Necrotizing Fasciitis: How Reliable are the Cutaneous Signs?

Ho Jun Kiat¹, Yap Hui En Natalie¹, Lateef Fatimah¹²

¹Yong Loo Lin Medical School, National University of Singapore, ²Senior Consultant, Department of Emergency Medicine, Singapore General Hospital, Associate Professor, Duke NUS Graduate Medical School, Singapore

Abstract

Necrotizing fasciitis (NF) is a surgical emergency. It is often aggressive and characterized by the rapidly progressive inflammatory infection of the fascia that causes extensive necrosis of the subcutaneous tissue and fascia, relatively sparing the muscle and skin tissue. As the disease progresses, thrombosis of the affected cutaneous perforators subsequently devascularizes the overlying skin. The course indeed can be a fulminant one. The diagnosis of NF, especially in the early stages, is extremely challenging, and it can be very close in presentation to other skin and subcutaneous tissue infections. The primary site of the pathology is the deep fascia. Necrosis of the tissues and fascia may manifest as erythema without sharp margins, swelling, warmth, shiny, and exquisitely tender areas. Pain out of proportion to physical examination findings may be observed. The subcutaneous tissue may be firm and indurated such that the underlying muscle groups cannot be distinctly palpated. Eventually, as the overlying skin is stripped of its blood supply, skin necrosis ensues and hemorrhagic bullae form. Bacteremia and sepsis invariably develop when the infection is well established. This paper discusses some of issues related to the cutaneous signs found in NF and also provides a review the current, available literature on the subject matter.

Keywords: Group A Streptococcus, hemorrhagic bulla, necrosis, necrotizing fasciitis, sepsis, types

INTRODUCTION

Necrotizing fasciitis (NF) is a surgical emergency. It is often aggressive and insidiously advancing, characterized by the rapidly progressive inflammatory infection of the fascia that causes extensive necrosis of the subcutaneous tissue and fascia, relatively sparing the muscle and skin tissue. This is primarily due to the better blood supply of the muscles as compared to the fascia. As the disease progresses, thrombosis of the affected cutaneous perforators subsequently devascularizes the overlying skin. The course indeed can be a fulminant one.[¹,²]

The primary site of the pathology is the deep fascia. Necrosis of the tissues and fascia may manifest as erythema without sharp margins, swelling, warmth, shiny, and exquisitely tender areas. Pain out of proportion to physical examination findings may be observed. The subcutaneous tissue may be firm and indurated such that the underlying muscle groups cannot be distinctly palpated. Eventually, as the overlying skin is stripped of its blood supply, skin necrosis ensues and hemorrhagic bullae form. Bacteremia and sepsis invariably develop when the infection is well established.[¹,²,⁴]

The stages and types of necrotizing fasciitis

Early diagnosis is important for treatment and saving the life of the patient. The diagnosis is primarily based on the clinical findings. Clinical characteristics of NF are usually classified in three stages. The early stage of NF may not be distinguished clinically from other soft-tissue infections such as erysipelas and cellulitis, but there are other helpful clinical features such as poorly defined and indistinct margins and tenderness beyond the involved area, warmth, swelling, and induration. In the intermediate stage, there is often blisters or bullae formation with serous fluid. Purpura may or may not be found but does not preclude the diagnosis of NF. The areas surrounding these lesions tend to be more erythematous as the advanced stage sets in with skin discoloration, duskeness, necrosis and at times, eschar tissue formation.[¹,²,⁴]

Address for correspondence: Prof. Lateef Fatimah, Department of Emergency Medicine, Singapore General Hospital, Outram Road, 1 Hospital Drive, 169608, Singapore. E-mail: fatimah.abd.lateef@singhealth.com.sg

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Kiat HJ, En Natalie YH, Fatimah L. Necrotizing fasciitis: How reliable are the cutaneous signs? J Emerg Trauma Shock 2017;10:205-10.

Received: 30.04.17. Accepted: 02.05.17.
The cutaneous signs pointing toward NF in the early stages are easily confused with cellulitis and other skin and subcutaneous infections. NF can be suspected if the followings are seen:\[3,4\]

- Rapid progression of the cutaneous lesion
- Poor therapeutic response to usual modality of treatment and drugs
- Blistering necrosis sets in
- Dusky and cyanosis of the tissue
- Extreme local tenderness, more exaggerated than what it tends to appear
- Associated systemic signs such as high temperature, sepsis, tachycardia, hypotension, and altered mental state presentation.

NF is typically classified based on bacterial morphology; Type I NF and Type II NF. Type I is characterized by the presence of polymicrobial bacteria involving both aerobic or anaerobic bacteria. In Type I infection, at least one anaerobic species of NF is also interesting. For example, this takes place when Group A streptococcus infection happens in combination with one or more facultative anaerobic streptococci (other than group A) and members of the Enterobacteriaceae (e.g., Escherichia coli, Enterobacter, Klebsiella, Proteus).\[5,6\]

Conversely, Type II NF is characterized by monomicrobial bacteria. It is most commonly caused by Group A Streptococcus (GAS). In cases with no clear portal of entry, the pathogenesis of infection likely consists of hematogenous translocation of GAS from the throat (asymptomatic or symptomatic pharyngitis) to a site of blunt trauma or muscle strain. Other common organisms include Aeromonas hydrophila and Vibrio vulnificus, which being marine bacteria, cause NF in association with freshwater and seawater injuries, respectively. Type III NF is also known as clostridial myonecrosis or gas gangrene. This type of skeletal muscle infection may also be related to recent surgery or trauma. Type IV NF, the more recently described type, is fungal NF. Candida species may be the etiological agent but at times can occur in combination with a bacterial etiology.\[4,6-12\]

The pathophysiology of NF is also interesting. For example, when Group A strep adheres and infects host cells, it will deliver 2 types of streptolysin toxins into these cells. These toxins impair the mechanism for quality control of protein synthesis. It also triggers a defense stress response which increases the production of asparaginase, which alters the gene expression profile and rate of proliferation which can be deadly in the host.\[13\]

There is also a phenomenon described as subacute NF which runs a more indolent course. In these cases, there may be complaints of areas of festering soft-tissue infection with minimal pain or discomfort. This can fester for weeks to months, before a sudden deterioration taking on a more fulminant course happens. This makes the diagnosis of NF even more challenging, especially if it takes on this more subacute course of progression. Some have considered the presentation and clinical signs too mild in these early stages entertain the possibility of NF. In retrospect, there have been cases whereby the progression is certain and delay in diagnosis can result in higher morbidity and mortality.\[14,15\]

**Objective**

The objective of this review is to determine the reliability of cutaneous signs in NF and to provide an update on what the latest literature has with regard to the aforementioned topic. It will also collate some of the more important observations and descriptions that have been made.

**Methodology**

Search engines such as PubMed, UpToDate, and Google Scholar were used in this literature review. These search engines were utilized in a systematic literature search from January 2000 to March 2017. The keywords used with “necrotizing fasciitis,” “cutaneous signs,” “diagnosis,” “retrospective studies,” and “reliability.” Results were filtered to include only retrospective studies undertaken in humans and published in English.

In the initial phase of search, it was noted that several literature reviews encompassing the similar topic had already been carried out. Of note, the most extensive, complete, and recent literature review was a prominent study: “Early diagnosis of necrotising fasciitis” by Goh et al. This study reviewed articles from January 1980 to May 2013 and incorporated a total of nine case studies. However, seven out of the nine studies included patients only till 2005.\[16\] This study is heavily quoted with more than seventy citations in much of the more recent literature or research surrounding NF. Thus, it was determined that an updating of the literature was necessary.

Studies were included if they met the following: (1) studies published after 2013; (2) studies beyond the time frame of the earlier literature review; and (3) studies that recorded the incidence of presenting signs and symptoms.

**Data extraction and assessment of methodological quality**

Data extraction and analysis were undertaken by two reviewers independently. Disagreements on the quality of the study chosen were resolved by consensus. Baseline data collected were year of publication, period of the study, country of study, and diagnosis of NF. Specific outcome data collected were incidence of signs and symptoms at presentation. This was based on the specific parameters provided by the earlier literature review by Goh et al. They include erythema, warmth, pain/tenderness, swelling, bullae, crepitus, and skin necrosis.\[16\]

**Discussion of Results**

**Reliability of cutaneous signs**

Based on the earlier literature review by Goh et al., the top three presenting clinical features in NF were swelling (80.8%), pain (79.0%), and erythema (70.7%). After reviewing the
recent literature, the results corroborated closely, with the most common initial signs seen remaining the same: swelling (79%), pain (76.9%) and erythema (69.6%) [Tables 1 and 2].

Classically, patients with NF present with the triad of pain, swelling, and erythema. Yet, other diagnoses present similarly, namely, soft-tissue infections such as cellulitis, impetigo, erysipelas, and early abscesses. The most consistent feature of early NF is that the pain is out of proportion to the swelling or erythema. Other distinct features may serve as diagnostic clues: Tenderness extending beyond the apparent involved area due to the spread of the infection along the fascia below the surface of the skin (the spread of enzymes and toxins causes irritation to its contact surfaces); margins of tissue involvement being indistinct; lymphangitis being rarely seen in NF because the infection is in the deep fascia and not in the skin; and the rapid progression of NF despite antibiotic therapy. Repeated physical examination and clinical assessment of the patient with a visual pain score and marking of the spread of the infection are useful. After 2 or 3 days of constitutional symptoms, suprallesional vesiculation and bullae formation may occur, with serosanguineous fluid leak (intermediate stage of NF).

The progression of NF is marked by the development of clear blisters/bullae. This is the clearest way to distinguish the intermediate stage between early NF (apart from the cutaneous features mentioned above) and late NF. Late stage of NF is characterized by skin necrosis and crepitus formation. It is noted that this corresponds with the review’s findings; bullae formation occurs in 44.5% while skin necrosis and crepitus occur less frequently 23.5% and 4.9%, respectively. Painless ulcers may spread along tissue planes. Black necrotic eschar may also be seen at the borders of the affected areas. In some cases, metastatic cutaneous plaques may occur. Other lesions include purpura with or without bullae formation which

### Table 1: Literature review from Goh et al.

| Country            | Elliott et al. | Frazee et al. | Dworkin et al. | Nisbet et al. | Singh et al. | Wong et al. | Hsiao et al. | Huang et al. | Park et al. | Total |
|--------------------|----------------|----------------|----------------|--------------|--------------|-------------|-------------|-------------|------------|-------|
| Time frame of study| 1985-1993      | 1990-2001      | 1999-2002      | 2000-2006    | 1990-1995    | 1997-2002   | 2002-2005   | 2003-2009   | 1998-2006  | 1985-2009 |
| Date of publication| 1996           | 2008           | 2009           | 2011         | 2002         | 2003        | 2008        | 2011        | 2009      | 1996-2011 |
| Number of patients | 198            | 122            | 80             | 82           | 75           | 89          | 128         | 472         | 217       | 1463   |

### Table 2: Updated literature review

| Country            | Stigt et al. | Hodgens et al. | Pauline et al. | Misiakos et al. | Arifi et al. | Kiralj et al. | Jabbour et al. | Wang et al. | Total |
|--------------------|--------------|----------------|----------------|-----------------|--------------|--------------|----------------|-------------|-------|
| Time frame of study| 2003-2013    | 2007-2012      | 2008-2013      | 2005-2015       | 2005-2010    | 2008-2012    | 2000-2013      | 2004-2011   | 2000-2015 |
| Date of publication| 2016         | 2015           | 2016           | 2017            | 2013         | 2015         | 2016           | 2013        | 2013-2017 |
| Number of patients | 58           | 46             | 67             | 62              | 22           | 216          | 331            | 115         | 917     |

### Table 1: Literature review from Goh et al.

| Signs and symptoms (%) | Erythema | Warmth | Pain or tenderness | Swelling | Bullae | Crepitus | Skin necrosis |
|------------------------|----------|--------|---------------------|----------|-------|----------|--------------|
|                        | 66.3     | -      | 72                  | 71       | -     | 31       | 31.1         |
|                        | 80.3     | -      | -                   | 87       | -     | 6.6      | 23.8         |
|                        | 71       | 72     | -                   | 99       | -     | 14       | 19           |
|                        |          |        | 72                  | 100      | 15    | 14       |              |
|                        |          |        | 100                 | 100      | 14    | -        |              |
|                        |          |        | 10                 |           | 14    | -        |              |
|                        |          |        |                    |           | -     |          |              |
|                        |          |        |                    |           | -     |          |              |
|                        |          |        |                    |           | -     |          |              |
|                        |          |        |                    |           | -     |          |              |

### Table 2: Updated literature review

| Signs and symptoms (%) | Erythema | Warmth | Pain or tenderness | Swelling | Bullae | Crepitus | Skin necrosis |
|------------------------|----------|--------|---------------------|----------|-------|----------|--------------|
|                        | 89.7     | 78     | 69.4                | 72       | -     | 95.7     | 9.7          |
|                        |          | 30     | 14                  | 76       | -     | 9.7      | 21.4         |
|                        |          |        |                     | 76       | -     | 22.6     |              |
|                        |          |        |                     | 46       | -     | 89       |              |
|                        |          |        |                     |           | -     | 84.7     |              |
|                        |          |        |                     |           | 75.9  | -        |              |
|                        |          |        |                     |           | -     | 22       |              |
|                        |          |        |                     |           | -     | 44.5     |              |
|                        |          |        |                     |           | 73    | -        |              |
|                        |          |        |                     |           | 80    | -        |              |
|                        |          |        |                     |           | 23.5  | -        |              |
does not preclude the diagnosis of NF. NF has also been observed to develop after skin biopsy, at needle puncture sites, after frost bites, open fracture sites, and even insect bite sites [Table 2]. [14,16,35-37]

As the disease progresses, virulent organisms and toxins are released into the bloodstream from infected soft tissue. This results in the initiation of a systemic toxic reaction which can result in hypotension, disseminated intravascular coagulation, and eventually multi-organ failure. [5,13,16,19]

There are some limitations of this article in terms of assessing the reliability of the cutaneous signs. First, the authors are unable to ascertain the exact nature of the pain as quoted by the various cases studies, i.e., if it was just mild tenderness or pain out of proportion as is classical in NF. Second, while the literature review includes the actual number of patients with NF with the relevant signs, it is unable to elicit the sensitivity and specificity of that particular sign as there are many differential diagnoses to the same sign. Sensitivity and specificities of the various clinical signs were also not included in any study or in any preliminary search.

Comparison between Eastern and Western studies

While analyzing the various articles from the preliminary search, the authors also noted the different pathophysiology of NF based on the geographical locations of the relevant case studies. Of significance, would be countries situated geographically next to oceans or water-bodies compared with countries that are considerably inland such as the USA or Europe.

In addition to recording the incidence of cutaneous signs in patients with NF, Park et al. (a South Korean study) determined that the microbiology of the disease has distinctive features reflective of its surrounding community. In his case, South Korea is a country with extensive sea coasts where the average water temperatures in the summer are >15°C. [25] Vibrio spp. have been found in warm coastal waters with temperatures ranging from 9°C to 21°C. A. hydrophila is isolated from freshwater or seawater in the late summer/early autumn when temperatures are approximately 20°C–25°C. Stonefish stings have also been implicated in NF. [25,38,39]

Likewise, the study also noted that marine bacteria such as Vibrio spp. have also been detected in other warm coastal regions, including Asia (Thailand, Taiwan, and Singapore), the Gulf of Mexico, South America, and Australia. In coastal areas, diverse marine bacteria should be considered as the major etiologic organisms causing NF after exposure to seafood and/or seawater. [25,38,39]

Conversely, a study undertaken in the Netherlands noted that there is a lack of marine-related bacteria (Vibrio spp. or A. hydrophila) from bacterial cultures in patients with NF. The causative organisms in their study were mainly Gram-positive bacteria, in particular the GAS. It is believed that this difference in pathogen could influence the course of the disease and the outcome of patients with NF (260).

According to Tsai et al., [38] Staphylococcus aureus and Streptococcus spp. (Gram-positive bacteria) were the most common microorganisms in the USA and Europe, and monomicrobial Gram-negative microorganisms were most common in Asia. Some authors conclude that clinical characteristics of Gram-negative infections are more fulminant than of Gram-positive infections. [20,25,26,28,30,39,40]

Use of imaging and laboratory results as diagnostic tools

The authors of this paper noted how studies would supplement the clinical diagnosis of NF with laboratory investigations and imaging modalities such as ultrasound scans, X-ray, computer-tomography (CT) scans, and magnetic resonance imaging (MRI). [41-46]

Studies that incorporate laboratory values into their studies often quote the Laboratory Risk indicator for Necrotizing Fasciitis (LRINEC) score. This laboratory score was a tool developed by a Singaporean-based study lead by Wong et al. [40] for distinguishing NF from other soft-tissue infection. The paper determined that the cutoff value for the LRINEC score was 6 points with a positive predictive value of 92.0% and negative predictive value of 96.0%. Thus, a value of 6 or more should rule in NF. However, a value <6 is unable to rule it out. [41-45]

However, there are papers such as Sigt et al. and Tsai et al. that stated the score is unsatisfactorily examined and remains invalidated for larger studies. [26,38] Despite its high specificity and negative predictive value, since the score was published, subsequent data have demonstrated its limited sensitivity.

Imaging modalities are also useful tools. Ultrasound scans can be used on an emergency basis to diagnose NF based on several key features such as subcutaneous thickening, air, and fascial fluid. [43]

Radiographic imaging studies, such as soft-tissue radiographs, CT scanning, and MRI, are most helpful if gas is identified in the tissue; this is seen most frequently in Type I NF or gas gangrene caused by clostridia. Asymmetric fascial thickening, fat stranding, and gas tracking along fascial planes are important imaging findings on CT and MRI scans. CT scans are estimated to have a sensitivity of 80% for detecting necrotizing soft-tissue infections. [44-46] According to Schmid et al., the sensitivity of MRI is 100% with a specificity of 86%. It is particularly helpful in the investigation of areas that have disproportionately severe tenderness and when nonspecific signs of sepsis are present. [47]

Conclusion

This literature review has demonstrated that the most common (cutaneous) presenting symptoms of NF are swelling, pain, and erythema. While other differential diagnoses may also present with similar results, there are diagnostic clues such as the nature of the pain (i.e., pain out of proportion to physical findings or extending beyond the area of involvement) as well as the further progression into the intermediate and later
stages of NF that makes cutaneous signs even more reliable. The observation of the constellation of signs as the disease evolves is also important as the progressive changes become more apparent. The pairing of serial close inspection and a high index of suspicion cannot be overemphasized. Even when there are other adjuncts such as radiological investigations and LRINEC scores available to better predict the possibility of the NF, it has to be stressed that NF is still a clinical diagnosis and clinical acumen is necessary. Such tools should only be used primarily for patients in whom the diagnosis is doubtful as NF is a surgical emergency and necessitates immediate treatment.

Final recommendations
One recommendation that this literature review proposes would be to reanalyze the raw data from each case study, to produce the eventual sensitivity and specificity of each cutaneous sign for NF; taking into account the differential diagnosis of soft-tissue infections which may also present as such.

The second recommendation would be to carry out a meta-analysis of the various case studies’ results and of the adjunct diagnostic tools. This will not only establish a more definitive answer to the reliability of cutaneous signs in the diagnosis of NF but also allow researchers to compare and rate the difference in the sensitivity and specificity between the different modalities – clinical, laboratory, and imaging – in the diagnosis of NF.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Majeski J, Majeski E. Necrotizing fasciitis: Improved survival with early recognition by tissue biopsy and aggressive surgical treatment. South Med J 1997;90:1065-8.
2. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis 2014;59:147-59.
3. Vayvada H, Demirdover C, Menderes A, Karaca C. Necrotising fasciitis in the central part of the body: Diagnosis, management and review of the literature. Int Wound J 2015;10:466-72.
4. Anaya DA, Dellinger EP. Necrotizing soft-tissue infection: Diagnosis and management. Clin Infect Dis 2007;44:705-10.
5. Brook I, Frazier EH. Clinical and microbiological features of necrotizing fasciitis. J Clin Microbiol 1995;33:2382-7.
6. Wong CH, Chang HC, Pasapathy S, Khin LW, Tan JL, Low CO. Necrotizing fasciitis: Clinical presentation, microbiology, and determinants of mortality. J Bone Joint Surg Am 2003;85A:1454-60.
7. Prasanna Kumar S, Ravikumar A, Somu L. Fungal necrotizing fasciitis of the head and neck in 3 patients with uncontrollable diabetes. Ear Nose Throat J 2014;93:E18-21.
8. Zhang M, Chelnis J, Mawn LA. Periorbital NF secondary to candida parapsilosis and strep pyogenes. Ophthalm Plast Reconstr Surg 2017; 33 (35 Suppl 1): S31-3.
9. Wagner JD, Prevel CD, Elluru R. Histoplasma capsulatum necrotizing myofascitis of the upper extremity. Ann Plast Surg 1996;36:330-3.
10. Elliott D, Kufera JA, Myers RA. The microbiology of necrotizing soft tissue infections. Am Surg 2000;179:361-6.
11. Johnson MA, Lyle G, Hanly M, Yeh KA. Aspergillus: A rare primary organism in soft-tissue infections. Am Surg 1998;64:122-6.
12. Amrith S, Hosdurga Pai V, Ling WW. Periorbital necrotizing fasciitis – A review. Acta Ophthalmol 2013;91:596-603.
13. Banuch M, Belotserkovsky I, Hertzog BB, Ravins M, Dov E, McVey KS, et al. An extracellular bacterial pathogen modulates host metabolism to regulate its own sensing and proliferation. Cell 2014;156:97-108.
14. Wang YS, Wong CH, Tay YK. Staging of necrotizing fasciitis based on the evolving cutaneous features. Int J Dermatol 2007;46:1036-41.
15. Yip HW, Wong OF, Lee HM. 12 year experience with necrotising fasciitis in an Intensive Care Unit of a local regional hospital. Hong Kong Emerg Med J 2016;23:257-65.
16. Goh T, Goh LG, Ang CH, Wong CH. Early diagnosis of necrotizing fasciitis. Br J Surg 2014;101:e19-25.
17. Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections. Risk factors for mortality and strategies for management. Ann Surg 1996;224:672-83.
18. Frazee BW, Fee C, Lynn J, Wang R, Bostrom A, Hargis C, 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 2008;34:139-46.
19. Dworkin MS, Westercamp MD, Park L, McIntyre A. The epidemiology of necrotizing fasciitis including factors associated with death and amputation. Epidemiol Infect 2009;137:1609-14.
20. Nisbet M, Ansell G, Lang S, Taylor S, Dzendrowskyj P, Holland D. Necrotizing fasciitis: Review of 82 cases in South Auckland. Intern Med J 2011;41:543-8.
21. Singh G, Sinha SK, Adhikary S, Babu KS, Ray P, Khanna SK. Necrotising infections of soft tissues – A clinical profile. Eur J Surg 2002;168:366-71.
22. Roje Z, Roje Z, Matic D, et al. Necrotising fasciitis: literature review of contemporary strategies in the diagnosis and management with 3 case reports. Torso, abdominal wall, upper and lower limbs. World J Emerg Surg 2011;6:46-50.
23. Hsiao CT, Weng HH, Yuan YD, Chen CT, Chen IC. Predictors of mortality in patients with necrotizing fasciitis. Am J Emerg Med 2008;26:170-5.
24. Huang KF, Hung MH, Lin YS, Lu CL, Liu C, Chen CC, et al. Independent predictors of mortality for necrotizing fasciitis: A retrospective analysis in a single institution. J Trauma 2011;71:467-73.
25. Park KH, Jung SJ, Jung YS, Shin JH, Hwang JH. Marine bacteria as a leading cause of necrotizing fasciitis in coastal areas of South Korea. Am J Trop Med Hyg 2009;80:646-50.
26. van Stigt SF, de Vries J, Bijker JB, Mollen RM, Hekma EJ, Lenxon SM, et al. Review of 58 patients with necrotizing fasciitis in the Netherlands. World J Emerg Surg 2016;11:21.
27. Hodgins N, Damkath-Thomas L, Shamsian N, Yew P, Lewis H, Khan K. Analysis of the increasing prevalence of necrotising fasciitis referrals to a regional plastic surgery unit: A retrospective case series. J Plast Reconstr Aesthet Surg 2015;68:304-11.
28. Kha P, Colot J, Gervolino S, Guerrier G. Necrotizing soft-tissue infections in New Caledonia: Epidemiology, clinical presentation, microbiology, and prognostic factors. Asian J Surg 2016; pii: S1015-958400149-9.
29. Misiakos EP, Bagias G, Papadopoulos I, Danias N, Patapiss P, Machairas N, et al. Early diagnosis and surgical treatment for necrotizing fasciitis: A multicenter study. Front Surg 2017;4:5.
30. Arifi HM, Ducib uti V, Ahmeti HR, Ismajli VH, Gashi MM, et al. A retrospective study of 22 patients with necrotising fasciitis treated at the University Clinical Center of Kosovo (2005-2010). Int Wound J 2013;10:461-5.
31. Pirajal AF, Janjic Z, Korkev J, Markov B, Marinkovic M. A 5-year retrospective analysis of necrotizing fasciitis – A single center experiences. Vojnosanit Pregl 2015;72:258-64.
32. Jabbour G, El-Menyar A, Peralta R, Shaikh N, Abdelrahman H, Malghem J, et al. Necrotising fasciitis patients in a single tertiary hospital. World J Emerg Surg 2016;11:40.
33. Wang JM, Lim HK. Necrotizing fasciitis: Eight-year experience and literature review. Braz J Infect Dis 2014;18:137-43.
34. Ali SS, Lateef F. Laboratory risk indicators for acute NF in the emergency department setting. J Acute Dis 2016;5:114-6.
35. Malghem J, Lecouvet FE, Omoumi P, Maldague BE, Vande Berg BC.
Necrotizing fasciitis: Contribution and limitations of diagnostic imaging. Joint Bone Spine 2013;80:146-54.
36. Bahebeck J, Sobgui E, Loic F, Nonga BN, Mbanya JC, Sosso M. Limb-threatening and life-threatening diabetic extremities: Clinical patterns and outcomes in 56 patients. J Foot Ankle Surg 2010;49:43-6.
37. Fustes-Morales A, Gutierrez-Castellon P, Duran-Mckinster C, Orozco-Covarrubias L, Tamayo-Sanchez L, Ruiz-Maldonado R. Necrotizing fasciitis: Report of 39 pediatric cases. Arch Dermatol 2002;138:893-9.
38. Tsai YH, Huang KC, Shen SH, Hsu WH, Peng KT, Huang TJ. Microbiology and surgical indicators of necrotizing fasciitis in a tertiary hospital of southwest Taiwan. Int J Infect Dis 2012;16:e159-65.
39. Tsai YH, Wen-Wei Hsu R, Huang KC, Huang TJ. Comparison of necrotizing fasciitis and sepsis caused by *Vibrio vulnificus* and *Staphylococcus aureus*. J Bone Joint Surg Am 2011;93:274-84.
40. Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: A tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004;32:1535-41.
41. Wilson MP, Schneir AB. A case of necrotizing fasciitis with a LRINEC score of zero: Clinical suspicion should trump scoring systems. J Emerg Med 2013;44:928-31.
42. Holland MJ. Application of the Laboratory Risk Indicator in Necrotising Fasciitis (LRINEC) score to patients in a tropical tertiary referral centre. Anaesth Intensive Care 2009;37:588-92.
43. Castleberg E, Jenson N, Dinh VA. Diagnosis of necrotizing fasciitis with bedside ultrasound: The STAFF Exam. West J Emerg Med 2014;15:111-3.
44. Zacharias N, Velmahos GC, Salama A, Alam HB, de Moya M, King DR, *et al.* Diagnosis of necrotizing soft tissue infections by computed tomography. Arch Surg 2010;145:452-5.
45. Becker M, Zbären P, Hermans R, Becker CD, Marchal F, Kurt AM, *et al.* Necrotizing fasciitis of the head and neck: Role of CT in diagnosis and management. Radiology 1997;202:471-6.
46. Wysocki MG, Santora TA, Shah RM, Friedman AC. Necrotizing fasciitis: CT characteristics. Radiology 1997;203:859-63.
47. Schmid MR, Kossmann T, Duwel S. Differentiation of necrotizing fasciitis and cellulitis using MR imaging. AJR Am J Roentgenol 1998;170:615-20.