a higher component of hematogenous spread than do other NSTIs and are associated with concomitant distant abscesses, most commonly found in the liver or brain [25]. Furthermore, cases involving carbapenem-resistant species are associated with increased mortality due to fewer antimicrobial options for treatment [23, 24]. *Aeromonas* species are facultative anaerobic gram-negative bacilli which are typically found in fresh or brackish water and sewage, with species *hydrophila, caviae,* and *sobria* responsible for the majority of associated NSTIs [26]. Their history and clinical presentation is similar to that of *Vibrio* infections, and they produce a potent exotoxin which results in myonecrosis and gas production, as in clostridial infections. Like *Vibrio* and *Klebsiella* NSTIs, *Aeromonas* infections are rare in immunocompetent patients, though a few cases have been reported after traumatic inoculation in heavily contaminated environments [27].

Clostridum is a genus of gram-positive bacteria that are obligate anaerobes. Multiple species including *Clostridium perfringens* have been identified in NSTIs. Clostridial infections may cluster in areas with heavy injection drug use. For example, King County, Washington, has a high prevalence of drug users who inject heroin. In a review of 10 years of autopsies of patients who died due to NSTIs, clostridial infections were identified as being significantly associated with injection drug use of black tar heroin [28, 29]. A retrospective review of patients treated in Seattle, Washington, identified a significant association between clostridial infections and an increase in mortality and limb loss [28]. NSTIs caused by *Clostridium septicum* are often associated with an underlying colonic malignancy [30, 31].

Fungi (i.e., *Candida* species) may also be found in both polymicrobial and monomicrobial NSTIs. There have been case reports of monomicrobial NSTIs due to *Aspergillus* [32, 33]. Zygomycotic NSTIs from *Apophysomyces* have been reported in trauma patients and in immunocompetent hosts [34–36]. Cryptococcocal NSTIs have also been reported, largely in immunocompromised patients [37, 38].

Pathophysiology

Spread of pathogens that cause NSTIs occurs through the production of a variety of endotoxins and exotoxins, many of which have already been mentioned. Toxins may cause tissue destruction, ischemia, and necrosis; endothelial damage, which results in increased tissue edema and impaired capillary blood flow; increased escape from host defenses such as phagocytosis and neutrophil infiltration at the site of infection; and activation of the coagulation cascade, which may cause vascular thrombosis and worsened tissue ischemia [2].

Clinical Presentation

NSTIs can be difficult to distinguish from other non-necrotizing infections. Early manifestations may include swelling, erythema, and warmth, which are nonspecific findings that are also present in patients with cellulitis (Fig. 40.2). Pain out of proportion to physical exam may be present. By the time NSTIs become clinically apparent and patients manifest "hard signs," the associated morbidity and mortality are increased because of the delay in diagnosis [40–42]. Hard signs include late skin manifestations such as bullae, crepitus, or skin necrosis (Figs. 40.3 and 40.4). Wang et al. performed an observational study of patients and developed a staging system based on the time course of symptoms and signs (Table 40.2) [39]; such hard signs are classified as Stage III or late findings. Furthermore, NSTI patients may present with hemodynamic instability and organ failure; the number of dysfunctional organ systems at admission is predictive of mortality [43].

Diagnosis

Multiple studies have demonstrated an association between a delay in diagnosis and worsened outcome from NSTIs [40–42]. The diagnosis may be obvious in the setting of the hard signs described above such as hemodynamic instability and late skin manifestations. However, these findings are only present in a small percentage of NSTI patients; in a matched case–control series, necrotic skin and hypotension each occurred in only 5 % of patients and no patients had crepitance [44]. Furthermore, as described previously, by the time bullae, crepitus, or skin necrosis are apparent on physical examination, the NSTI has already progressed to an intermediate or late stage.

Compounding the difficulties in diagnosis are the similarities in presentation between early stage NSTIs and cellulitis such as fever, pain, swelling, tenderness, erythema, and warmth. In a matched case–control study, Wall et al. compared physical examination findings, laboratory values, and radiologic findings in patients with necrotizing fasciitis to those with a non-necrotizing soft tissue infection [44]. They found that the parameters with the highest sensitivity for necrotizing fasciitis were white blood cell count greater than 14×10^9/L, sodium less than 135 mmol/L, and blood

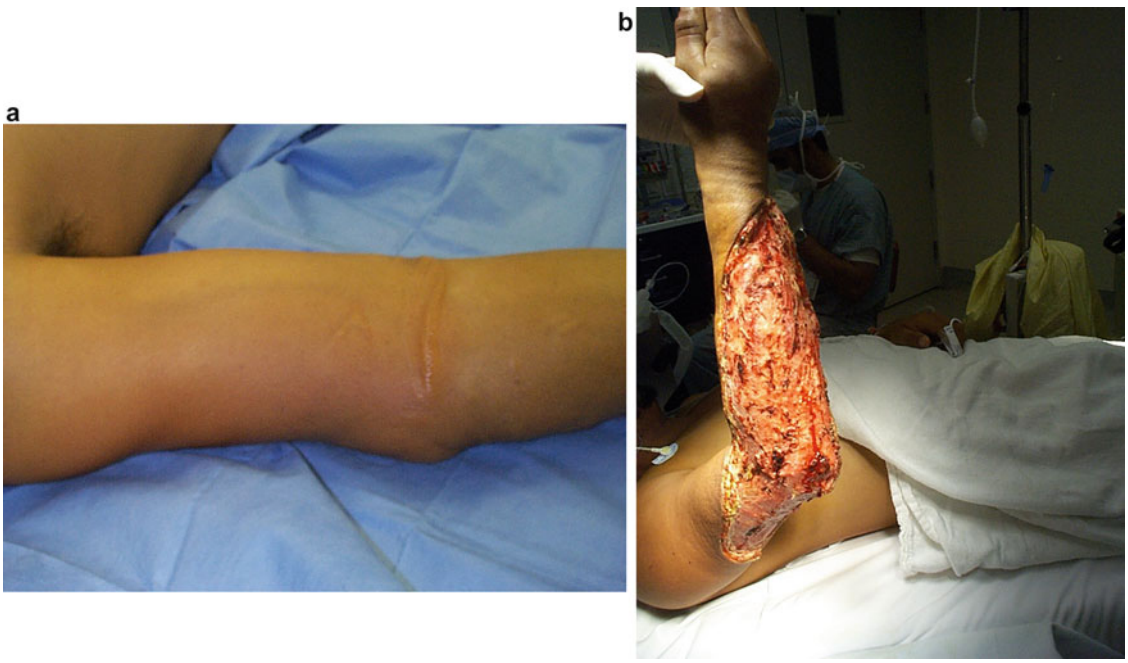

Fig. 40.2 (**a**) This patient has minimal skin manifestations of NSTI other than erythema and swelling, characteristic of Stage I or early NSTI as proposed by Wang et al. [43]. (**b**) The same patient after debridement of necrotic infected tissue

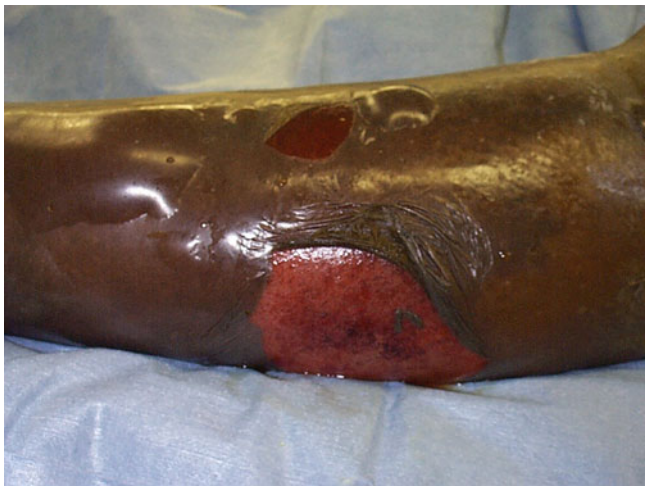

Fig. 40.3 This patient has multiple blisters filled with serous fluid, characteristic of Stage II

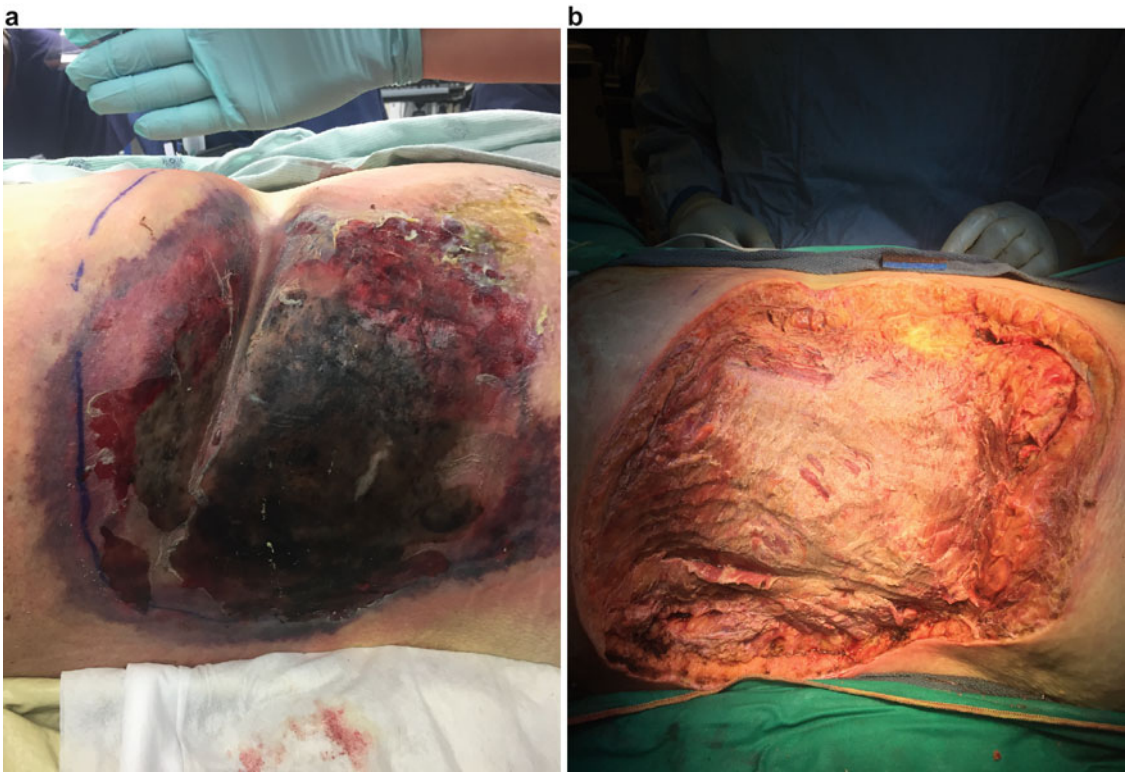

Fig. 40.4 (**a**) This patient had skin necrosis and crepitus of the flank characteristic of Stage III. (**b**) The same patient after debridement of necrotic infected tissue. (Courtesy of Bryan A. Cotton MD, MPH)

Table 40.2 Stages of evolving necrotizing soft tissue infection based on cutaneous changes [39]

Stage	Time course	Symptoms and signs
Stage I	Early	Tenderness to palpation (extending beyond the apparent area of skin involvement)
		Erythema
		Swelling
		Warmth
Stage II	Intermediate	Blister or bullae formation (serous fluid)
Stage III	Late	Crepitus
		Skin anesthesia
		Skin necrosis with dusky discoloration

From Wang YS, Wong CH, Tay YK. Staging of necrotizing fasciitis based on the evolving cutaneous features. *Int J Dermatol*. 2007;46(10):1036–1041, with permission

urea nitrogen greater than 15 mg/dL. The parameters with the highest specificity (100 % for all) were tense edema, bullae, sodium less than 135 mmol/L, and chloride less than 95 mmol/L. Based on these findings, Wall et al. developed a simple model to assist in diagnosing NSTIs [45]. A corrected serum sodium (for glucose) of less than 135 mmol/L or a white blood cell count of greater than 14.3 $\times 10^9$/L had a 90 % sensitivity and a 76 % specificity for necrotizing fasciitis. This model correctly classified 18/19 (95 %) of patients who had no "hard signs."

Another commonly used model for diagnosing an NSTI is the Laboratory Risk Indicator for NECrotizing fasciitis (LRINEC) score [46]. Six laboratory parameters are included in the score and are weighted from 1 to 4 points for a total possible score of 13 (Table 40.3). The probability of necrotizing infections was less than 50 % with a cutoff score of less than or equal to 5, but increased to greater than 75 % with a cutoff score of greater than or equal to 8. A cutoff score of 6 had a positive predictive value (PPV) of 92 % and a negative predictive value (NPV) of 96 % in the original validation dataset. The LRINEC score has not been validated across other patient populations and settings [47, 48], although one study suggested that it may function as both a diagnostic and prognostic tool [49]. Thus, the LRINEC score may be useful in select patient populations in increasing the suspicion for a necrotizing infection, but further studies are required. As with all diagnostic tools, the predictive values are dependent on the incidence of the disease in the population, and the utility of a test in changing management depends on the level of suspicion for the disease (or the pretest probability).

Table 40.3 Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score; a cutoff six points had a 92 % positive predictive value and a 96 % negative predictive value [46]

Variable (units)	Score
C-reactive protein (mg/dL)	
<150	0
≥150	4
Total white cell count (per mm^3)	
<15	0
15–25	1
>25	2
Hemoglobin (g/dL)	
>13.5	0
11–13.5	1
<11	2
Sodium (mmol/L)	
≥135	0
<135	2
Creatinine (μmol/L)	
≤141	0
>141	2
Glucose (mmol/L)	
≤10	0
>10	1

From Wong C-H, Khin L-W, Heng K-S, Tan K-C, Low C-O. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med*. 2004;32(7):1535–1541, with permission

Several recent studies have advocated for the addition of serum lactate level as a diagnostic tool. Schwartz et al. found that only arterial lactate was predictive of both mortality and limb loss. In addition, while using the well-defined parameters of decreased serum sodium and elevated WBC served as an adequate screening tool, the addition of serum lactate level greater than or equal to 6 mmol/L had both a sensitivity and NPV of 100 % [50].

Radiographic imaging may be helpful in improving diagnostic efficiency. In the case–control study by Wall et al., 39 % of patients with necrotizing fasciitis had gas on plain film versus 5 % of patients with a non-necrotizing infection [45]. However, gas on X-ray only had a sensitivity of 39 %. Ultrasonography has been increasingly used as an adjunct in the diagnosis of NSTIs [51–55]. Ultrasound has the advantage of being rapidly performed at bedside, unlike computed tomography (CT) and magnetic resonance imaging (MRI), and it may be helpful in differentiating simple cellulitis from necrotizing fasciitis in a timely fashion. In a prospective observational study of 62 patients with clinically suspected NSTI, Yen et al. found that ultrasound had a sensitivity of 88.2 %, specificity of 93.3 %, PPV of 95.4 %, NPV of 95.4 %, and diagnostic accuracy of 91.9 % for NSTI, as confirmed by subsequent surgical exploration [52]. Sonographic findings consistent with necrotizing fasciitis include subcutaneous thickening, air, and fascial fluid, which may be recalled using the mnemonic "STAFF" [55]. While ultrasonography has become increasingly available, its utility is limited by variability in operator training and expertise. Thus, currently there is insufficient evidence to recommend routine use of ultrasound in the diagnosis of NSTIs.

Traditionally, although CT and MRI have been reported to be useful adjuncts in the diagnosis of NSTIs, there has been a hesitation to recommend their routine use due to potential delays in obtaining the studies. However, as technology continues to evolve, these studies may become more feasibly and efficiently obtained. In a study of 67 patients without indication for immediate surgical exploration for NSTI, CT scans had 100 % sensitivity and 81 % specificity for diagnosing NSTIs [56–58]. Three out of eight patients with a false-positive CT scan had fluid collections identified that ultimately were diagnosed as abscesses associated with pyomyositis [58]. Another study by McGillicuddy et al. reported that 305/715 (43 %) of NSTI patients diagnosed over a 10-year period at a single center underwent CT scan. They developed a scoring system of five CT findings to aid in the diagnosis of NSTIs (Table 40.4). A score of greater than 6 had 86 % sensitivity,

Table 40.4 Computed tomography (CT) NSTI Scoring System: a score of >6 points had an 86 % sensitivity and a 92 % specificity for the diagnosis of NSTI [59]

Variable	Points
Fascial air	5
Muscle/fascial edema	4
Fluid tracking	3
Lymphadenopathy	2
Subcutaneous edema	1

From McGillicuddy EA, Lischuk AW, Schuster KM et al. Development of a computed tomography-based scoring system for necrotizing soft-tissue infections. *J Trauma*. 2011;70(4):894–899, with permission

92 % specificity, 64 % positive predictive value (PPV), and 86 % negative predictive value (NPV) [59]. Further prospective validation studies are planned.

MRI has been used to diagnose NSTIs, but like CT has a high sensitivity but a low specificity [2]. Findings on T2-weighted images have included: gas or low signal intensity in the deep fascia [60, 61], abnormal deep fascial thickening with or without contrast enhancement [60, 62, 63], peripheral high signal intensity in muscles [60, 64], extensive involvement of the deep fascia [60], and involvement of three or more compartments in one extremity [60]. However, several authors have noted that MRI tends to overestimate the extent of deep fascial involvement [54, 65]. Concerns about availability, potential delay in diagnosis and subsequent intervention, and lack of well-defined criteria for distinguishing NSTIs from non-necrotizing infections still limit the widespread use of MRIs for this purpose.

Fluid and tissue sampling have also been suggested for diagnosing NSTIs. A 22-gauge needle with a 10-mL syringe has been used to aspirate fluid in the setting of soft tissue infections [66]. In a study of 50 patients in whom aspiration biopsy was performed, cultures were positive in 81 % of patients not on antimicrobial therapy, but the percentage dropped to 30 % in patients receiving antimicrobial treatment. Growth of an organism on aspirate was not specific as the cultures were taken from patients with cellulitis, ulcers, chronic osteomyelitis, and infected surgical wounds. Furthermore, although the organisms on aspirate were similar to those in surgical specimens among patients who were subsequently debrided, there was often a delay to growth of an organism in the aspiration fluid (up to 72 h) [66]. There is inadequate evidence to recommend the routine use of aspiration biopsy to diagnose NSTIs.

Ultimately, the diagnosis of an NSTI is confirmed by surgical exploration, either at the bedside (if the patient is clinically unstable) or in the operating room. Typical gross findings include loss of tissue resistance to blunt dissection, thrombosis of subcutaneous vessels, presence of foul-smelling and/or dishwater fluid, and grayish appearance of fascia with or without obvious tissue necrosis. These findings are sufficient to confirm the diagnosis, but if the surgeon is still uncertain, frozen-section biopsy can be performed. Frozen-section biopsy for rapid and early diagnosis of necrotizing fasciitis was advocated by Stamenkovic and Lew in 1984 [67]. They recommended obtaining at least a 10×7×7 mm incisional biopsy of soft tissue under local anesthetic. Histologic samples from patients who did not undergo frozen-section biopsy demonstrated further extension of the necrosis representative of progressive disease. Use of frozen-section biopsy, however, is limited by the availability of a pathologist to read the samples, and NSTIs are usually associated with obvious findings such as those described previously.

Management

The mainstay of treatment for NSTIs is administration of broad spectrum antibiotics and prompt and aggressive surgical debridement of infected tissues (Fig. 40.5). Randomized trials of adjunctive treatments are lacking, and synthesis of observational studies is hampered by: (1) a lack of standardized terminology and (2) heterogeneity in patient populations, bacteriology, and management strategies.

Surgical Management

Recognizing the lack of randomized trials to guide management, the Surgical Infection Society (SIS) and the Infectious Diseases Society of America (IDSA) Guidelines for the Treatment of Complicated Skin and Soft Tissue Infections strongly recommend timely and adequate surgical debridement to improve outcome [1, 68]. General caveats for operative debridement include complete resection of necrotic tissues and drainage of fluid collections. Non-viability of tissues is often marked by easy separation from surrounding structures, thrombosis of blood vessels and lack of arterial bleeding, and lack of muscle contraction. Tissue should be cultured to guide postoperative antibiotic management.

Source control may require aggressive surgical management. Ten to 25 % of patients required amputations in several cases series [15, 28, 40, 69], and approximately a quarter of patients with extremity involvement required amputation in two series [15, 28]. Guillotine or through-joint amputations can be done expeditiously at the initial operation if the patient is hemodynamically unstable and/or the level of involvement is not clearly defined. SIS guidelines recommend frequent reevaluation or return to the operating room within 24 h of the initial debridement to determine the adequacy of source control and to verify the lack of progression [1]. Repeat operative exploration is continued until source control has been achieved and no more tissue requires debridement. In order to more conclusively determine the

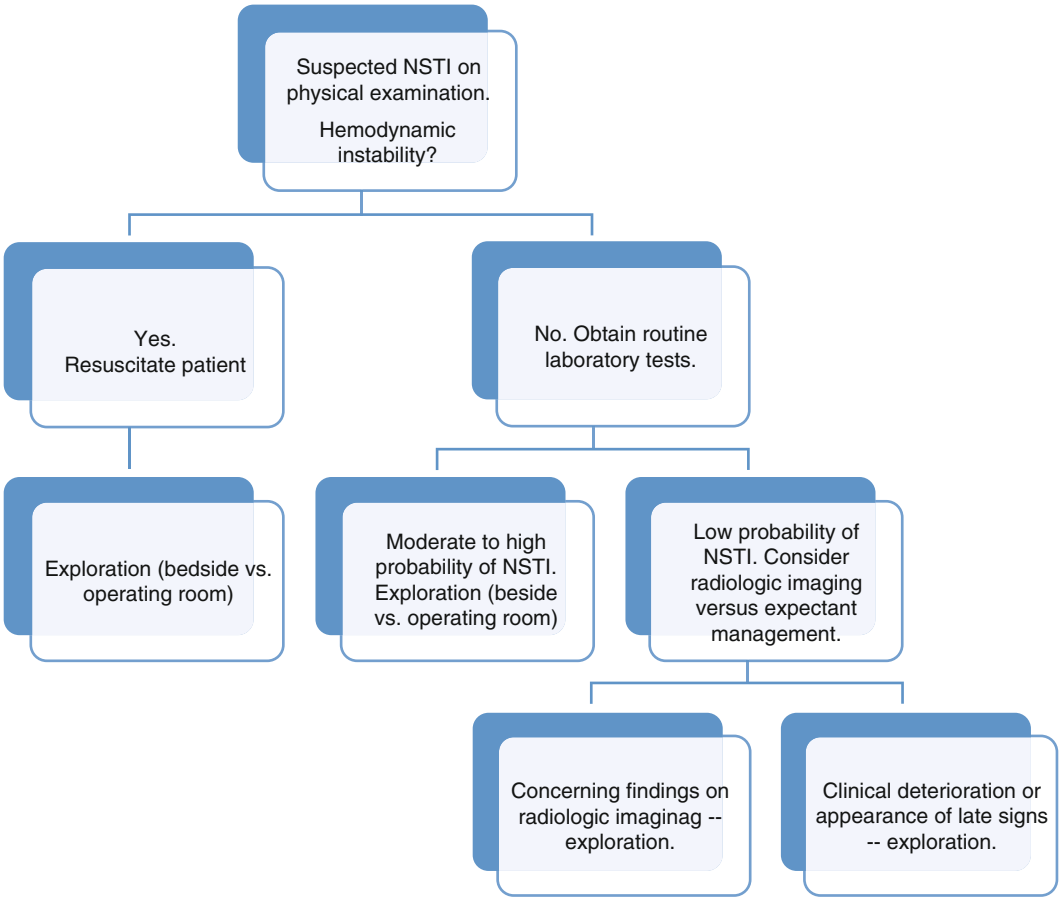

Fig. 40.5 Algorithm for management of a patient with a suspected NSTI

success of surgical debridement, Friederichs et al. found that the procalcitonin ratio from postoperative day 1 to day 2 following major surgical procedures for NSTIs identified persistent infection [70]. They found that a ratio of 1.14 had a sensitivity of 83.3 %, specificity of 71.4 %, PPV of 75.8 %, and NPV of 80 % for successful treatment. In the clinical setting, a ratio below the cutoff should raise suspicion for persistence of the infectious focus and suggests a need for more radical reoperation or an earlier life-saving amputation.

Management of open wounds associated with aggressive surgical debridement has traditionally been to employ wet-to-dry dressings, but there have been increasing reports of negative pressure wound therapy usage [71]. Some of the clinical benefits of negative pressure wound therapy include reduction of wound area secondary to enhanced wound retraction, promotion of granulation tissue formation in an optimally moist wound milieu, continuation of effective wound cleansing with removal of small tissue debris by suction after adequate primary surgical debridement, and continuous removal of wound exudate within a closed hygienic system [72]. However, additional research and quantitative assessment is needed prior to comprehensive recommendations for use in NSTIs. Ultimately, large wounds that do not heal by secondary intent may require coverage with split thickness skin grafts or musculocutaneous flaps.

Antibiotic Therapy

Early, empiric, broad spectrum antibiotics are strongly recommended for the treatment of NSTIs. Antibiotic coverage should include activity against aerobic and anaerobic gram-positive and gram-negative organisms. The SIS Guidelines recommend several effective single-agent regimens including carbapenems (i.e., ertapenem), other beta-lactam antibiotics (i.e., piperacillin/tazobactam), and glycylcyclines that are similar to tetracyclines (i.e., tigecycline) [1]. However, antibiotic combinations with the same coverage can also be used. If Group A streptococcal infections are suspected, penicillin is the drug of choice with or without a protein synthesis-inhibitory agent [1]. If clostridial infections are suspected, a protein synthesis inhibitor is again recommended to prevent production of exotoxins that contribute to the organism's rapid spread. If *Vibrio* infections

are suspected, tetracyclines (i.e., doxycycline), quinolones (i.e., ciprofloxacin), and third-generation cephalosporins or carbapenems can be used. In severe cases with rapidly progressive infections, combination therapy with cell-wall-active agents and a tetracycline should be used. There are no evidence-based guidelines regarding the length of antibiotic therapy—whether a set duration should be predetermined or whether clinical criteria should be used such as 3 days after the resolution of signs of systemic toxicity and local infection have resolved [73–75].

Supportive Care

While the mainstays of therapy are rapid and aggressive surgical debridement and antibiotic therapy, supportive care is important as well given that these patients are at high risk of death. Perioperative resuscitation of patients with septic shock and severe sepsis should be performed using evidence-based guidelines [76]. Postoperative care should include supplemental nutrition, preferentially enteral, given the increase in predicted energy requirements of NSTI patients [73].

Adjunctive Therapies

There are a number of adjunctive therapies that have been suggested but there is a paucity of high quality evidence to support their use. Hyperbaric oxygen therapy (HBOT) has been proposed to improve outcome—the resultant increased partial pressure of oxygen in infected tissues may improve polymorphonuclear leukocyte function and wound healing [77]. In animal studies, HBOT has been shown at the tissue level to reduce edema, stimulate fibroblast growth, increase the killing ability of leukocytes by augmenting the oxidative burst, have independent cytotoxic effects on some anaerobes, inhibit bacterial toxin elaboration and release, and enhance antibiotic efficacy [78]. Retrospective studies have conflicting results as to whether or not HBOT confers a mortality benefit in NSTI patients [79–81]. These uncontrolled studies may have an inherent selection bias in that hemodynamically stable patients may be more likely to be able to be safely transported to the hyperbaric chamber and therefore have improved outcomes. Furthermore, it is unknown whether there is a potential harm in transporting these patients or whether use of HBOT may delay definitive surgical therapy. The largest available study to date included over 1500 patients from 14 centers. When stratified for severity of illness, HBOT was only identified to convey a morbidity and mortality benefit in the most severely ill patients [82]. The SIS guidelines conclude that there is insufficient evidence to make a recommendation regarding HBOT for treating NSTIs [1].

Intravenous immunoglobulin (IVIG) has been suggested in patients with severe Group A streptococcal or staphylococcal infections or TSS. The proposed mechanisms of action include binding of bacterial toxins and inhibition of binding of bacterial superantigens to T-cell receptors with resultant down-regulation of the inflammatory response. Despite the biological plausibility, data are limited to case reports and expert opinion. The only randomized trial of IVIG in streptococcal toxic shock syndrome was terminated early due to slow recruitment and was underpowered to identify either a mortality benefit or harms from adverse effects [83]. The SIS guidelines gave only a weak recommendation based on low or very low quality evidence for the use of IVIG in patients with TSS due to staphylococcal or streptococcal NSTIs [1].

Plasmapheresis has also been suggested as an adjunctive therapy for NSTI patients, but evidence specific to this patient population is limited to a single case report [84]. Plasmapheresis has been studied in the treatment of septic shock and severe sepsis. The biological rationale is that separation of the cellular and plasma components of circulating blood allows circulating inflammatory mediators or toxins to be removed. One small single-center trial of plasmapheresis in severe sepsis and septic shock demonstrated a reduction in 28-day all-cause mortality [85], but confirmatory multicenter effectiveness trials are lacking. The SIS guidelines determined that there was insufficient evidence to make a recommendation regarding plasmapheresis or other extracorporeal treatments for NSTIs [1].

Immunomodulation is a promising therapy for improving outcomes after NSTIs by limiting the overwhelming host response to bacterial superantigens. In a typical immune response, a small proportion of T cells interact with antigens to generate a limited but tailored response to infection. However, bacterial superantigens cause a nonspecific expansion and release of proinflammatory cytokines, ultimately resulting in septic shock and multiple organ failure [86]. AB103 is a novel synthetic CD28 mimetic octapeptide which selectively inhibits the direct binding of superantigen exotoxins to the CD28 costimulatory receptor on T helper lymphocytes [86]. In murine models, Ramachandran et al. demonstrated that administration of a single dose of AB103 increased survival when given up to 5 h after infection, reduced inflammatory cytokine expression and bacterial burden at the site of infection, and improved muscle inflammation in a dose-dependent manner, without compromising cellular or humoral immunity [87]. AB103 has a dual mechanism of action—modulating the innate immune response to exotoxins and endotoxins in gram-positive infections and attenuating CD28 signaling independent of superantigens in gram-negative infections [86]. A recent prospective randomized, placebo controlled multicenter trial reported that AB103 resulted in an improvement in the Sequential Organ

Failure Assessment (SOFA) Score as compared to placebo, but found no statistically significant difference in the number of debridements, intensive care unit-free and ventilator-free days, or plasma and tissue cytokine levels [86]. This phase 2a trial suggests that immunomodulation may be a safe and promising strategy for treating NSTIs.

Mortality

The acute mortality of NSTIs had been reported to be unchanging for many decades, ranging from 25 to 35 % [2]. Several case series between 2000 and 2009 have reported lower mortality rates between 10 and 20 % [15, 21, 88–90]. Mortality in an analysis of more than 10,000 hospitalized patients with NSTIs was 10.9 % [88]. This apparent recent reduction in mortality may be due to a true improvement in the diagnosis and management of NSTIs or to changing patient populations, inconsistency in the definition of NSTIs, or differences in the virulence of bacterial strains causing NSTIs.

There are multiple predictors of mortality reported in the literature including advanced age, presence of comorbidities, and severity of disease on admission [28, 41, 68]. Furthermore, delay in intervention has also been associated with increased mortality [40, 41, 68]. Other authors have proposed weighted scoring systems for predicting mortality. As previously mentioned, the LRINEC score greater than 6 has been associated with increased mortality [49]. Anaya et al. developed a scoring system that assigned points based on six variables: heart rate >110 beats per minute, temperature <36 °F, creatinine >1.5 mg/dL, age >50 years, white blood cell count greater than 40,000/mm^3, and hematocrit greater than 50 % [90]. This model was 87 % accurate in predicting mortality in a validation set derived from two different patient populations but needs to be validated in larger multicenter studies. More recently, Faraklas et al. developed and validated a 30-day postoperative mortality risk calculator for patients with NSTI using National Surgical Quality Improvement Project (NSQIP) data collected between 2005 and 2010 [91]. In 1392 patients, 30-day mortality was found to be 13 %, and seven independent variables were identified that correlated with mortality including: age older than 60 years, functional status (defined as partially or totally dependent), dialysis requirement, American Society of Anesthesiologists physical status classification of four or higher, need for emergent surgery, presence of septic shock, and low platelet count (defined as <150 K/uL). This predictive model was used to develop an interactive risk calculator for the probability of dying. Unlike prior scoring systems which focus primarily on diagnosis or need for operative intervention, this calculator allows clinicians to have better informed discussions with patients and families about mortality risk in this particular set of complex critically ill patients.

Morbidity

There is a paucity of studies evaluating morbidity among NSTI survivors. Amputations are common amongst patients with extremity involvement. Two series reported that approximately a quarter of patients with extremity involvement require an amputation [15, 28]. Pham et al. reported that 30 % of patients had mild to severe physical limitation at hospital discharge [92]. On multivariate analysis, extremity involvement, independent of amputation status, was associated with a higher functional limitation class [28].

Compared with population norms, NSTI patients have been found to have a higher incidence of functional and psychological impairments and significant difficulties with return to pre-injury employment [93, 94]. The severity of the disease and the aggressive treatment are associated with significant disfigurement, loss of function, and psychological sequelae. Multidisciplinary care, which extends from early wound care through reconstruction and long-term rehabilitation, is of paramount importance to attaining the best long-term functional and quality of life outcomes [94]. In a qualitative study of NSTI survivors and their spouses or partners, survivors had decreased health related quality of life (HRQOL) and significant impairments in physical, emotional, and social functioning [93]. Furthermore, an increased prevalence of post-traumatic stress disorder (PTSD) was noted in both the patients and their partners. Factors independently associated with lower HRQOL included upper extremity amputation, greater than five debridements, greater than ten intensive care unit days, renal failure without return of function before discharge, and involvement of the hand and face. Wound coverage procedures, less than three debridements, and involvement of the trunk or perineum were independently associated with higher HRQOL. This work illustrates the multidimensional nature of recovery for patients with NSTIs, and that this recovery occurs in the broader psychosocial context of the survivors, their family, friends, and society, the nature of which we are only beginning to understand.

Follow-up

In addition to an acute mortality risk, NSTI patients have an increased risk of long-term mortality and morbidity. Light et al. performed a study of 345 NSTI survivors followed for 15 years; the estimated median age of death was significantly younger than that for population-based controls [95]. In particular, there was a significantly increased risk of subsequent death due to infectious causes in NSTI survivors (14 % versus 2.9 %). The authors recommended the following: counseling patients regarding the increased mortality risk; broadening indications for immunizations; and pursuing aggressive modification of other risk factors for death such

as obesity, diabetes, smoking, and atherosclerotic disease. They also identified a need for further research into the genetic and social determinants of this excess mortality risk.

Conclusion

NSTIs are associated with significant morbidity and mortality. Despite advances in critical care, the mainstays of therapy have remained largely unchanged over the last several decades: prompt recognition, early and aggressive debridement, and broad spectrum antibiotics. Diagnosis remains challenging given the lack of specificity of many of the early signs and symptoms, but advances in imaging may prove to be helpful. Further studies are required to identify adjunctive therapies and to determine their benefit in treating NSTIs.

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