INTERNAL MEDICINE

□ REVIEW ARTICLE □

Necrotizing Fasciitis

Taro Shimizu[1] and Yasuharu Tokuda[2]

Abstract

Necrotizing fasciitis (NF) is a necrotizing soft tissue infection that can cause rapid local tissue destruction, necrosis and life-threatening severe sepsis. Predisposing conditions for NF include diabetes, malignancy, alcohol abuse, and chronic liver and kidney diseases. NF is classified into two categories (types 1 and 2) based on causative microorganisms. The initial clinical picture of NF mimics that of cellulitis or erysipelas, including fever, pain, tenderness, swelling and erythema. The cardinal manifestations of NF are severe pain at onset out of proportion to local findings, hemorrhagic bullae and/or vital sign abnormality. In such cases, NF should be strongly suspected and immediate surgical intervention should be considered, along with broad-spectrum antimicrobials and general supportive measures, regardless of the findings of imaging tests.

Key words: necrotizing fasciitis, review

(Inter Med 49: 1051-1057, 2010)
(DOI: 10.2169/internalmedicine.49.2964)

Introduction

Necrotizing fasciitis (NF) is a life-threatening soft tissue infection that was first described by Hippocrates around the fifth century. The etiology has been recognized for centuries and the term "Necrotizing Fasciitis" was first used by Joseph Jones, a former Confederate Army surgeon, in 1871 (1). From the clinical point of view, NF is defined as a severe infection of the deep soft tissue, including fascia. It progresses rapidly, leading to significant morbidity and mortality. NF is classically caused by group A streptococcus (Type 2 NF) and may develop Streptococcal Toxic Shock Syndrome (STSS) which is characterized by shock and multiple organ failure due to toxin by group A streptococcus. NF sometimes overlaps with STSS [in 40% of patients with NF, and 6% with other patients ($p<0.001$)] (2). Distinguishing NF from other soft tissue infections is notoriously difficult but crucial, since NF is a surgical emergency that should be treated as a major alarm that requires timely and aggressive surgical debridement. Hence, this disease challenges the diagnostic skills and surgical fortitude of physicians. In this review, we provide a broad description of the clinical characteristics of NF, ranging from epidemiology to overall management.

Epidemiology

The US Centers for Disease Control and Prevention (CDC) has estimated that more than 500 to 1,000 cases of NF are diagnosed each year in the United States (2). However, the accuracy of this estimate is difficult to ascertain because of the many synonyms for these entities. The annual rate of NF has been reported to be 0.40 cases per 100,000 population (3), with a recent exponential increase in this rate (4). NF is caused by infection, and the predisposing factors are considered to include drugs, hypersensitivity, vascular problems, burn, insect bite, needle stick injury, and trauma (5-10). NF can lead to severe sepsis, specifically in patients with immunosuppression, diabetes, malignancy, drug abuse, and chronic kidney disease (11-15). Several reports also indicate that intravenous drug use is a leading risk factor for NF (16-19). NF is seen more frequently in winter, although cases with NF by *Vibrio vulnificus* are seen more frequently in summer seasons, is more common in men (4), and occurs at any age, although the incidence increases with higher age. About 50% of patients have a history of skin injury, 25% have experienced blunt trauma, and 70% have one or more chronic illnesses. Half of cases occur in a single lower limb and one-third in a single upper limb.

[1]Rollins School of Public Health, Emory University, Georgia, Atlanta, USA and [2]Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki
Received for publication October 2, 2009; Accepted for publication February 16, 2010
Correspondence to Dr. Taro Shimizu, shimizutaro7@gmail.com

Symptomatology

NF is difficult to diagnose in the early stage because of nonspecific signs such as tenderness, swelling, erythema, and pain at the affected site that mimic non-severe soft tissue infections (NSTIs) such as cellulitis and erysipelas (10, 11, 20). Among them, the cardinal manifestation in NF is severe pain at onset out of proportion to physical findings (4, 21, 22). *Vibrio* and *Aeromonas* are well known waterborne organisms that cause NF with high mortality through infection of patients with chronic illnesses, especially in the liver. Careful history taking concerning seawater exposure or fish stings (23) with liver or spleen dysfunction is the key to narrowing down the candidate organism.

Physical Diagnosis

Fever (>38℃) is often absent (44%), but tachycardia (>100 beats/min) is usually found (59%), while hypotension (<100 mm Hg) (21%) and tachypnea (>20/min) (26%) are sometimes present. These three vital sign abnormalities suggest NF rather than NSTI with odds ratios (OR) of 3.4 (1.6-7.4), 4.5 (1.7-11.8), and 2.6 (1.1-6.0), respectively (24). Although NF can occur anywhere on the body, it is more common in the extremities (36-55%), trunk (18-64%) and perineum (up to 36%) (11, 18, 25-27). Infected sites have erythema (80%), induration (66%), tenderness (54%), fluctuance (35%), skin necrosis (23%), and bullae (11%) (24). The positive likelihood ratio of the presence of bullae for NF compared to NSTI is 3.5 (1.0-11.9). In another study (17), NF patients differed from NSTI with respect to increased tense edema (23% vs. 3%, $p<0.0002$), purplish skin discoloration (10% vs. 1%, $p=0.02$), and sensory or motor deficit (13% vs. 3%, $p=0.03$). Skin necrosis was present among 6% of NF patients compared to 2% of those with NSTI. The initial physical findings of NF are usually erythematous and ecchymotic skin lesions, but these may rapidly evolve into hemorrhagic bullae, which indicate the occlusion of deep blood vessels in the fascia or muscle compartments; thus the presence of bullae is an especially important diagnostic clue (see Fig. 1). There are variants of NF which involve specific areas of the body, including Ludwig's angina (submandibular space) and Fournier's gangrene (scrotum and penis or vulva) and these can show an explosive onset and aggressive clinical course.

Laboratory Tests

Multiple organ dysfunction may reflect liver and kidney disorders, coagulopathy, and elevated serum creatine kinase (CK) due to severe sepsis (11, 18, 22, 29, 30). Compared to patients with NSTI, leukocytosis is commonly present (84%) (11, 29), especially for patients with WBC $>20\times10^9$/L (OR 3.7; 95% CI 1.6-8.5), blood urea nitrogen >18 mg/dL (OR 6.8; 95% CI 2.9-16.3), and serum creatinine ≥1.2 mg/dL (OR 4.5; 95% CI 1.1-19.5). One study suggested that WBC >15,400/mm^3 and serum Na <135 mmol/L with a careful physical examination may help to separate NF from NSTI in cases that are strongly suspected to be NF[11]. Another study also suggested that CRP>16 mg/dL or CK >600 IU/L should prompt clinicians to exclude a diagnosis of group A streptococcus (GAS) NF and to perform a more expansive diagnostic investigation (31). It is notable that WBC and CRP may not be useful in patients with liver cirrhosis because of impairment of protein-productive function of liver for inflammatory response.

The Laboratory Risk Indicator for NF (LRINEC) score was developed with the hope of yielding diagnostic clues for NF, even early in its evolution (29, 32). This score includes an elevated CRP >150 mg/L (4 points), WBC >25,000/mm^3, blood hemoglobin <11 g/dL, Na <135 mmol/L, serum creatinine >141 μmol/L (2 points each), and blood glucose >10 mmol/L (1 point). The total possible score is 13, and a retrospective study indicated that a score ≥6 was highly indicative of NF, with a 92% positive predictive value and a 96% negative predictive value (33, 34). Frozen section biopsy, computed tomography (CT), magnetic resonance imaging (MRI), or a bedside finger test should be considered for patients with equivocal clinical findings but a moderate or high risk for NF based on the LRINEC score (>5). This score can be helpful in stratifying patients into risk categories for NF, in allocating diagnostic resources, and ultimately in aiding the early recognition of NF. However, since clinical acumen remains of paramount importance, emergent debridement must be performed regardless of the score in cases that are strongly suspected to be NF.

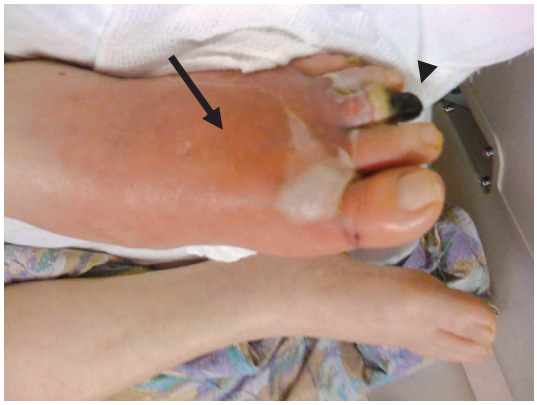

Figure 1. A 50-year-old diabetic woman presented with fever and painful swelling of the left foot with erythema, local heat and bullae (arrow). There was chronic diabetic gangrene of the 3rd phalanx (arrow head). Surgical exploration revealed necrotizing soft tissue infection (necrotizing fasciitis) and subcutaneous abscess. Blood and tissue culture grew methicillin-sensitive *Staphylococcus aureus*. This photograph was obtained with permission of the patient.

Table 1. Causative Bacteria of Type 1 and Type 2 Necrotizing Fasciitis

type 1
polymicrobial infections including anaerobes.
type 2
Streptococcus pyogenes (Group A Streptococcus)
Staphylococcus aureus, including methicillin-sensitive and resistant
Other microbiological etiologies
Vibrio vulnificus
Aeromonas hydrophila
Enterobacteriaceae (*Escherichia coli*, *Pseudomonas* spp., and *Klebsiella* spp)

Bedside Tests

The finger test and frozen section have been used as complementary diagnostic modalities in patients with an equivocal diagnosis. The finger test is a bedside procedure in which, under local anesthesia, a 2-cm incision is made down to the deep fascia and gentle probing of the index finger is performed at the level of the deep fascia. Lack of bleeding, presence of characteristic "dishwater pus", and lack of tissue resistance to blunt finger dissection are features of a positive finger test and indicate NF (35). Another reasonable approach is a bedside incisional biopsy down to the fascial level and an immediate frozen section, culture and gram stain (36). Routine MRI for all patients at the first suspicion of NF is not cost effective (14). Low tissue oxygen saturation measured by near-infrared spectroscopy throughout the involved lower extremities is valuable in differentiating NF from NSTI. Sensitivity is 100% and specificity is 97% at a cut-off saturation level of <70% (33), and this noninvasive method may offer a reliable assessment of lower extremities at risk for NF.

Imaging Tests

Radiologic studies are only considered as adjunct measures for doubtful cases and cannot be used to exclude NF, since many false-negative results can occur with definite NF. Moreover, the extent of debridement can be determined only by physical findings in surgery. A plain radiograph is also usually not helpful, although one study found that 7 of 22 (32%) NF patients had gas on plain X-ray, compared to 6 of 224 (3%) non-NF patients (17). CT (37) or MRI (38) may localize and clarify the extent of tissue involvement by evidence of soft tissue air (24) in a limited subgroup of NF patients (39). However, in particular, MRI can be too sensitive due to its overestimation of deep tissue involvement, and that does not differentiate NF from cellulitis (40). One thing we have to note is that the clinical manifestation of patients with compromised conditions such as diabetes may appear milder than the degree of actual tissue damage shown in images.

Microbiology

Gram staining of affected tissues can be used for microbiological diagnosis in NF. Blood and debrided tissues should also be sent for culture. Microscopic examination may reveal coagulation necrosis of superficial fascia, subcutaneous fat, and occasionally deep fascia. Inflammatory cellular infiltration, thrombosis of blood vessels, and necrosis of subcutaneous glands may be present (41), with or without apparent bacterial infiltration. NF is categorized as types 1 and 2 on the basis of microbiological cultures (22, 28, 42): type 1 is a polymicrobial infection by aerobic and anaerobic bacteria in people with immunocompromised or chronic diseases such as diabetes; type 2 involves group A Streptococcus (GAS) with or without a coexisting staphylococcal infection which can occur in any age group even without any complicated medical illnesses. The pathophysiology of GAS NF has been associated with Streptococcal M proteins type 1 and 3 (14, 40), exotoxins A and B, or mitogenic factors that stimulate the immune system to cause cytokine storm, leading to shock, organ failure, and myocardial and immune suppression. Proteases and other enzymes generated from *Streptococcus* may also contribute to tissue destruction (22). It is unclear which type is dominant (42-48) and a substantial portion of cultures have been found to be negative for NF in these studies, which may be due to the prior use of antibiotics before obtaining the wound culture.

In an analysis of wound and blood cultures (49), blood cultures with a single organism, multiple organisms and no organism were found in 27%, 2% and 71% of cases, respectively. For the wound cultures (49), a single organism, multiple organisms, and no organism were found in 53%, 23% and 23% of cases, respectively. In terms of monomicrobial infections, *Streptococcul* spp. (especially group A), *S. aureus, V. vulnificus, A. hydrophila*, *Enterobacteriaceae* (*Escherichia coli*, *Pseudomonas* spp., and *Klebsiella* spp.), *Clostridium perfringens* (*gas gangrene*) and anaerobic streptococcus are common. Table 1 shows microorganisms causing NF. Although *Aeromonas hydrophila* and *Vibrio vulnificus* are rare organisms, they produce several virulent factors that can lead to fatal sepsis more rapidly than in cases with *Streptococcus pyogenes* (50-53), resulting in up to a 50% mortality rate within 48 hours after admission (54). Most

Table 2. Treatment of Necrotizing Fasciitis, First-line Antimicrobial Agent, by Infection Type

Mixed infection	*Streptococcus* infection
Ampicillin-sulbactam	Penicillin
or	**plus**
pipellacillin-tazobactam	clindamycin
plus	*S. aureus* infection
clindamycin	Cefazolin
plus	Vancomycin(for resistant strains)
ciprofloxacin	Clindamycin
Imipenem/cilastatin	*Clostridium* infection
Meropenem	Clindamycin
Cefotaxime	Penicillin
plus	
metronidazole	
or	
Clindamycin	

[a] If *Staphylococcus* infection is present or suspected, add an appropriate agent. iv, intravenously.

(Alteration from IDSA(Infectious Disease Society of America) guideline: http://www.idsociety.org/Content.aspx?id=9088.)

patients infected with *Vibrio vulnificus* have a history of underlying chronic illness (cirrhosis, alcoholic liver disease, gouty arthritis, chronic renal failure, or diabetes mellitus) or chronic use of steroids (55). Chronic hepatic dysfunction or adrenal insufficiency may alter neutrophil and macrophage functions, resulting in immunosuppression. In cirrhotic patients, these marine organisms can easily establish systemic bacteremia by gaining access to the gastrointestinal tract and escaping phagocytosis by the Kuppfer cells of the reticuloendothelial system in the liver, due to shunting through the portal-systemic circulation (56). This can facilitate rapid spread of infection and result in septic shock.

Medical Therapy

Patients with suspected NF should be empirically and immediately managed with broad-spectrum antibiotics covering the commonly suspected organisms. Table 2 shows the first-line antimicrobial agents of NF. In type 1 infection, the antibiotic treatment should be determined based on history, Gram stain and culture. The advocated initial treatment includes ampicillin or ampicillin-sulbactam combined with metronidazole or clindamycin (11, 18, 26, 27). The coverage of anaerobes is quite essential for type 1 disease. Metronidazole or clindamycin, or the use of beta-lactams with beta-lactamase inhibiter or carbapenems are appropriate choice for anaerobes. If patients have histories of prior hospitalization or antibiotics exposure, broader gram-negative coverage should be necessary as an initial empirical therapy. ampicillin- sulbactam, piperacillin-tazobactum, ticarcillin-clavulanate, higher generation cephalosporins or carbapenems are the candidate agents in this setting. In type 2 disease, the causative organism is mostly GAS but sometimes MSSA/MRSA. In place of ampicillin/penicillin, first generation cephalosporins (such as cefazolin) or vancomycin can be used for coverage of methicillin-sensitive *Staphylococcus aureus* (*MSSA*) or methicillin-resistant *Staphylococcus aureus* (*MRSA*), respectively. Several authors suggest that clindamycin is superior to penicillin in overwhelming streptococcal infections (57), since clindamycin works by inhibiting bacterial protein synthesis and is not subject to the inoculum effect of large numbers of slow-growing organisms with depressed expression of penicillin-binding proteins (22). Furthermore, another study proposed that clinicians should consider adding clindamycin to the beta-lactam antibiotic regimen when NF or myositis is present (58). On the other hand, it is remarkable that the emerging clindamycin resistance of *Streptococcus pyogenes* may have serious implications in the treatment of severe S. pyogenes infections (59). Antimicrobials should be narrowed down based on the results of initial blood, wound and tissue cultures, but should be continued until the infection is under control and for at least 48 hour after the temperature and WBC have returned to normal or after stabilization of clinical conditions. Early use of tetracyclines (including doxycycline and minocycline) and third-generation cephalosporins is crucial if *Vibrio* infection is suspected, since this greatly reduces the mortality rate (60-64). The duration of the antibiotic therapy for NF is generally recommended from four to six weeks, as it is deep-seeded infection. Intravenous immunoglobulin (IVIG) is reasonable and a desirable option to neutralize streptococcal toxins. Several authors argue that high dose IVIG may benefit in severe GAS infections (65-69). Although these studies evaluated a small number of patients and thus there is a need for further studies, it is worth considering as a possible option in severe cases. Evidence on adjunctive treatment with hyperbaric therapy has yet to be established. The guideline for management of NF is available in the Infectious Diseases Society of America (IDSA) webpage (http://www.idsociety.org/Content.aspx?id=9088.)

Surgical Therapy

Surgical debridement is the mainstay of treatment of NF

and results in significantly improved mortality compared to cases in which surgery is delayed for even a few hours (25). When NF is suspected, patients should be brought to an operating room as soon as possible for a "search and destroy" mission of aggressive and extensive debridement. Involved tissues should be resected thoroughly until there is no further evidence of infection. Initial surgery is the most important determinant for survival and the wound must be inspected closely after the initial debridement. If further debridement is needed, the patient must be returned to the operating room swiftly. A "second-look" surgery is typically done 12 to 24 hours after the initial debridement. Patients with NF may require anywhere from five to 40 sessions of surgery, and one study found an average of 33 debridements and grafting procedures (3). Removal of the tissues with adequate margins is recommended, rather than leaving only actively infected or necrotic tissue, otherwise it could relapse from the remaining infected tissue. While early aggressive surgery is crucial for improving survival (25, 44, 46, 64-73), it is not a predictor of mortality when the pathogens are *Aeromonas* or *Vibrio* (49). In such cases, more aggressive intervention may be indicated; for example, an early operation within 12 hours, not merely within 24 hours (74, 75). The characteristic feature of NF is easy separation of the fascia from other tissues by blunt dissection, due to necrosis of the fascia and liquefaction of subcutaneous tissue. Muscle is usually spared, but myonecrosis may develop secondary to the accompanying compartment syndrome. Careful follow-up of the surgical wound is also important to detect the development of surgical site infection.

Surgical consultation is indicated for patients with the following conditions: 1) unusual pain, 2) skin color change such as ecchymosis, 3) altered mental status, 4) elevated band formed in the differential WBC count, 5) metabolic acidosis, and 6) emergence of hemorrhagic bullae, especially in cirrhotic conditions (56). Prior to surgery, supportive measures are also of paramount importance, including hemodynamic support, wound care, and nutritional support. Hemodynamic instability is often present, and stabilizing these conditions in an intensive care unit is important to ensure that the patient endures the disease and surgery. Once the infection is controlled, daily dressing is needed at the bedside under sedation, followed by secondary suturing of the wounds with or without split skin grafts to cover the exposed underlying tissues. Dressing changes with hydrogel may assist tissue granulation (19). Although costly, a vacuum-assisted wound closing (VAC) device has been found to be effective for non-healing limb wounds, with reduced morbidity compared to the conventional technique (76). Nutritional support is required from the first day of admission, for compensation for lost protein and fluid from the large wounds. Metabolic demands are similar to those of other major trauma or burns. In general, patients with severe tissue defects should receive twice their basal caloric requirements (77). A nasogastric tube for feeding is sometimes required to maintain adequate enteral nutrition.

Prognosis

The mortality of NF has been reported in recent studies to be approximately 25%, but it is higher in some reports (10, 11, 18, 19, 25, 43). Patients with toxic shock syndrome (TSS) have a higher mortality of 67% (4). An advanced age (>65 years old); hypotension, leucopenia, and bacteremia; *Aeromonas* or *Vibrio* infection; band-form blood leukocytes >10%; high APACHE (Acute Physiology, Age, and Chronic Health Evaluation) II scores (>13); and use of NSAIDs in GAS NF are also associated with increased mortality (4, 49, 50, 78-80). Regarding the use of specific antimicrobials (4), there appears to be a trend toward better survival with therapy including clindamycin.

Prevention

There have been few studies on contact prophylaxis, but this issue has been discussed by the Ontario group (4), who found a 12% rate of colonization among 152 household contacts of patients with invasive GAS infections. The secondary incidence for invasive GAS infection was about 3/1,000 among household contacts of NF patients, with the risk estimated to be similar to that in contacts of patients with sporadic meningococcal infection. Hence, although the best approach to prophylaxis is unclear, careful hand washing is recommended among healthcare providers and family members. All contacts should be counseled about signs and symptoms of infection and, if these are recognized, advised to go immediately to an emergency department for a full examination and prompt treatment.

Conclusions

NF is an uncommon but serious infectious disease for which accurate diagnosis is often difficult at the initial presentation, which may result in a delay of appropriate surgical intervention. Predisposing factors and conditions include an older age, chronic illness (such as alcoholism and diabetes mellitus) and male gender, as well as possibly underlying immune deficiency. NF patients commonly present with severe pain at infected sites with erythema and tenderness. NF should be strongly suspected when the severity of pain seems to be dissociated from the physical findings (usually in one limb), along with clinical and laboratory signs of severity and organ dysfunction. Urgent surgical consultation is required as soon as possible. Treatment includes definitive surgical debridement in conjunction with antimicrobials and hemodynamic stabilization. Surgical debridement should be performed frequently (even daily) until the acute tissue destruction has been controlled. Overall mortality remains high and is increased by factors such as hypotension, bacteremia, *Vibrio* or *Aeromonas* as causative microorganisms, and high APACHE II scores. Outcomes are also influenced by prompt

diagnosis, the timing and extent of surgical treatment, and management of postoperative complications.

Acknowledgement

This study was supported by a research grant (No. H19-016) from the Japanese Ministry of Health, Labor and Welfare.

References

1. Jones J. Surgical Memoirs of the War of the Rebellion. In: Investigation upon the nature, causes and treatment of hospital gangrene as it prevailed in the Confederate armies. US Sanitary Commission, New York, NY, 1871: 1861-1865.
2. The Centers for Disease Control and Prevention, 2009. Group A Streptococcal (GAS) disease http://www.cdc.gov/ncidod/dbmd/diseaseinfo/groupastreptococcal_g.htm Severe *Streptcoccus pyogenes* Infections, United Kingdom, 2003-2004 http://www.cdc.gov/EID/content/14/2/pdfs/202.pdf Superantigens and Streptococcal Toxic Shock Syndrome http://www.cdc.gov/ncidod/EID/vol9no10/03-0042.htm
3. File TM Jr, Tan JS, DiPersio JR. Group A streptococcal necrotizing fasciitis. Diagnosing and treating the "flesh-eating bacteria syndrome". Cleve Clin J Med **65**: 241-249, 1998.
4. Kaul R, McGeer A, Low DE, Green K, Schwartz B. Population-based surveillance for Group A streptococcal necrotizing fasciitis: clinical features, prognostic indicators, and microbiologic analysis of seventy-seven cases. Ontario Group A Streptococcal Study. Am J Med **103**: 18-24, 1997.
5. Made S. Skin and soft tissue infections. Top Emerg Med **25**: 117-122, 2003.
6. Horn JR, Danziger LH, Davis RJ. Warfarin-induced skin necrosis: report of four cases. Am J Hosp Pharm **38**: 1763-1768, 1981.
7. Wolf D, Ben-Yehuda A, Okon E, Naparstek Y. Nodular vasculitis associated with propylthiouracil therapy. Cutis **49**: 253-255, 1992.
8. Fan PC, Chang HN. Hypersensitivity to mosquito bite: a case report. Gaoxiong Yi Xue Ke Xue Za Zhi **11**: 420-424, 1995.
9. Perkins JMT, Magee TR, Galland RB. Phlegmasia caerulea dolens and venous gangrene. Br J Surg **83**: 10-23, 1996.
10. Singh G, Sinha SK, Adhikary S, Babu KS, Ray P, Khanna SK. Necrotising infections of soft tissues--a clinical profile. Eur J Surg **168**: 366-371, 2002.
11. Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections. Risk factors for mortality and strategies for management. Ann Surg **224**: 672-683, 1996.
12. Kotrappa KS, Bansal RS, Amin NM. Necrotizing fasciitis. Am Fam Physician **53**: 1691-1697, 1996.
13. Gonzalez MH. Necrotizing fasciitis and gangrene of the upper extremity. Hand Clin **14**: 635-645, 1998.
14. Green RJ, Dafoe DC, Raffin TA. Necrotizing fasciitis. Chest **110**: 219-229, 1996.
15. Chapnick EK, Abter EI. Necrotizing soft-tissue infections. Infect Dis Clin North Am **10**: 835-855, 1996.
16. Chen JL, Fullerton KE, Flynn NM. Necrotizing fasciitis associated with injection drug use. Clin Infect Dis **33**: 6-15, 2001.
17. Wall DB, Klein SR, Black S, de Virgilio C. A simple model to help distinguish necrotizing fasciitis from non-necrotizing soft tissue infection. J Am Coll Surg **191**: 227-231, 2000.
18. Bosshardt TL, Henderson VJ, Organ CH Jr. Necrotizing soft-tissue infections. Arch Surg **131**: 846-852, 1996.
19. Childers BJ, Potyondy LD, Nachreiner R, et al. Necrotizing fasciitis: a fourteen-year retrospective study of 163 consecutive patients. Am Surg **68**: 109-116, 2002.
20. Burget T. Necrotizing fasciitis? The hazards of delay. J R Soc Med **88**: 342-343, 1995.
21. Hoge CW, Schwartz B, Talkington DF, Breiman RF, MacNeill EM, Englender SJ. The changing epidemiology of invasive Group A streptococcal infections and the emergence of streptococcal toxic shock-like syndrome. A retrospective population-based study. JAMA **269**: 384-389, 1993.
22. Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. N Engl J Med **334**: 240-245, 1996.
23. Hlady WG, Klontz KC. The epidemiology of Vibrio infections in Florida, 1981-1993. J Infect Dis **173**: 1176-1183, 1996.
24. Frazee BW, Fee C, Lynn J, et al. Community-acquired necrotizing soft tissue infections: a review of 122 cases presenting to a single emergency department over 12 years. J Emerg Med **34**: 139-146, 2008.
25. McHenry CR, Piotrowski JJ, Petrinic D, Malangoni MA. Determinants of mortality for necrotizing soft-tissue infections. Ann Surg **221**: 558-563, 1995.
26. Lille ST, Sato TT, Engrav LH, Foy H, Jurkovich GJ. Necrotizing soft tissue infections: obstacles in diagnosis. J Am Coll Surg **182**: 7-11, 1996.
27. Rubinstein E, Dehertogh D, Brettman L. Severe necrotizing soft tissue infections: report of 22 cases. Conn Med **59**: 67-72, 1995.
28. Fontes RA Jr, Ogilvie CM, Miclau T. Necrotizing soft-tissue infections. J Am Acad Orthop Surg **8**: 151-158, 2000.
29. Wong C, Khin L. Clinical relevance of the LRINEC (laboratory risk indicator for necrotizing fasciitis) score for assessment of early necrotizing fasciitis. Crit Care Med **33**: 1677, 2005.
30. Wall DB, de Virgilio C, Black S, Klein SR. Objective criteria may asssist in distinguishing necrotizing fasciitis from non-necrotizing soft tissue infection. Am J Surg **179**: 17-21, 2000.
31. Majeski JA, Alexander JW. Early diagnosis, nutrition support, and immediate extensive debridement improve survival necrotizing fasiciitis. Am J Surg **145**: 785-787, 1983.
32. Wong C, Khin L, Heng K, Tan K, Low C. The LRINEC (laboratory risk indicator for necrotizing fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med **32**: 1535-1541, 2004.
33. Wang T, Hung CR. Role of tissue oxygen saturation monitoring in diagnosing necrotizing fasciitis of the lower limbs. Ann Emerg Med **44**: 222-228, 2004.
34. Wong C, Wang Y. The diagnosis of necrotizing fasciitis. Curr Opin Infect Dis **18**: 101-106, 2005.
35. Andreasen TJ, Green SD, Childers BJ. Massive infectious soft tissue injury: diagnosis and management of necrotizing fasciitis and purpura fulminans. Plast Reconstr Surg **107**: 1025-1034, 2001.
36. Majeski J, Majeski E. Improved survival with early recognition by tissue biopsy and aggressive surgical treatment. South Med J **90**: 1065-1068, 1997.
37. Yamaoka M, Furusawa K, Uematsu T, Yasuda K. Early evaluation of necrotizing fasciitis with use of CT. J Craniomaxillofac Surg **22**: 268-271, 1994.
38. Rahmouni A, Chosidow O, Mathieu D, et al. MR imaging in acute infectious cellulitis. Radiology **192**: 493-496, 1994.
39. Fugitt JB, Puckett ML, Quigley MM, Kerr SM. Necrotizing fasciitis. Radiographics **24**: 1472-1476, 2004.
40. Schmid MR, Kossmann T, Duewell S. Differentiation of necrotizing fasciitis and cellulitis using MR imaging. AJR Am J Roentgenol **170**: 615, 1998.
41. Scully R, Mark E, McNeely W, McNeely B. Case records of the Massachusetts General Hospital. N Engl J Med **331**: 1362-1368, 1994.
42. Elliott D, Kufera JA, Myers RA. The microbiology of necrotizing soft tissue infections. Am J Surg **179**: 361-366, 2000.
43. Wong CH, Chang HC, Pasupathy S, Khin LW, Tan JL, Low CO.

Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. J Bone Joint Surg Am **85-A**: 1454-1460, 2003.

44. Stone DR, Gorbach SL. Necrotizing fasciitis. The changing spectrum. Dermatol Clin **15**: 213-220, 1997.

45. Zahar JR, Goveia J, Lesprit P, Brun-Buisson C. Severe soft tissue infections of the extremities in patients admitted to an intensive care unit. Clin Microbiol Infect **11**: 79-82, 2005.

46. Qazi SA, Mohammed AA, Saber EI, Mirza SM. Necrotizing fasciitis. Role of early surgical intervention. Saudi Med J **25**: 890-894, 2004.

47. Endorf FW, Supple KG, Gamelli RL. The evolving characteristics and care of necrotizing soft-tissue infections. Burns **31**: 269-273, 2005.

48. Taviloglu K, Cabioglu N, Cagatay A, et al. Idiopathic necrotizing fasciitis: risk factors and strategies for management. Am Surg **71**: 315-320, 2005.

49. Hsiao CT, Weng HH, Yuan YD, Chen CT, Chen IC. Predictors of mortality in patients with necrotizing fasciitis. Am J Emerg Med **26**: 170-175, 2008.

50. Seal DV. Necrotizing fasciitis. Curr Opin Infect Dis **14**: 127-132, 2001.

51. Fujisawa N, Yamada H, Kohda H, Tadano J. Necrotizing fasciitis caused by Vibrio vulnificus differs from that caused by streptococcal infection. J Infect **36**: 313-316, 1998.

52. Cerveny KE, DePaola A, Duckworth DH, Gulig PA. Phage therapy of local and systemic disease caused by Vibrio vulnificus in iron-dextran-treated mice. Infect Immun **70**: 6251-6262, 2002.

53. Howard RJ, Lieb S. Soft-tissue infections caused by halophilic marine vibrios. Arch Surg **123**: 245-249, 1988.

54. Chiang SR, Chuang YC. Vibrio vulnificus infection: clinical manifestations, pathogenesis, and antimicrobial therapy. J Microbiol Immunol Infect **36**: 81-88, 2003.

55. Chuang YC, Yuan CY, Liu CY, Lan CK, Huang AH. Vibrio vulnificus infection in Taiwan: report of 28 cases and review of clinical manifestations and treatment. Clin Infect Dis **15**: 271-276, 1992.

56. Liu BM, Hsiao CT, Chung KJ, Kung CT, Hung SC, Liu PP. Hemorrhagic bullae represent an ominous sign for cirrhotic patients. J Emerg Med **34**: 277-281, 2008.

57. Zimbelman J, Palmer A, Todd J. Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive Streptococcus pyogenes infection. Pediatr Infect Dis J **18**: 1096, 1999.

58. Mulla ZD. Treatment options in the management of necrotising fasciitis caused by Group A Streptococcus. Expert Opin Pharmacother **5**: 1695-1700, 2004.

59. Walsh SR, Ferraro MJ, Durand ML. Clindamycin-resistant Streptococcus pyogenes: report of a case. Diagn Microbiol Infect Dis **49**: 223-225, 2004.

60. Dalsgaard A, Frimodt-Moller N, Bruun B, Hoi L, Larsen JL. Clinical manifestations and molecular epidemiology of Vibrio vulnificus infections in Denmark. Eur J Clin Microbiol Infect Dis **15**: 227-232, 1996.

61. Tang HJ, Chang MC, Ko WC, Huang KY, Lee CL, Chuang YC. *In vitro* and *in vivo* activities of newer fluoroquinolones against Vibrio vulnificus. Antimicrob Agents Chemother **46**: 3580-3584, 2002.

62. Liu JW, Lee IK, Tang HJ, et al. Prognostic factors and antibiotics in Vibrio vulnificus septicemia. Arch Intern Med **166**: 2117-2123, 2006.

63. Bowdre JH, Poole MD, Oliver JD. Edema and hemoconcentration in mice experimentally infected with Vibrio vulnificus. Infect Immun **32**: 1193-1199, 1981.

64. Klontz KC, Lieb S, Schreiber M, Janowski HT, Baldy LM, Gunn RA. Syndromes of Vibrio vulnificus infections. Clinical and epidemiologic features in Florida cases, 1981-1987. Ann Intern Med **109**: 318-323, 1988.

65. Norrby-Teglund A, Muller MP, Mcgeer A, et al. Successful management of severe group A streptococcal soft tissue infection using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a concervative surgical approach. Scand J Infect Dis **37**: 166, 2005.

66. Kaul R, McGEER A, Norrby-Teglund A. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome—a comparative observational study. Clin Infect dis **28**: 800-807, 1998.

67. Barry W, Hudgins L, Donta S, et al. Intravenous immunoglobulin therapy for toxic shock syndrome. J Am Med Assoc **267**: 3315-3316, 1992.

68. Young JM. Necrotising fasciitis. Lancet **343**: 1426, 1994.

69. Lamothe F, D'Amico P, Ghosen P, et al. Clinical usefulness of intravenous gammaglobulins in group A streptococcal infections: case report and review. Clin Infect Dis **21**: 1469-1470, 1995.

70. Cunningham JD, Silver L, Rudikoff D. Necrotizing fasciitis: a plea for early diagnosis and treatment. Mount Sinai J Med **68**: 253-261, 2001.

71. Voros D, Pissiotis C, Georgantas D, Katsaragakis S, Antoniou S, Papadimitriou J. Role of early and extensive surgery in the treatment of severe necrotizing soft tissue infection. Br J Surg **80**: 1190-1191, 1993.

72. Ward RG, Walsh MS. Necrotizing fasciitis: 10 years' experience in a district general hospital. Br J Surg **78**: 488-489, 1991.

73. Bilton BD, Zibari GB, McMillan RW, Aultman DF, Dunn G, McDonald JC. Aggressive surgical management of necrotizing fasciitis serves to decrease mortality: a retrospective study. Am Surg **64**: 397-400, 1998.

74. Riseman JF, Zamboni WA, Curtis A, Graham DR, Konrad HR, Ross DS. Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridements. Surgery **108**: 847-850, 1990.

75. Frota Filho JD, Drews C, Leaães P, et al. Postoperative necrotizing fasciitis of the thorax in cardiac surgery. Arq Bras Cardiol **76**: 245-254, 2001.

76. Huang W, Hsieh S, Hsieh C, Schoung J, Huang T. Use of vacuum-assisted wound closure to manage limb wounds in patients suffering from acute necrotizing fasciitis. Asian J Surg **29**: 135-139, 2006.

77. Simonart T, Simonart JM, Derdelinckx I, et al. Value of standard laboratory tests for the early recognition of group A β-Hemolytic streptococcal necrotizing fasciitis. Clin Infect Dis **32**: e9-e12, 2000.

78. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med **13**: 818-829, 1985.

79. Yilmazlar T, Ozturk E, Alsoy A, Ozguc H. Necrotizing soft tissue infections: APACHE II score, dissemination, and survival. World J Surg **31**: 1858-1862, 2007.

80. Rimailho A, Riou B, Richar C, Auzepy P. Fulminant necrotizing fasciitis and nonsteroidal anti-inflammatory drugs. J Infect Dis **155**: 143-145, 1987.