

## Current Concept Review

# Pediatric Necrotizing Fasciitis

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### Abstract

Necrotizing fasciitis (NF) is a rapidly progressing bacterial infection of the subcutaneous tissue that can be life-threatening. Without prompt diagnosis and treatment, it can lead to septic shock, organ failure, and death. Due to the rarity of this disease in the pediatric population and the fact that initial symptoms are frequently nonspecific, NF in children is often misdiagnosed as cellulitis, which delays the correct treatment. Physicians must maintain a high index of suspicion and keep NF in mind because rapid surgical debridement is necessary to reduce morbidity and mortality. The purpose of this article is to better characterize what is currently known about NF within the pediatric population. In this article, the microbiology, pathophysiology, clinical manifestations, diagnosis, and treatment of pediatric NF are reviewed, and key differences between adult and pediatric NF are highlighted.

### Key Concepts

- One must keep Necrotizing Fasciitis in mind when dealing with soft tissue infections.
- A common symptom is a disproportionate level of pain for what can appear to be cellulitis.
- Prompt treatment must include early, thorough, and frequently multiple debridements.
- As a result of low incidences, collaborative multiple-center studies are needed to improve our level of understanding.

### Introduction

Necrotizing Fasciitis (NF) is a potentially life-threatening soft tissue infection characterized by rapid disease progression and extensive necrosis of the fascia and subcutaneous tissue.<sup>1</sup> NF is one of

the most challenging infections faced by surgeons because it is rare and lacks early, pathognomonic signs. Although more common in adults, NF also affects the pediatric population. Most often, pediatric NF

presents in previously healthy children with symptoms of edema, induration, erythema, or signs of sepsis.<sup>2</sup> Because clinical manifestations range from a fulminant presentation to a subtle and insidious development, it is extremely difficult to diagnose. Diagnosis of NF is further impeded because infection progresses below the skin surface and cutaneous manifestations disguise the severity of the disease. Without treatment, NF can lead to systemic toxicity, amputation of affected extremities, and can be fatal.<sup>2,3</sup> As a result, patient survival requires a high index of suspicion, early detection, and treatment with broad-spectrum antibiotics, surgical debridement, and supportive care. Frequently, multiple surgical debridements are required.<sup>4</sup> Even with treatment, NF often results in significant morbidity and mortality with rates of up to 35% in adults and 10% in children.<sup>3</sup>

### ***Illustrative Case***

A five-year-old, previously healthy female presented to clinic with a 2-day history of ankle pain and difficulty ambulating after jumping in a puddle. Her father reported a temperature of 100 degrees F accompanied by worsening pain at home. Upon arrival in clinic, her temperature was 103.1 degrees F, and she appeared lethargic. On exam, she had no obvious wounds but displayed exquisite tenderness along the lateral aspect of the distal fibula and mild erythema. Her labs were as follows: WBC of  $40.6 \times 10^9/L$ , HGB of 11.7 g/dL, CRP of 5.9mg/dL, and Na of 131mmol/L. Ultrasound did not demonstrate a drainable fluid collection, so she was started on clindamycin for presumed cellulitis.

Overnight, she remained febrile with progressive erythema extending proximally from her ankle to her knee. Blood cultures were positive for MRSA. An emergent MRI demonstrated fluid tracking along the fascial planes circumferentially to the knee.

She was taken emergently to the OR for debridement along all fascial compartments of the leg to the knee. Purulence was found around the fibula and murky fluid tracked all along the tissue planes medially and laterally

from the ankle to knee joint with partially devitalized peroneal musculature. She was placed on vancomycin and clindamycin for 14 days from negative blood cultures.

Following surgery, she was monitored in the PICU due to hypoxemia and tachycardia. She ultimately required four surgical debridements with primary wound closure performed during her final surgery. Fortunately, she recovered with full active and passive range of motion of the knee and ankle and the ability to participate in all activities without pain.

### **Epidemiology**

Compared to adult patients, pediatric NF is relatively rare with an estimated incidence of between 0.02 and 0.08 per 100,000 children per year. Incidence has been noted to be higher in children less than 5 years of age.<sup>5</sup> Recent studies have shown that the incidence of pediatric NF has increased in recent years, perhaps due to better disease reporting and increased microbial virulence and resistance as a result of increased antibiotic use.<sup>6,7</sup>

### **Etiology**

NF can present in any area of the body and requires inoculation with causal bacteria into the subcutaneous tissue. In children, NF may arise from minor lesions in previously healthy patients (e.g., after circumcision, umbilical vein catheterization, inguinal hernia repair, or even an insect bite).<sup>8</sup> Although rare, concurrent varicella has also been recognized as a starting point for infection in children. Inoculation with causative microbes may also occur via hematogenous spread to sites of nonpenetrating trauma (e.g., muscle strain).<sup>9</sup> In roughly 25% of cases, NF has been reported without any known trauma.<sup>10</sup> NF can be classified based on the type of bacteria present in the infection. In addition to different microbial etiologies, each class has differences in presentation and patient demographics.

### **Type I Infections**

Type I NF, also known as synergistic or subacute NF, is responsible for 80% of all NF cases and is the most

common necrotizing soft tissue infection (NSTI) type in adults.<sup>11</sup> Although it is rarely seen in children, it occurs more often in infants less than 1 year of age. Specifically, it has been seen in neonates following circumcision and in those with omphalitis.<sup>12,13</sup> Type I NF infections are polymicrobial and caused by a combination of gram-positive cocci, gram-negative rods, and typically at least one anaerobic species. Commonly isolated pathogens include non-group A *Streptococcus species*, *Klebsiella species*, *Escherichia coli*, and *Bacteroides species*.<sup>6</sup> In addition, *Pseudomonas* has been isolated in approximately one-fourth of microbiologically confirmed cases.<sup>14</sup>

## Type II Infections

Type II infections account for approximately 15% of all NF cases and are usually monomicrobial and caused by gram-positive organisms.<sup>11</sup> Compared to Type I infections, Type II infections are initially more insidious but progress rapidly.<sup>15</sup> The most common Type II NF is usually caused by group A beta-hemolytic *Streptococcus (GAS)* alone or infrequently with *Staphylococcus aureus*.<sup>2</sup> Type II infections tend to occur on the extremities but also can arise on the trunk.<sup>3</sup> Patients who present with Type II infections are typically young and previously healthy. These patients may have a history of recent trauma, laceration, burn, surgery, or IV drug use.<sup>16-19</sup> However, in many cases, the disease may appear to have arisen spontaneously. In approximately 50% of cases, necrotizing infections caused by GAS can also be associated with toxic shock syndrome.<sup>20</sup> Although previously an uncommon cause of NF, community-acquired methicillin-resistant *S. aureus (MRSA)* is now cultured in up to 40% of NF infections.<sup>6</sup>

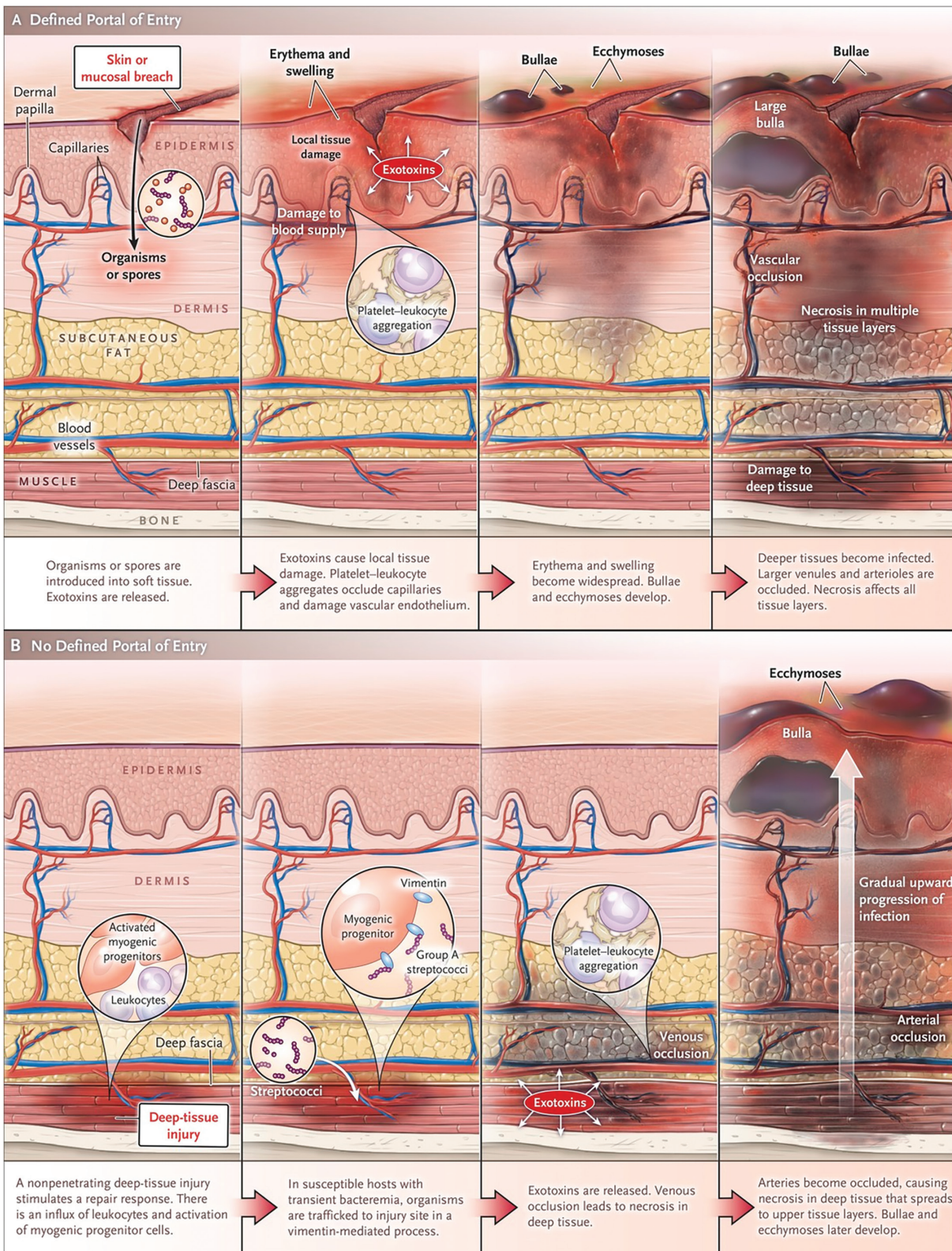
## Pathology

The underlying pathophysiology of NF is similar among all types. However, the clinical features and speed of disease progression differ depending upon the causal organism. The primary site of pathology for NF infections is the superficial fascia. Bacteria then invade subcutaneous tissue, producing endotoxins,

exotoxins, and enzymes such as hyaluronidase, which cause the infection to spread rapidly and lead to tissue ischemia, liquefactive necrosis, and systemic illness (Figure 1). Underlying infections may progress as rapidly as 1 inch per hour with innocuous changes to the outer layers of skin.<sup>6</sup>

In NF infections, some organisms such as *Staphylococcus aureus* and *Streptococcus species* develop M-1 and M-3 proteins, which serve to improve the pathogens' ability to adhere to tissue and evade phagocytosis. In addition, bacterial pathogens frequently produce exotoxins A, B, C, Streptolysin O, and superantigens. Production of exotoxins can make pathogens more virulent and increase the rate of infection. Exotoxins A and B damage endothelium, compromise microvascular integrity, and exit blood vessels, causing tissue edema and reduced capillary blood flow. Toxins A, B, and streptolysin O, trigger the production of cytokines by CD4 cells and macrophages. Production of the Th1 cytokine leads to the formation of TNF alpha and can eventually aid in the development of myonecrosis. In addition, massive cytokine release produces a systemic inflammatory response syndrome (SIRS), which may progress to septic shock, multisystem organ failure, and loss of life.<sup>15</sup>

The key feature of the pathophysiology of NF is thrombosis of perforating vessels of the skin and subcutaneous tissue. The extent of infection is usually much larger than what is evidenced by skin findings alone because thrombosis of large numbers of vast dermal capillary beds must occur before skin changes reflecting necrosis arise. Thrombosis in NF patients is the result of the local hypercoagulable state, platelet-neutrophil plugging of vessels, and increased interstitial pressure. These three factors combine to contribute to decreased capillary blood flow to end tissues and result in tissue ischemia.<sup>6</sup> Superantigens stimulate T cells directly, activating the complement system, the bradykinin-kallikrein system, and the coagulation cascade, thereby worsening small vessel thrombosis and tissue ischemia.<sup>15</sup> Tissue ischemia prevents



**Figure 1.** Evolution of Necrotizing Fasciitis or Myonecrosis. Panel A shows the evolution of infections with a defined portal of entry. Panel B shows the evolution of group A streptococcal infection with no defined portal of entry (cryptogenic infection). Stevens DL, Bryant AE. *N Engl J Med* 2017;377:2253-2265. Reproduced with permission from the New England Journal of Medicine.

oxidative destruction of bacteria by polymorphonuclear cells, which eventually become lysed producing a classic ‘dishwater fluid.’ Further, tissue ischemia prevents adequate delivery of antibiotics, therefore, antibiotic therapy alone does not provide much value. Surgical debridement is crucial for treatment of NF infections.<sup>15</sup>

Migration of infection results from rapid bacterial multiplication within viable tissue. Fibrous attachments between subcutaneous tissues and fasciae limit spread to areas like the hands, feet, and scalp. However, a lack of fibrous attachments in the trunk and limbs, leaves the potential for widespread infection and tissue damage. NF can also spread to venous and lymphatic channels, resulting in edema.<sup>21</sup> The spread of bacteria results in thrombosis of blood vessels in dermal papilla, resulting in ischemia and gangrene of subcutaneous fat and dermis (Figure 2). As more blood vessels become occluded and nerves are infarcted, patients typically experience progressive skin ischemia and a worsening,

“crescendo” pain.<sup>15</sup> If the infection reaches the muscle, myositis occurs. Gas-producing organisms can lead to the formation of gas within the tissues (Figure 3).<sup>2</sup> Without treatment, infections continue to spread beneath apparently healthy skin in a horizontal manner, progressively leading to bullae formation, ulceration, and finally, skin necrosis.<sup>22,23</sup>

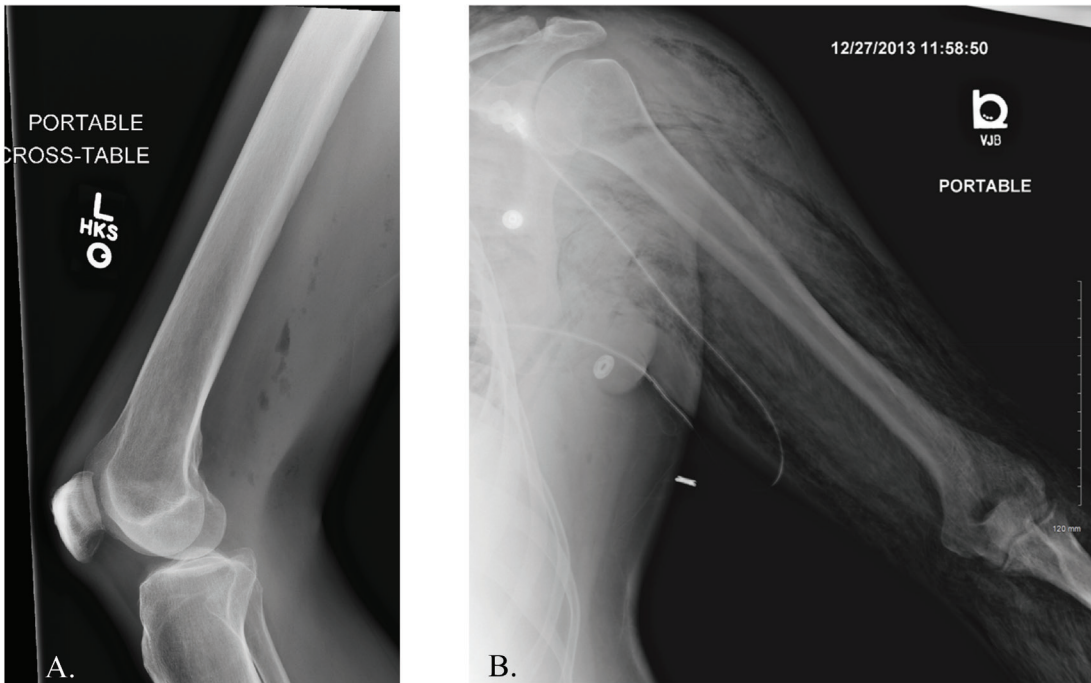
### Clinical Manifestations

NF manifests in a variety of ways, making it extremely difficult to recognize and diagnose. It has been shown that only 10-40% of patients present with a ‘classic’ history of rapidly worsening pain related to trauma or a break in the skin within 48 hours of symptom onset.<sup>6</sup> Although it can affect any region or part of the body, pediatric NF is most often seen in the abdomen, perineum, and extremities (lower extremities more commonly than upper extremities). These infections typically present acutely over the course of a few hours but have also been known to present sub-acutely, taking several days to develop.<sup>3</sup> Due to the potential for extensive tissue destruction, systemic toxicity, amputation, and death, early recognition of NF is crucial. Although some patients present with little or no pain, the most critical early distinctive symptom of NF is a disproportionate level of pain as compared to physical findings.

Patients often experience severe pain but may display only mild erythema or swelling over the affected area. Further, because NF initially affects the subcutaneous tissue, these patients experience tenderness and pain that commonly extends far beyond the apparent site of infection.<sup>6</sup> This characteristic “pain out of proportion” symptom, however, can be difficult to discern in children. Therefore, in pediatrics, the most identified early symptoms include fever, erythema, localized swelling, and tenderness or pain. In some cases, marked edema may become so severe that it leads to compartment syndrome with complicating myonecrosis requiring fasciotomy. Differentiating NF from other soft tissue infections can be difficult at the beginning, but in NF symptoms progress, and patients become sicker more quickly.



**Figure 2.** Skin lesions of a patient presenting with NF.



**Figure 3.** (A) X-ray of the left lateral thigh from an adult with NF shows evidence of mild fascial air-tracking. (B) X-ray of the left upper extremity from an adult with NF showing extensive subcutaneous and fascial tracking air in a severe case of NF.

Some patients may present solely with systemic symptoms such as fever (102 to 105 degrees F), tachycardia, and systemic toxicity. They may also present with hypotension or develop hypotension as the infection progresses.<sup>24</sup> Some other common, generalized symptoms that these patients have been reported to experience include malaise, myalgias, diarrhea, and anorexia.<sup>2,25,26</sup> These patients require a thorough physical exam to try and elicit a localizing area, especially in cases of non-penetrating trauma.

The infective process of NF progresses rapidly over hours or several days. Skin color typically changes from reddish-purple to patches of blue-gray. Within 3 to 5 days of onset, the skin begins to break down and bullae can develop.<sup>27</sup> Although crepitus from subcutaneous gas or skin necrosis is often described as a hallmark symptom of NF, Sarani and colleagues showed that it was present in only 13-31% of patients.<sup>6</sup>

The rate of progression of NF can vary. Patients with NF in the later stages of the disease often show symptoms

and signs of septic shock, toxic shock syndrome, and multiorgan failure. These patients can develop tachycardia, tachypnea, fever or hypothermia, hypotension, cardiac arrhythmias, metabolic acidosis, abnormal renal and liver function, coagulopathy, and thrombocytopenia, and carry a high rate of mortality.<sup>8</sup>

### Laboratory Findings

Laboratory findings in NF patients are generally nonspecific. Some lab abnormalities that have been identified in association with NF are listed in Table 1.

Elevations in CK and AST are suggestive of deep infection involving muscle or fascia (myositis or myonecrosis as opposed to cellulitis). Hypocalcemia can be a sign fat necrosis and calcium deposit in necrotic tissues. Patients may also develop disseminated intravascular coagulation (DIC) with changes in serum clotting parameters.

Blood cultures are positive in approximately 60% of patients with monomicrobial (Type II) NF and are

**Table 1. Common Lab Findings in Patients With NF<sup>25,28-30</sup>**

Leukocytosis with left shift
Thrombocytopenia
Elevated inflammatory markers (ESR, CRP)
Elevated CK
Elevated AST
Elevated serum creatinine
Elevated lactate
Hypocalcemia
Hypoalbuminemia
Hyponatremia
Metabolic acidosis
Anemia

routinely positive in patients with necrotizing myositis.<sup>31</sup> However, the blood culture yield is much lower (as low as 20%) in patients with polymicrobial (Type I) NF.<sup>17,18</sup> In addition, cultures may not reflect all of the organisms involved in polymicrobial infections. Although percutaneous needle aspiration of the advancing edge can be useful, tissue cultures taken from surgical debridements are preferred. Both tissues and aspirates should be Gram stained and cultured. Fungal culture is recommended in high-risk immunocompromised patients.<sup>6,32</sup>

### Laboratory Scoring Systems for the Prediction of NF

In 2004, Wong and colleagues developed the LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) scoring system. This is a clinical tool designed to distinguish NF from other soft tissue infections. The tool, shown in Table 2, is based on the following six values: white cell count, hemoglobin, sodium, serum glucose, creatinine, and C-reactive protein.<sup>41</sup> Each variable is awarded points based on its independent predictive value for positive diagnosis. The overall LRINEC score is calculated by adding up each of the six predictive

**Table 2. LRINEC Scoring System<sup>8</sup>**

Variable	Score
C-Reactive protein (mg/L)	
<150	0
≥150	4
WBC (cells/mm <sup>3</sup> )	
<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 (μg/L)	
≤141	0
>141	2
Glucose (mmol/L)	
≤10	0
>10	1

factors, and scores greater than 6 have been shown to be predictive of NF in adults.<sup>8</sup>

While the LRINEC scoring system has proven to be a reliable diagnostic tool in adults, it has not been validated in children. In 2016, Putnam et al. conducted a case-control study to determine the utility of the LRINEC in children and found that a simplified version of the LRINEC score (P-LRINEC), using only serum CRP and sodium, was more predictive of pediatric NSTI than the original scoring system. Specifically, they showed that a CRP >20 mg/L had a sensitivity of 95% and a serum sodium of <135 mEq/L had a specificity of 95%. While the P-LRINEC had a strong predictive value in this study,

it remains externally and prospectively unvalidated.<sup>6</sup> Therefore, this tool should not be used to rule out NF. It is important to note that if suspicion is high for NF based on clinical history and physical exam, operative debridement should be initiated immediately regardless of the P-LRINEC score.

## Imaging

Radiographic imaging studies can be useful to help determine whether an NF infection is present. However, it is important to realize that imaging is not a definitive diagnostic procedure, and it should never delay surgery.

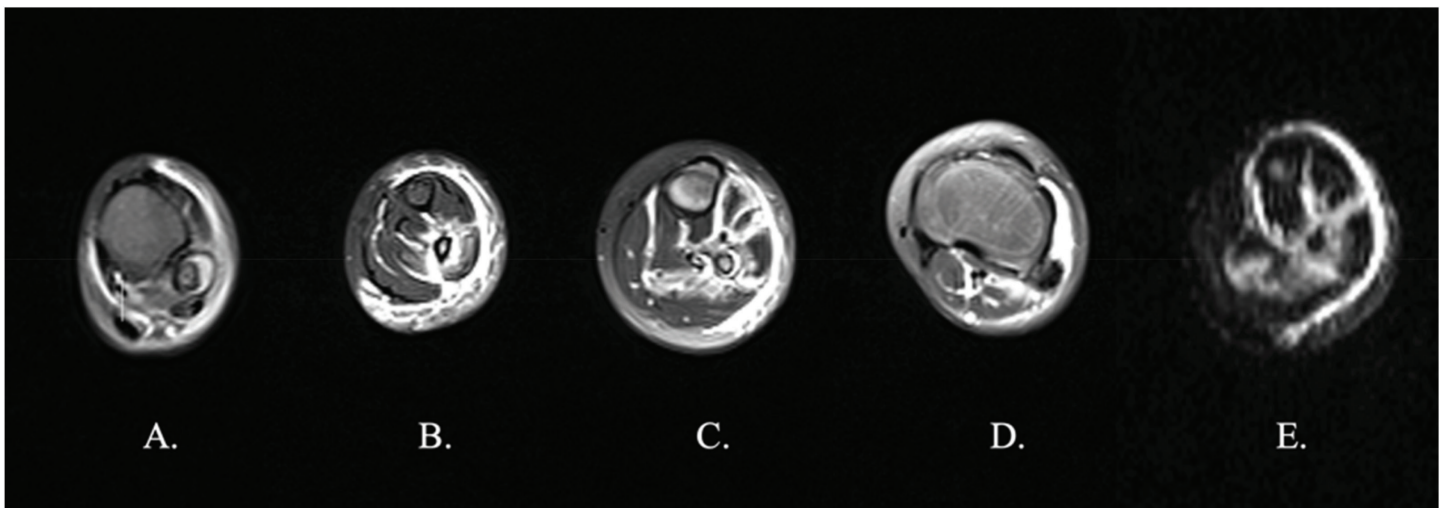
Computed tomography (CT) scan, ultrasound, and magnetic resonance imaging (MRI) have all been used to image cases of NF.<sup>37</sup> CT scans can reveal deep fascial thickening and the presence of fluid and gas within soft tissue planes in and around the superficial fascia. The best initial radiographic imaging exam is a CT scan, with a sensitivity of 88.5% and specificity of 93.3% for fascial gas, which is more commonly seen in patients with clostridial infection or polymicrobial (Type I) NF.<sup>38,39</sup> This finding is highly specific for NF and should result in immediate surgical intervention. Ultrasound identifies features suggestive of thickening, distortion, and fluid collections along the deep fascia. MRI with gadolinium differentiates necrotic and inflamed or edematous tissue.

T2-weighted images on MRI are probably the best radiological adjunctive investigation for NF (Figure 4), which may show fluid in and around many of the fascial planes. However, the definitive diagnosis of necrotizing infection can be established only by surgical exploration.<sup>40</sup>

## Diagnosis and Decision for Surgical Exploration

Early recognition of necrotizing infection is critical; rapid progression to extensive destruction can occur, leading to systemic toxicity, limb loss, and/or death.<sup>28,33,34</sup> Diagnosis is frequently difficult and delayed diagnoses can have serious implications. NF should be suspected in patients with soft tissue infection (erythema, edema, warmth) and signs of systemic illness (fever, hemodynamic instability) in association with crepitus, progression of clinical manifestations, and/or severe pain.<sup>24</sup> Watching closely for rapid clinic progression of skin erythema is important. The skin may be marked and followed hourly for other changes as described above. Their pain may progress to other regions quickly as well.

Although history and physical examination are important clues that can aid in increasing suspicion of NF, diagnosis of NF is essentially clinical. The gold standard



**Figure 4.** MRI Axial views. (A) T2 FS distally, (B) T2 FS distal third, (C) T2 FS proximal third, (D) T2 FS proximally, (E) Post Contrast middle of leg.

is surgical exploration.<sup>3</sup> When there is clinical suspicion for a NF infection, surgical exploration should not be delayed while awaiting results of radiographic imaging, tissue culture, or other diagnostic information.<sup>35</sup>

The diagnosis of necrotizing infection is confirmed upon operative findings that include dull gray, swollen, necrotic fascia, easy separation of normally adherent superficial fascia during blunt dissection accompanied by a lack of bleeding, and presence of foul-smelling “dishwater” pus.<sup>36</sup> The presence of fascial necrosis, myonecrosis, or loss of fascial integrity along tissue planes are also diagnostic. Intraoperative specimens should be sent for stat Gram stain, culture, and pathology is routinely collected in all cases of apparent infection.<sup>8</sup>

## Treatment

Treatment of NF requires a combination of broad surgical debridement, broad-spectrum antibiotics, and hemodynamic support. It is important to emphasize that NF is a surgical emergency, and early debridement is critical. Studies have shown that administration of antibiotic therapy alone, without surgical debridement, is associated with a mortality rate near 100% of cases.<sup>42</sup> The goal of surgical treatment is to aggressively debride all necrotic tissue until healthy, bleeding tissue is present. Debridement should be repeated every 24 to 48 hours until no necrotic tissue remains.<sup>43</sup> For severe cases of NF, amputation may be necessary to achieve source control. Empiric treatment of NF should also include broad-spectrum antibiotic therapy with aerobic and anaerobic coverage, including methicillin-resistant *Staphylococcus aureus* (MRSA) coverage.<sup>42</sup> Antibiotics should be administered immediately after obtaining blood cultures and should be continued until no further debridement is needed and the patient’s hemodynamic status has normalized.<sup>44</sup> NF can be complicated by other infections, such as endocarditis or osteomyelitis. In these cases, the antibiotic duration may be extended for treatment of the non-NF diagnosis. Recommended antibiotic regimens for the treatment of pediatric NF are shown in Table 3 below.<sup>32,40,45-49</sup>

In certain cases, especially associated with streptococcal toxic shock syndrome, critical care support with intravenous fluids, albumin replacement, and vasopressors may be required.<sup>25</sup> It is recommended that patients with NF and streptococcal toxic shock syndrome be given intravenous immune globulin (IVIG). This recommendation is supported by a recent meta-analysis conducted by Parks et al. that showed that use of IVIG in treating STSS was correlated with a near 50% decline in mortality at 30 days as compared to use of clindamycin alone.<sup>50</sup>

## Surgical Exploration

Patients with NF may appear well in the early stages of infection. However, because they often deteriorate within hours of presentation, a high index of suspicion for NF is sufficient to initiate surgical exploration.<sup>40,42,51</sup> Studies show that delays in initial debridement greater than 24 hours are associated with high morbidity and mortality.<sup>41,52,53</sup>

Because early intervention is critical, initial debridement should take place at the facility where the diagnosis is first suspected whenever possible. Holena et al. showed that patients debrided at the hospital to which they initially presented had a significantly lower mortality rate (8.7%) than those who were transferred without debridement (15.5%).<sup>54</sup> After initial debridement, it is recommended that patients be transferred to a burn center or similar facility accustomed to caring for infections of this nature.<sup>3,55-58</sup> Approximately 10-20% of all NF patients may require an amputation.<sup>59</sup> Amputation should be considered in life-threatening cases if repeated debridements are unlikely to achieve source control or when no good reconstructive options exist.<sup>7,60-62</sup>

Multiple debridements may be necessary prior to beginning reconstruction,<sup>3,58,63</sup> and upon completion of the initial debridement, a subsequent debridement surgery should be scheduled and performed within 24 hours. However, if the patient’s condition begins to decline, an earlier procedure may be warranted. Lab results can be monitored and may signal the need

**Table 3. Antibiotic Recommendations for the Treatment of NF in Children<sup>32,40,45-49</sup>**

Type of Infection	Antimicrobial Agent	Alternative in Severe Penicillin Hypersensitivity
Options for Empiric Treatment or Mixed Infection	Piperacillin-tazobactam 60-75 mg/kg/dose every 6 h IV	Aminoglycoside Or Fluoroquinolone <b>Plus</b> Metronidazole
	Meropenem 20 mg/kg/dose every 8 h IV	
	Ertapenem 15 mg/kg/dose every 12 h IV	
	Imipenem 15-25 mg/kg/dose every 6 h IV	
	<b>Plus</b> Vancomycin 15-20 mg/kg/dose every 6 h IV Or Daptomycin Children ≤ 6 years: 12 mg/kg/dose every 24 h IV Children ≥ 7 years: 9 mg/kg/dose every 24 h IV	
Group A Streptococcus	Penicillin 60,000 – 100,000 units/kg/dose every 6 h IV	Vancomycin Or Daptomycin
	<b>Plus</b> Clindamycin 10-13 mg/kg/dose every 8 h IV	
<i>Aeromonas spp</i> or <i>Vibrio vulnificus</i>	Ceftriaxone 50-100 mg/kg/dose every 24 hrs IV	Aminoglycoside <b>Plus</b> Trimethoprim- sulfamethoxazole
	<b>Plus</b> Doxycycline 2.2 mg/kg/dose every 12 hrs Or Ciprofloxacin 10 mg/kg/dose every 8 to 12 hrs IV	

for earlier or repeat debridement. CRP, lactate, or procalcitonin (PCT) levels should be obtained every 6 to 8 hours. These biomarkers may indicate the severity of infection. PCT most closely correlates with infection severity and aids in determining the course of antibiotic treatment.<sup>30,64</sup>

### Wound Care

Following debridement, microbial pathogens present in NF wounds can lead to delayed wound healing.

Thus, topical antimicrobials are often used as adjunct treatments. Commonly used agents are discussed in Table 4. Most of these agents can have negative cytotoxic effects on healthy cells. Therefore, in choosing a topical antiseptic agent, it is important to consider its antiseptic efficacy in relation to its cytotoxicity.<sup>65,66</sup> In order to minimize the risk of contractures or deformities, it is also important to avoid wound dressings that inhibit mobility, especially in cases that involve the hand, neck, and extremities.

**Table 4. Topical Antimicrobials and Therapies Used in the Treatment of NF<sup>65-72</sup>**

Timing	Antimicrobials/Therapies	Notes
Early (Before formation of granulation tissue, when dressing changes are frequent)	*0.025% Sodium hypochlorite (1:20 Dakin solution <sup>†</sup> ) <i>alternating with</i> Polyhexamethylene biguanide (PHMB)/betaine	<ul style="list-style-type: none"> <li>• Potent, broad-spectrum</li> <li>• Low host-cell cytotoxicity<sup>†</sup></li> <li>• Ability to perforate biofilms</li> <li>• Resistance is rare</li> </ul>
	Acetic acid	<ul style="list-style-type: none"> <li>• Bactericidal against most gram (+) and gram (-) organisms, including <i>Pseudomonas</i></li> <li>• Inhibits epithelialization/can be cytotoxic</li> <li>• Limited activity against biofilms</li> </ul>
	Mafenide acetate	<ul style="list-style-type: none"> <li>• Potent carbonic anhydrase inhibitor</li> <li>• Covers <i>Pseudomonas</i></li> <li>• Inhibits epithelialization/can be cytotoxic</li> <li>• Used as an alternative to silver sulfadiazine</li> </ul>
	Povidone Iodine	<ul style="list-style-type: none"> <li>• Broad-spectrum</li> <li>• Limited use due to cytotoxicity</li> <li>• Causes stinging and erythema</li> <li>• Resistance is rare</li> </ul>
Late (After formation of granulation tissue, when dressing changes are less frequent)	*Silver-containing dressings (e.g., Acticoat)	<ul style="list-style-type: none"> <li>• Broad-spectrum coverage</li> <li>• Useful to prepare wounds for skin grafting</li> <li>• Can result in silver toxicity</li> <li>• Minimal resistance to pathogens</li> <li>• Permits dressing change intervals up to 72 hrs</li> </ul>
	*Negative Pressure Wound Therapy (NPWT)	<ul style="list-style-type: none"> <li>• Used for dressing changes &gt;48 hrs apart</li> <li>• Allows for control of excess exudate</li> <li>• Stimulates granulation tissue formation</li> <li>• Useful in preparation for skin grafts or flaps</li> </ul>

\*Indicates favored treatment regimens.

<sup>†</sup>Sodium hypochlorite solution becomes significantly more cytotoxic at concentrations >0.025%.

## Post-Acute Treatment and Reconstruction

Wound coverage and closure become important when surgical debridement is no longer required. This stage of the treatment process should not be considered until the patient is stable and all necrotic or infected areas have been completely debrided. At this stage, healthy granulation tissue can often be seen in the wound bed. In order to reduce heat and fluid loss and protect the wound from exposure to inflammatory stimuli, temporary donor allografts may be used. Use of this form of skin coverage allows the patient time to further recover and allows the surgical team time to develop a reconstruction

plan that is best for the patient. If the temporary allograft adheres, it is likely that an autograft will also be effective.<sup>73,74</sup>

Split-thickness autografting can be used for definitive reconstruction in the majority of NF cases. Some patients may need additional forms of coverage such as fasciocutaneous or muscle flaps if they have exposed bones, tendons, or neurovascular structures. Benefits of muscle flaps include their predictable blood supply pattern and their ability to conform to defects and thus these are often favored. However, fasciocutaneous flaps should be utilized when covering pressure areas such as

the elbow, sacrum, or ischial tuberosity because of their increased durability.<sup>75</sup>

Use of dermal substitutes, such as Matriderm or Integra may be beneficial in some NF patients. They have been correlated with increased skin durability and laxity and, in some cases, may replace the need for flap surgery.<sup>76,77</sup> These materials are avoided during the acute stages because infection can complicate their application.

Postoperative morbidity is considerable with the potential for substantial scarring and disfigurement.<sup>2</sup> Many patients experience muscle loss as a result of surgical debridements and require prolonged rehabilitation. Following reconstructive surgery, patients with NF often benefit from the same rehabilitative services that burn patients receive. It is essential to ensure that dressings and splints that facilitate physical activity are used. Therapists can design specific programs based on the patient's age, comorbidities, and functional level prior to NF, as well as the stage of surgical intervention and the location and severity of NF. Therapies used include strength and flexibility training, splinting, and scar massage.<sup>78</sup>

## Mortality

The case fatality rate of NF infections in children is approximately 10%. Mortality rates in neonates have been shown to be as high as 59%.<sup>79</sup> Mortality rates are largely dependent upon timing and adequacy of debridement, with a significant increase in mortality when surgery is delayed for greater than 24 hours.<sup>17</sup> Mortality rates are also significantly higher for patients with streptococcal toxic shock syndrome and diabetes.<sup>59,80</sup>

## Summary

Although NF infections in pediatric patients are rare, they are life-threatening, and early diagnosis is critical. Unlike in adults, NF in children typically occurs in otherwise healthy patients. Its initial presentation frequently mimics that of less serious skin infections, such as cellulitis. It is imperative that pediatric orthopaedic surgeons have a high level of clinical awareness and be up to date on

emerging diagnostic tools like the P-LRINEC, which may aid in early diagnosis. It is essential that all children with suspected NF undergo early surgical debridement to prevent delay in treatment.

Despite the potentially grave consequences of NF for children, research in the field is lacking due to the extremely low incidence of pediatric NF and the difficulty of developing assessment and treatment recommendations from these small series. Systematic multi-institutional studies are needed to develop and validate prognostic tools such as the P-LRINEC.

## Disclaimer

The authors report no conflicts of interest related to this manuscript.

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