



## 111.1 Introduction

NF is a rare but life-threatening infection of soft tissue. NF commonly occurs in subcutaneous tissue and the superficial fascia of the extremities, rapidly spreads throughout the body, and causes sepsis and multiple organ failure. The mortality rate of NF is not low, and delayed diagnosis and treatment can cause patient death. However, it is difficult to diagnose the patient as having NF in the early stages. You need to become able to diagnose earlier and treat more appropriately. In this chapter, we describe NF, especially its diagnosis and treatment.

### Learning Goals

- You become able to understand that early diagnosis and early treatment are important.
- You become able to explain how to diagnose NF.
- You become able to understand and perform surgical treatment for NF.

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## 111.1.1 Epidemiology

The incidence of NF has been reported to range between 0.3 and 5 cases per 100,000 people per year [1–4], though this varies by country and region.

## 111.1.2 Etiology

NF occurs by a bacterial infection in the subcutaneous tissue and superficial fascia. NF also occurs in the trunk, head, and neck, but often in the extremities [5]. The risk factors are reported to be increasing age, diabetes mellitus, alcoholism, malnutrition, peripheral vascular disease, heart disease, renal failure, cancer, immune system impairment, chronic skin infection, IV drug abuse, and post-operation [5–7]. NF generally develops in patients after either penetrating trauma or non-penetrating trauma (muscle strain, sprain, or contusion), a mucosal breach (mucosal tear), or a skin breach (varicella lesions, insect bites, or injection drugs).

## 111.1.3 Classification

NF is classified into four categories according to etiology and microbiology [8] (Table 111.1). Type I infection is polymicrobial infection involving aerobic and anaerobic bacteria. It is

**Table 111.1** Classification of NF based on etiology and microbiology

Type	Etiology	Microorganisms
I	Polymicrobial Synergistic Often bowel flora-derived	Mixed anaerobes and aerobes <i>E. coli</i> <i>Pseudomonas</i> spp. <i>Bacteroides</i> spp.
II	Often monomicrobial Skin- or throat-derived	Group A $\beta$ -hemolytic <i>streptococcus</i> (GAS) Occasionally with <i>Staphylococcus aureus</i>
III	Gram-negative Often marine-related organisms	<i>Vibrio</i> spp. mainly <i>Pasteurella multocida</i> <i>Haemophilus influenzae</i> <i>Klebsiella</i> spp. <i>Aeromonas</i> spp.
IV	Fungal Usually trauma-associated Immunocompetent patients	<i>Candida</i> spp. in immunocompromised patients <i>Zygomycetes</i> in immunocompetent patients

more likely to occur in elderly people and people with underlying illnesses. Type II infection is monomicrobial infection. Causative bacteria are Gram-positive bacteria including group A *streptococcus* and methicillin-resistant *Staphylococcus aureus* (MRSA). Type II infection can occur in young people and healthy people. Type III infection is infection caused by *Vibrio vulnificus* and *Aeromonas hydrophila*. Type IV infection is fungal infection. It is more likely to occur in immunocompromised patients.

### 111.1.4 Pathophysiology

It is suggested that there are two processes for how NF occurs [6]. One is that infection initially occurs in subcutaneous tissues with a portal of bacterial entry. Bacteria invade subcutaneous tissues through wounds after penetrating trauma or breaches of skin and mucosa, and infection extends to deep tissues. The other is that infection spontaneously occurs in deep tissues without a portal of bacterial entry. Infection occurs in deep tissues after non-penetrating trauma or without trauma and extends to superficial tissues.



**Fig. 111.1** The patient had felt sick since 4 days ago, and erythema appeared in his left upper extremity 1 day ago. Because swelling and pain also appeared, he visited us. Cellulitis was suspected initially. However, the LRINEC score was 6, and symptoms were getting worse. We diagnosed as NF. We made a skin incision and collected a specimen. Group A streptococcus was found in the specimen. We amputated his left upper extremity on the same day

Only mild erythema is initially observed on the skin (Fig. 111.1). Within a few days, the inflammation worsens, the skin turns dusky and purplish, and bullae appear. Patients often get bacteremia, and metastatic infections may be observed. The skin becomes ischemic, and tissues rapidly become gangrenous [6, 9]. As a result, patients die.

## 111.2 Diagnosis

### 111.2.1 Clinical Presentation

The main clinical presentations of NF are reported to be soft tissue edema (75%), erythema (72%), severe pain (72%), tenderness (68%), fever (60%), skin bullae, and necrosis (38%) [10]. But patients may initially complain of malaise, myalgias, diarrhea, and anorexia [6]. Some patients have no cutaneous findings in the early stages. As a result, the diagnosis may be incorrect or delayed.

In the case of occurring initially in the deep tissues by group A *streptococcus*, the patient may complain of severe pain that does not match the cutaneous findings. It is said to increase pain and can be a clue

for diagnosis. However, it may be absent or weakened in patients taking painkillers [6].

Patients get worse in a few days, and tachycardia, leukocytosis, acidosis, and hyperglycemia begin to be observed. When these symptoms have been observed, patients may already be septic.

### 111.2.2 Test

Chin-Ho Wong et al. reported that the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is useful to detect NF in its early stage [11]. You check the total white blood cell count, hemoglobin, sodium, glucose, serum creatinine, and C-reactive protein in the laboratory findings (Table 111.2). When the LRINEC score is 6 or 7, NF is suspected, but other soft tissue infections are also possible. When the LRINEC score is 8 or greater, there is a 75% risk of NF. However, the LRINEC score is low sensitive, and you can't rule out NF even if the LRINEC score is low [12].

In radiography, computed tomography (CT), and magnetic resonance imaging (MRI), soft tissue swelling in patients with group A streptococcal infection and gas in the tissues of patients with Type I infection or gas gangrene will be found [6]. However, these findings may

also be found in other soft tissue infections and are not specific to NF. CT may show the involvement of the fascia and its lack of enhancement [13]. MRI may show hyperintensity and thickening of intermuscular fascia on T2-weighted images [14]. Though CT and MRI are sensitive, it takes time to perform both. Bedside ultrasound may also show subcutaneous tissue thickening with fluid accumulation and subcutaneous gas in the affected area [15]. It can be performed simply and quickly and may be useful for early diagnosis, but its sensitivity is relatively low.

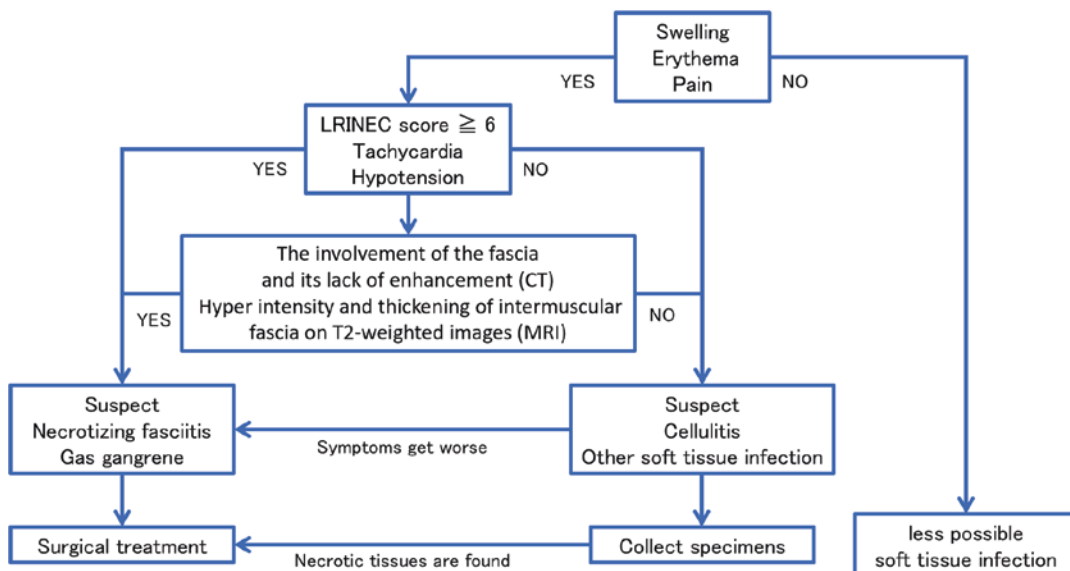
The most useful test is to remove the affected tissues surgically (Flowchart 111.1). Some studies suggested that frozen section soft tissue biopsy is useful for the early diagnosis of NF [16, 17]. However, a frozen section may not contain lesions, and it is less reliable than removing tissues surgically. When you have removed tissues surgically, you can perform debridement or amputation at the same time. The obtained specimens are used for Gram's staining and culture, which are crucial for identifying causative bacteria and giving antibiotic treatment [6].

**Table 111.2** LRINRC score

	Value	Score
CRP (mg/L)	<150	0
	≥150	4
WBC (/mm)	<15	0
	15–25	1
	≥25	2
Hb (g/dL)	≥13.5	0
	11–13.5	1
	<11	2
Sodium (mmol/L)	≥135	0
	<135	2
Creatinine (mg/dL)	<1.6	0
	≥1.6	2
Glucose (mg/dL)	<180	0
	≥180	1

#### Differential Diagnosis

Though it is difficult to distinguish NF from other soft tissue infections such as cellulitis, the LRINEC score is helpful for diagnosis. When symptoms are progressing rapidly, NF is more likely. Clinical presentations that distinguish NF from cellulitis are reported to be pain out of proportion, recent surgery, hypotension, diarrhea, altered mental status, erythema progressing beyond marked margins, skin fluctuance, hemorrhagic bullae, and skin necrosis [18]. Gas gangrene is necrotizing soft tissue infection as well as NF. It occurs in muscle tissues by gas-producing bacteria, such as *Clostridium* species.



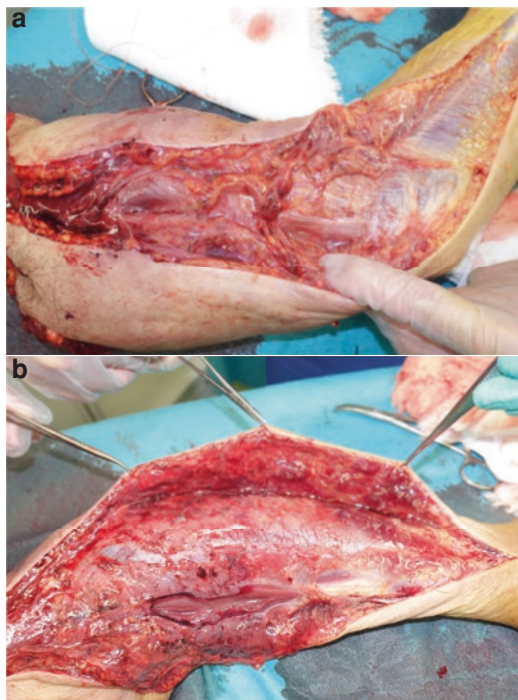
**Flowchart 111.1** Algorithm of diagnosis

## 111.3 Treatment

### 111.3.1 Surgical Treatment

You should not hesitate to perform surgery because surgical treatment is most important in the treatment of NF. When you have suspected NF, you should perform surgery as possible as early. Some studies suggested that early surgery decreases the mortality of NF [19, 20]. In surgery, you identify the extent of infection, evaluate the need for debridement or amputation of an extremity, and perform debridement or amputation of an extremity if necessary (Fig. 111.2). You can also obtain specimens for Gram's staining and culture. It is important to remove infected or necrotic tissues as widely and appropriately as possible in the first surgery [10, 21, 22].

The next day, you should re-examine the surgical site and evaluate the need for additional surgical removal. If necessary, you should remove infected or necrotic tissues additionally. You should evaluate the affected area and surgically remove bad tissues many times until you have performed complete elimination of infected or necrotic tissues [10, 23].



**Fig. 111.2** Left shoulder disarticulation was performed. Subcutaneous tissue and fascia inside the left upper arm looked necrotic (a). Fascia outside the left upper arm and in forearm extension side also looked necrotic (b). Because the affected area extended to the chest, we performed left pectoralis major fascia resection additionally

After you have controlled the infection of the affected area and removed all infected or necrotic tissues completely, you close the wound. However, you can't often perform primary closure because soft tissues and skin have been widely removed. You need to reconstruct the soft tissues and close the wound with muscle flaps and skin grafts.

Some studies suggested that negative pressure wound therapy (NPWT) is effective for reconstructing soft tissues [24, 25]. NPWT improves the local wound environment through contraction of the wound, stabilization of the wound environment, removal of extracellular fluid, and micro-deformation at the foam-wound interface. Additionally, NPWT speeds wound healing and increases blood flow around wounds. As a result, NPWT can reduce the time to wound closure [26].

### 111.3.2 Medical Treatment

Infectious Diseases Society of America (ISDA) recommends that you start empiric antibiotic treatment broadly in consideration of both poly-

microbial (mixed aerobic and anaerobic bacteria) and monomicrobial (group A *streptococcus*, community-acquired MRSA) infections [21]. You should treat with vancomycin, linezolid, or daptomycin plus piperacillin-tazobactam or a carbapenem, or plus ceftriaxone and metronidazole, or plus fluoroquinolone and metronidazole, as empiric therapy. You should change antibiotics appropriately when you have detected the sensitivity of causative bacteria (Table 111.3). You should treat with clindamycin plus penicillin when the causative bacteria are group A *streptococcus*. Streptococcal toxin and cytokine production can be suppressed by clindamycin, but there are group A *Streptococcus* that are resistant to clindamycin. Therefore, you should use penicillin too. You should continue antibiotic treatment until you have found no necrotic tissues and the patient has got better and had no fever for 2–3 days [21].

The efficacy of intravenous immune globulin (IVIG) in streptococcal toxic shock syndrome has been studied because it is considered that IVIG may be beneficial to patients by neutralizing streptococcal toxin [21]. Some studies sug-

**Table 111.3** Antibiotic treatment

Type of infection	First-line antibiotic agent	Adult dosage
Mixed infections	Piperacillin-tazobactam plus vancomycin	3.37 g every 6–8 h 30 mg/kg/day in 2 divided doses
	Imipenem-cilastatin	1 g every 6–8 h
	Meropenem	1 g every 8 h
	Ertapenem	1 g daily
	Cefotaxime plus metronidazole or clindamycin	2 g every 6 h 500 mg every 6 h 600–900 mg every 8 h
<i>Streptococcus</i>	Penicillin plus clindamycin	2–4 million units every 4–6 h 600–900 mg every 8 h
<i>Staphylococcus aureus</i>	Nafcillin	1–2 g every 4 h
	Oxacillin	1–2 g every 4 h
	Cefazolin	1 g every 8 h
	Vancomycin (for resistant strains)	30 mg/kg/day in 2 divided doses
	Clindamycin	600–900 mg every 8 h
<i>Clostridium</i> species	Clindamycin plus penicillin	600–900 mg every 8 h 2–4 million units every 4–6 h
<i>Aeromonas hydrophila</i>	Doxycycline plus ciprofloxacin or ceftriaxone	100 mg every 12 h 500 mg every 12 h 1–2 g every 24 h
<i>Vibrio vulnificus</i>	Doxycycline plus ceftriaxone or cefotaxime	100 mg every 12 h 1 g 4 times daily 2 g 3 times daily

gested that IVIG has benefits, but the sample size was not enough in one study [27]. In the other study, more patients were undergoing surgery and receiving clindamycin in the IVIG group than in the control group [28]. In a recent study, IVIG did not improve mortality and hospital length of stay in NF [29].

Some studies suggested that hyperbaric oxygen therapy (HBOT) significantly decreases the mortality of NF [30, 31]. But other studies suggested that HBOT has no benefit [32, 33]. Because HBOT needs time to perform, it may interfere with surgical treatment, and its benefit is controversial.

### 111.3.3 Prognosis

The mortality of NF has been reported to be 20–30% [3, 34, 35], even if appropriate treatment has been performed. The longer it takes to diagnose and treat, the higher the mortality is. When you have not performed debridement or amputation early and appropriately, the result is treatment failure and a poor prognosis. As NF progresses, it causes sepsis and multiple organ failure. Therefore, patients need not only surgical and antibiotic treatment but also systemic treatment according to their symptoms.

#### Dos and Don'ts

- Do not miss the timing for performing surgery.
- Do not hesitate to perform debridement and amputation of an extremity.
- Remove infected and necrotic tissues appropriately and repeatedly.
- Check Gram's staining and culture, and choose antibiotics appropriately.

#### Take-Home Messages

- It is important to diagnose and treat NF as soon as possible.
- Obtaining specimens from the affected area surgically is most useful in the diagnosis.
- You must repeat this step to remove infected and necrotic tissues until they are not found.

#### Questions

1. Which are the causative bacteria when healthy people get necrotizing fasciitis?
  - A. Mixed bacteria
  - B. Group A *streptococcus*
  - C. *Vibrio vulnificus*
  - D. Fungus
2. Which are the causative bacteria when people with diabetes mellitus get necrotizing fasciitis?
  - A. Mixed bacteria
  - B. Group A *streptococcus*
  - C. *Vibrio vulnificus*
  - D. Fungus
3. Choose one of the following that is not a skin finding of necrotizing fasciitis.
  - A. Tenderness
  - B. Edema
  - C. Itch
  - D. Erythema
4. Which test is most useful for necrotizing fasciitis?
  - A. Blood test
  - B. Blood culture
  - C. Diagnostic resection
  - D. Radiograph



5. The blood tests performed on the patient suspected of having necrotizing fasciitis are the following. Total white cell count is 18/mm. Hemoglobin is 12.0 g/dL. Sodium is 136 mmol/L. Creatinine is 1.7 mg/dL. Glucose is 160 mg/dL. C-reactive protein is 160 mg/L. How much is the LRINEC score?
- 5
  - 6
  - 7
  - 8
6. Which of the following may not be visible on CT in patients with necrotizing fasciitis?
- Soft tissue swelling
  - Involvement of the fascia
  - Gas in the tissues
  - Enhancement of the fascia
7. Which treatment is most important for necrotizing fasciitis?
- Antibiotic treatment
  - Fluid infusion
  - Incisional drainage
  - Debridement or amputation of an extremity
8. To what extent should you remove tissues from the patient when you perform surgery for the patient with necrotizing fasciitis?
- To remove the affected tissues once
  - To amputate an affected extremity
  - To remove infected or necrotic tissues many times
  - To collect the affected tissues
9. Which is not appropriate as empiric therapy for necrotizing fasciitis?
- Daptomycin plus piperacillin-tazobactam
  - Vancomycin plus carbapenem
  - Linezolid plus metronidazole
  - Vancomycin plus piperacillin-tazobactam

10. How high is the mortality rate of necrotizing fasciitis?
- 5–10%
  - 20–30%
  - 40–50%
  - 70–80%

**Answer:** 1. B; 2. A; 3. C; 4. C; 5. D; 6. D; 7. D; 8. C; 9. C; 10. B

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## Further Reading

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