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Severe Skin and Soft Tissue Infection of Patients Admitted to Intensive Care Units

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Skin and soft tissue infections (SSTIs) can occasionally progress to life-threatening conditions, such as septic shock, requiring intensive care unit admission. Their risk factors include diabetes mellitus, chronic renal failure, chronic vascular disease, malignancy, and acquired immune deficiency syndrome. However, early diagnosis is challenging due to initially benign skin lesions and the absence of systemic symptoms such as fever. This review focuses on severe bacterial infections such as necrotizing fasciitis, gas gangrene, and toxic shock syndrome, examining their etiology and management. These severe SSTIs should be understood for the early diagnosis, appropriate treatment, and improved patient outcomes. Dermatologists play a vital role in recognizing and managing these infections.

Key Words: Gas gangrene, Necrotizing fasciitis, Skin and soft tissue infections, Toxic shock syndrome

INTRODUCTION

Skin and soft tissue infections (SSTIs) can occasionally be severe to cause septic shock, necessitating intensive care unit admission. The Extended Prevalence of Infection in Intensive Care (EPIC II) study reported that the respiratory tract was the most common site of infection, accounting for 64% of infections, followed by the abdomen (20%), bloodstream (15%), renal tract/genitourinary system (14%), and skin (6.6%)[1]. Another study reported that following the respiratory tract (62.9%) and abdominal infections (25.3%), SSTIs (8.7%) are the third most frequent cause of septic shock[2]. A previous study reported 1,250 episodes of SSTIs of patients admitted to the hospital via emergency departments, and 3.3% had septic syndrome[3]. Given the high mortality and morbidity rates associated with SSTIs, understanding the causes and risk factors of these infections is important for delivering quality healthcare. Risk factors of severe SSTIs include diabetes mellitus, chronic renal failure, chronic vascular disease, malignancy, and acquired immune deficiency syndrome. Diagnosing the disease at its early stages is challenging because of initially benign skin lesions and the absence of hemodynamic instability[4]. The typical onset of SSTIs is sudden over several days, and they are most commonly caused by bacteria[5]. This study aimed to review severe bacterial infections, including necrotizing fasciitis (NF), gas gangrene (GG), and toxic shock syndrome (TSS), and to evaluate the etiology and management of severe SSTIs.

SEVERE SKIN AND SOFT TISSUE INFECTIONS

1. Necrotizing fasciitis

NF refers to skin, subcutaneous tissue, and muscle fascial

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infections, characterized by necrosis in these structures[4]. In the vast majority of cases, NF begins with the inoculation of pathogens through skin injuries caused by trauma, perforating wounds, human or animal bites, insect bites, minor procedures, catheter insertion, medication or illicit drug injection, post-varicella complications, and other factors, including contusions without skin breakage[6].

1) Clinical manifestations

NF most commonly develops in the lower limbs; however, it can also affect the upper limbs, trunk, head, and neck. The initial lesion might present mild erythema, which becomes widespread within 24 to 72 h. The deeper the lesion, the darker the skin and becomes a dusky and later purplish color, and consequently, blisters form. Bacteremia is frequently present, and metastatic infections may occur. With the onset of bruising and blisters, tissue destruction is severe, with apparent signs of systemic toxicity and organ failure[7]. Since cutaneous manifestations are not initially detected, the infection is often misdiagnosed, or the correct diagnosis is delayed, resulting in a mortality rate of >70%[8].

2) Microbial classification

Microbial classification is widely used to classify NF classification: type I is characterized by the disease caused by a synergistic association between aerobic and anaerobic bacteria, type II is caused mainly by group A beta-hemolytic streptococci (GAS), type III is caused by gram-negative rods including *Aeromonas* and *Vibrio* spp., and type IV is rarely reported but caused by fungal infection. NF type I is generally observed in the elderly or those with underlying illnesses. Unlike type I infections, type II NF may occur in any age group and persons without any underlying disease. However, recent reports of monomicrobial NF caused by *Enterobacteriales*, mainly occurring in immunocompromised patients, with higher mortality than in type 1 and 2 NF, suggested that this classification be reconsidered[9]. Type I infection is commonly associated with gas in the tissue and thus is difficult to distinguish from GG due to clostridial infection. Some studies reported that type II infections have accounted for 55 to 87% of all NF cases[10,11]. In contrast, type I infections have been more prevalent in other studies[12], and some studies reported that the incidence of the two types of infection has been similar[7,13,14]. A recent meta-analysis (a total of 8,718 patients from 105 studies included) revealed a 53% and 37.9% pooled prevalence of polymicrobial and monomicrobial infections, respectively[15].

3) Diagnosis

Diagnosing necrotizing soft tissue infection is challenging because its early signs might be similar to those of non-necrotizing soft tissue infections, such as erythema and edema. Moreover, fever occurred in only 40% of cases[7]. Nausea, vomiting, and diarrhea can be initial signs of toxemia caused by group A streptococcal infection, although these symptoms are frequently mistaken for food poisoning or a viral infection[7].

(1) Imaging

Imaging should not delay urgent surgical exploration, particularly for patients in shock. In stable and equivocal cases, magnetic resonance imaging is the most effective method to diagnose NF in the limbs. It might provide valuable diagnostic clues when thickened fascia (>3 mm) with hypersignal on fat-suppressed T2-weighted sequences are seen[16]. Standard X-rays have poor sensitivity and can only detect NF with gas in the soft tissue at advanced stages. A computed tomography scan is of little diagnostic value for limb NF but should be performed for abdominoperineal or cervicofacial infections to detect the portal of entry and guide surgical management[16].

(2) Laboratory investigations

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) is calculated from serum C-reactive protein, leukocyte count, hemoglobin, sodium, creatinine, and glucose levels to differentiate necrotizing soft tissue infections from non-necrotizing ones and to predict patient outcomes[17] (Table 1). However, the diagnostic performance of the LINEC score remains controversial.

(3) Microbiological diagnosis

Blood cultures, fine-needle aspiration in skin necrosis areas, and intraoperative deep tissue biopsy have been recommended by the Infectious Diseases Society of America for microbiological diagnosis, rather than superficial wound swabs, which are unreliable due to high contamination risk[16,18]. Blood cultures are positive in 11~60% of cases, whereas intraoperative tissue biopsies are positive in 80%. Fine-needle aspiration of the necrotic skin is a simple and quick procedure, yielding positive cultures in up to 73% of cases. Ultrasound-guided aspiration of the fluid along the fascia may also be helpful[16].

Table 1. Laboratory Risk Indicator for Necrotizing Fasciitis [LRINEC]

Parameters	Values	Score (%)
Hb (g/dL)	>13.5	0
	11~13.5	1
	<11	2
Leukocytes (10^9/L)	<15	0
	15~25	1
	>25	2
Sodium (mmoL/L)	<135	2
Creatinine (moL/mL)	>1.41	2
Glucose	>100	1
C-reactive protein	>15	4

Adapted from Wong et al. (2004)[17]
The sum of scores <5, ≤50% risk (low risk); between 6 and 7, intermediate risk; >8, 75% risk (high risk)

2. Gas gangrene

Clostridial GG or clostridial myonecrosis is a rare but life-threatening necrotizing soft tissue infection caused by anaerobic, spore-forming, and gas-producing clostridium subspecies[19]. *Clostridium perfringens* is the most common etiological agent of GG[5]. Because it is anaerobic, it is usually preceded by deep penetrating injury and exposure to contaminated soil or water. The incubation period between the injury and the onset of symptoms is approximately 1~3 days but can be as short as hours[5]. Patients of clostridial GG have a significantly increased mortality risk of up to 100% due to early septic shock caused by clostridial toxins. Detecting clinical differences between NF and GG is difficult in the initial stages[19]. The combination of severe pain, disproportionate tachycardia relative to the fever, and crepitus is highly indicative of clostridial myonecrosis[20].

1) Treatment of necrotizing fasciitis and gas gangrene

The antibiotic treatment should empirically cover polymicrobial NF, targeting gram-positive, gram-negative, and anaerobic bacteria, especially high-risk patients. Combined with antibacterial therapy, surgical debridement is also an essential emergency procedure[6]. Suspected cases of clostridial myonecrosis particularly require emergency surgical exploration and debridement of all involved muscles[5]. An intravenous broad-spectrum β-lactam should be used (e.g., piperacillin [4 g every 6 h] plus tazobactam [0.5 g every 6 h] or cefotaxime [2 g every 6 h]). Suspected methicillin-resistant *S. aureus* (MRSA) can be covered by the inclusion of vancomycin (30 mg/kg loading dose before 30 mg/kg per 24 h continuous infusion) or daptomycin (8~12 mg/kg every 24 h) or linezolid (600 mg every 12 h), whereas resistant gram-negative strains can be covered by the use of carbapenems (e.g., meropenem [1~2 g every 8 h]). Aminoglycosides gentamicin [5~8 mg/kg over 30 min every 24 h] or amikacin [25~30 mg/kg over 30 min every 24 h]) should be considered to further broaden the spectrum only in cases of septic shock[16,18]. Clindamycin should be administered in cases of clostridial myonecrosis or GAS infection. Clindamycin inhibits the synthesis of clostridial exotoxins, lessens their systemic effects[19], and reduces streptococcal toxin production and disease severity with improved bacterial clearance[16]. For other NF type III infections, current guidelines recommend that *A. hydrophila* infections be treated with doxycycline plus either ciprofloxacin or ceftriaxone[18]. A combination of doxycycline plus either ceftriaxone or cefotaxime is recommended for *V. vulnificus* infections[18].

TOXIC SHOCK SYNDROME

TSS is an acute, multisystem, toxin-mediated illness, typically resulting in shock and multiorgan failure early in its clinical course. Its annual incidence suggested to range from 1.5 to 11 per 100,000 people[21]. It is caused by toxin-producing strains *S. aureus* and *S. pyogenes*[22]. Bacterial toxins, known as superantigens, are protein toxins that trigger excessive and unconventional T-cell activation. This activation results in the downstream activation of other cell types and the release of cytokines and chemokines, resulting in a cytokine storm, hypotension, and disseminated intravascular coagulation[22]. However, not all patients colonized or infected with a toxin-producing strain of *S. aureus* or *S. pyogenes* develop TSS. The response to the bacterial and toxic challenges may largely depend on the interaction between the host immune system and the pathogen[22]. The absence of antibodies to superantigens seems to be a significant risk factor for TSS development[23]. Host genetic factors, such as MHC class II haplotype, may influence the intensity of the inflammatory response[24].

1. Staphylococcal toxic shock syndrome

Staphylococcal TSS typically begins suddenly, resembling the onset of influenza, with fever, gastrointestinal distress, and severe muscle pain. The source of the infection is often superficial, including complicated burns or surgical wounds or stem from a foreign object[22]. Desquamation is a characteristic late characteristic of staphylococcal TSS, occurring 10~21 days after the disease onset[22]. Postoperative TSS occurs within 10 days, and in many cases, clinically significant surgical site infection is lacking at the time of presentation[25]. Notably, blood cultures test positive in <5% of staphylococcal TSS cases[22].

2. Streptococcal toxic shock syndrome

Streptococcal TSS more commonly occurs due to deep-seated invasive soft tissue infections such as NF, cellulitis, and myositis[22]. An influenza-like illness also commonly occurs at the early stages characterized by fever, sore throat, swollen lymph nodes, and gastrointestinal distress[22]. About 60% of patients with streptococcal TSS have positive blood cul-

Table 2. Diagnostic criteria for staphylococcal and streptococcal TSS according to CDC recommendations

Staphylococcal TSS	Streptococcal TSS
Clinical criteria	
1. Fever ≥38.9℃. 2. Rash—diffuse macular erythroderma. 3. Desquamation—1~2 weeks after the onset of the illness, particularly on palms and soles. 4. Hypotension—systolic blood pressure ≤90 mm Hg for adults or <5th percentile for children aged <16 years. 5. Multisystem involvement—at least three of the following: a. Gastrointestinal—vomiting or diarrhea b. Muscular—severe myalgia or elevated creatine phosphokinase twice the upper limit of normal c. Mucous membranes—hyperemia of any mucosal surface d. Renal—blood urea nitrogen or creatinine twice the upper normal limit e. Hepatic—total bilirubin twice-upper normal limit f. Hematological—platelets ≤100,000/mm^3 g. Central nervous system disorientation, combativeness, or alterations in consciousness without focal neurological signs	1. Hypotension—systolic blood pressure ≤90 mm Hg in adults or <the fifth percentile by age for children aged <16 years. 2. Two or more of the following signs: a. Renal impairment: Creatinine greater than or equal to 2 mg/dL (>177 μmol/L) for adults or greater than or equal to twice the upper limit to normal age. In the presence of a preexisting renal disease, greater than twofold elevation over the baseline level b. Coagulopathy—platelets of ≤100,000/mm^3 or disseminated intravascular coagulation c. Hepatic involvement: Alanine aminotransferase, aspartate aminotransferase, or total bilirubin twice the upper normal limit. In the presence preexisting liver disease, greater than twofold increase over the baseline level d. ARDS e. Generalized, erythematous, macular rash that may desquamate f. Soft tissue necrosis, including necrotizing fasciitis, myositis, or gangrene.
Laboratory criteria	
Negative results on the following tests: a. Blood, throat, or CSF (blood culture may be positive for *S. aureus*) b. Rise in titer to Rocky Mountain spotted fever, leptospirosis, or measles.	Isolation of group A β-hemolytic streptococci: a. From a normally sterile site (blood, CSF, joint, pericardial, pleural, peritoneal fluid, tissue biopsy); b. From a nonsterile site (throat, vagina, sputum).
Case classification - Probable TSS: a case that meets four of the five clinical and laboratory criteria. - Confirmed TSS: a case that meets all five clinical (including desquamation) and laboratory criteria.	**Case classification** - Probable TTS: a case which fulfills clinical case definition and isolation of group A β-hemolytic streptococci from a normally nonsterile site in the absence of other etiologies for the illness. - Definite TSS: a case that fulfills clinical case definition and isolation of group A β-hemolytic streptococci from a normally sterile site.

TSS: toxic shock syndrome; CSF: cerebrospinal fluid; ARDS: adult respiratory distress syndrome

tures[26]. The mortality rate associated with streptococcal TSS is significantly higher than that of staphylococcal TSS, with incidence as high as 80% when associated with myositis[27].

3. Diagnosis

The Centers for Disease Control and Prevention (CDC) establishes several criteria for diagnosing TSS, though specific components differ between streptococcal and staphylococcus TSS[21,22,28] (Table 2).

4. Treatment

Patients should receive intensive care and resuscitation. With unknown causative organisms, empirical antibiotic therapy should target gram-positive cocci, including traditionally penicillinase-resistant penicillin (e.g., oxacillin, nafcillin) or a first-generation cephalosporin[21]. However, with the increasing occurrence of methicillin-resistant *Staphylococcus aureus*, vancomycin or linezolid is advised for the initial treatment, depending on the local prevalence[21]. GAS remains exquisitely sensitive to β-lactam agents, including penicillin G, an agent often considered one of the first-line therapies[22]. Regarding NF-associated TSS, infection is mostly polymicrobial, and broad-spectrum beta-lactam therapy such as piperacillin plus tazobactam should be administered[28].

CONCLUSIONS

The diseases discussed here and others should be understood and considered as a differential diagnosis, Dermatologists play a crucial role in the suspicion, early diagnosis, and treatment or referral of potentially severe or fatal SSTIs.

CONFLICT OF INTEREST

In relation to this article, I declare that there is no conflict of interest.

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