*Available online at http://www.journalcra.com*

*International Journal of Current Research*
*Vol. 7, Issue, 04, pp.14563-14570, April, 2015*

**INTERNATIONAL JOURNAL OF CURRENT RESEARCH**

**ISSN: 0975-833X**

## RESEARCH ARTICLE

# NECROTIZING FASCIITIS; DIAGNOSTIC PARAMETERS FOR EARLY DETECTION AND SUBSEQUENT IMPROVED SURGICAL OUTCOME

**[1]Omar Abdelraheem, [2,*]Osama Ismail and [3]Ahmed RH Ahmed**

[1]General Surgery Sohag University, Egypt
[2]Vascular Surgery Sohag University, Egypt
[3]Pathology Sohag University, Egypt

**ARTICLE INFO**

***Article History:***
Received 20th January, 2015
Received in revised form
06th February, 2015
Accepted 25th March, 2015
Published online 28th April, 2015

***Key words:***

Necrotizing Fasciitis,
Surgical Outcome.

**ABSTRACT**

**Aim of the work**: To identify the pattern of clinical manifestation and surgical outcome in relation to timing of presentation and surgical interference.

**Patients and methods**: This prospective study was carried out in Surgery Department, Sohag University Hospital from July 2010 to April 2014. Necrotizing fasciitis (NF) was diagnosed clinically and confirmed by intraoperative findings and routine postoperative histopathological study. Clinical criteria in association to laboratory values e.g. total leucocytic count; band leucocytes percentage and serum Na were recorded. According to these criteria, patients were classified into 2 groups: group A; 26 patients with objective criteria of NF and group B; 136 patients with criteria of non-NF (control group).

**Results:** There were a statistically significant differences between NF and non NF patients with respect to pain, tense edema, bullae, skin discoloration and crepitation (P= 0.04, 0.01, 0.032, 0.023, and 0.045 respectively). Elevated WBCs >15.4 $\times 10^9$ /L was found in 69% of group A patients and 8% of group B ($p$=0.0001). Band form leucocytes percentage >10% was observed in 23.08 % of group A and 6.61% of group B (p=0.0001). Serum Na<135 mm/L was observed in 85% and10% of group A and B respectively (($p$=0.0001). Repeated wide surgical debridement was done to 22 patients of group A and the remaining 4 cases were subjected to major extremity amputations. The overall mortality was 27% (7 patients) for group A (NF group) versus zero% for group B (non-NF group) (p<0.0001). Among patients underlying early debridement within 12 hours of admission (n=17), there was 3 deaths (18%) versus 4 deaths out of 9 (44.4 %) were recorded in patients with delayed operation ($P$< 0.05).

**Conclusion:** NF is a potentially fatal disease. Early diagnosis remains the cornerstone in achieving reasonable surgical outcome. In patients with clinical suspicious, laboratory parameters include WBCs >15.4×$10^9$/L , serum Na < 135 mmol/L and band form leucocytes percentage > 10% may be helpful in early diagnosis.



## INTRODUCTION

Necrotizing fasciitis (NF) is a rare soft tissue infection characterized by rapid spread of inflammation and necrosis starting from the fascia and extends to muscles and subcutaneous fat with subsequent necrosis of the overlying skin. (Lancerotto *et al.,* 2012) The incidence of NF in adults was reported to be 0.40 cases per 100,000 population (File *et al.,* 1998) ,while in children, it was reported to be double fold incidence with fulminant course and high mortality rate. (Fustes Morales *et al.,* 2002) This disease is generally classified into 3 categories; Type 1: polymicrobial infection, Type 2: infection with a group A β-haemolytic streptococcus or staphylococcus aureus, and Type 3: infection with gram negative bacilli such as vibrio. (Salcido, 2007; Sarani *et al.,* 2009; Tsai *et al.,* 2010). Diabetes mellitus is the most common co morbidity for NF that represents 18% - 60% of cases. Other risk factors include obesity, peripheral vascular disease, alcohol abuse, malnutrition, smoking, ischemic heart disease, corticosteroids, malignancy and immunosuppressive drugs (Bellapianta *et al.,* 2009) Although numerous risk factors have been identified, half of all cases occur in previously healthy individuals. (Dufel and Martino, 2006) The two commonest pitfalls in management of NF are failure of early diagnosis and inadequate surgical debridement. NF is often misdiagnosed as non-necrotizing soft tissue infection (e.g. cellulites or simple abscess) and this is responsible for delay in diagnosis and subsequent management. (Urschel, 1999) A plethora of diagnostic studies was based on certain hard clinical signs; hemodynamic instability, crepitation, skin necrosis and bullae and associated soft tissue gases on x-ray. These manifestations

***Corresponding author: Osama Ismail,***
*Vascular Surgery, Sohag University, Egypt.*

may be present in small percentage of patients. (Callahan *et al.,* 1998) Many authors suggested that, beside the clinical signs, simple laboratory parameters including leucocytic count (WBCs) $>15.4\times10^9$, serum sodium (Na) <135mmol/L and band form leucocytes percentage ≥ 10% may help in early recognition from non necrotizing soft tissue infections (non-NF). (Lancerotto *et al.,* 2012; Wall *et al.,* 2000; Lee *et al.,* 2011) Pathologically, NF is characterized by necrosis which is often associated with variable acute and chronic inflammatory cell infiltrate. (Hidalgo-Grass, 2004) An important finding is thrombosis of blood vessels which occurs due to damage of blood vessel wall by the inflammatory reaction. The histological key feature in distinguishing NF from non-NF is location of the inflammatory reaction in the subcutaneous fat, fascia and muscle in addition to the dermis. Diagnosis of NF by frozen section is challenging. In an appropriate setting, the presence of edema and neutrophils in the deeper tissue supports the diagnosis. (Elder *et al.,* 2005) Wong *et al,.* (Wong *et al.,* 2004) classified NF patients into low, intermediate and high-risk categories by using a scoring system (LRINEC) (laboratory risk indicator for necrotizing fasciitis), that based on C-reactive protein, leucocytic count, hemoglobin, serum Na, creatinine, and glucose levels at admission. The main objective of this study is to identify the pattern of clinical presentation and surgical outcome in relation to timing of presentation and surgical interference.

## PATIENTS AND METHODS

This prospective study was carried out in Surgery Department, Sohag University Hospital from July 2010 to April 2014. NF was diagnosed clinically and confirmed by intraoperative findings including presence of grayish necrotic skin, subcutaneous fat and fascia and a purulent foul-smelling discharge. Beside the clinical manifestations and intraoperative findings, routine postoperative histopathological study was performed to confirm the diagnosis. On the other hand, non-NF was defined intraoperatively as infection without evidence of necrotic fascia or muscles.

The main objective criteria for each patient were recorded. These criteria included vital signs specially mean systolic blood pressure (SBP), heart rate, respiratory rate and physical findings including presence of bullae, crepitation, purplish skin discoloration and skin necrosis in association to laboratory values on admission such as total leucocytic count, band leucocytes percentage and serum Na. In addition, plain x-ray was done in suspected cases for detection of soft tissue gases. According to these criteria, patients were classified into 2 groups:- group A; 26 patients with objective criteria of NF and group B; 136 patients with objective criteria of non-NF infection (control group). Both groups were compared by demographic data, etiology, site of infection, concomitant medical conditions, time of admission to surgery, number of operative debridements and postoperative surgical outcome. Our protocol for management of group (A) was urgent and aggressive debridement until fresh bleeding occurs from adjacent viable subcutaneous tissues and underlying muscles. All necrotic tissues, including the fascia must be removed aiming to reduce the bacterial load, facilitate recovery and proper aeration of tissues to act as an antagonistic factor of anaerobic bacteria (Fig. 1,2,3). Repeated operative debridement was performed to all cases of group A and some cases of group B when needed to prevent further progression of infection. Amputation was done when debridement of necrotic and gangrenous tissues leaves non salvageable limb. NF of the perineum (Fournier gangrene) is also unique because of their proximity to the anal verge with the need for frequent wound care due to soiling from stool (Fig. 4). For this reason, some of those patients needed diverting colostomy aiming to protect the surrounding perineal skin and soft tissue from infection spread which may be needed for eventual reconstruction. Reconstructive surgery was applied when the general condition became stabilized and the infection was fully eradicated. In some cases, wound coverage was achieved by either split thickness skin graft or tissue transfer. Empirical parenteral broad spectrum antibiotics was used until antibiotic culture and sensitivity was carried out. Our empiric therapy regimen consisted of combined four antimicrobial agents; penicillin G, clindamycin, vancomycin, and gentamicin as advised by Hakkarainen *et al*,. (Hakkarainen *et al.,* 2014).

In some patients suffering from elevated creatinine level, quinolones replaced aminoglycosides to avoid their nephrotoxic effect. In group (B) (control group), incision and drainage was done under cover of broad spectrum antibiotics. Further debridement was needed in some cases. On the other hand, cellulitis was treated with antibiotics only. Postoperative histopathological study was done routinely for all cases to prove the diagnosis by deep fascia necrosis and heavy infiltration with suppurative inflammatory cells; neutrophiles, pus cells and macrophages (Figure 5).

### Statistical analysis

Continuous variables were compared using t-student's test, t-test, and discrete variables were analyzed using Chi-square test. p value < 0.05 was considered statistically significant.

## RESULTS

Twenty-six patients with proved diagnosis of NF were identified and represented in group A. During the same period, 136 cases with non-NF were treated and included in group B. Demographic data and patients criteria of both groups were compared in table (1).

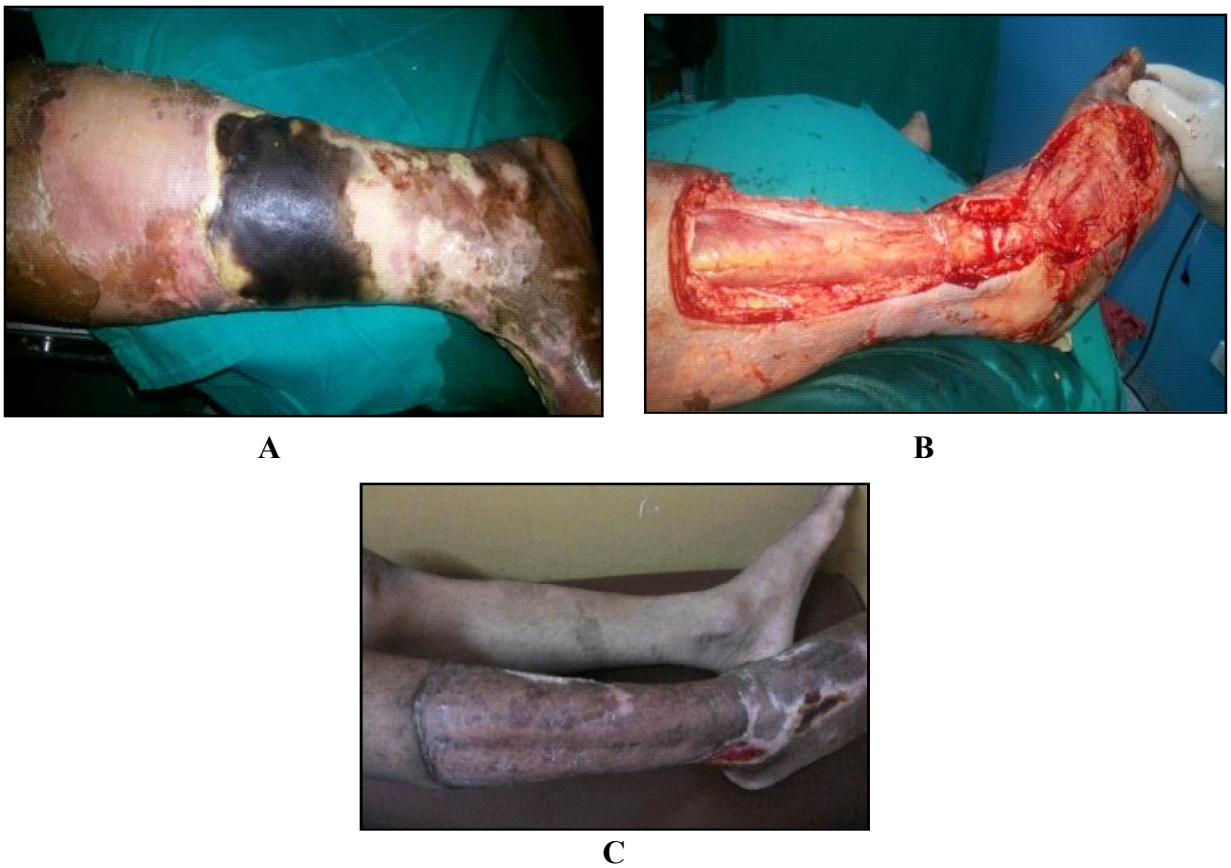
On admission, group A patients had significant lower mean systolic blood pressure than group B ( 95 versus 120 mmHg ; p = 0.001) and had significant higher heart rate (100 versus 95 beat / minute ; p =0.007). Both respiratory rate and temperature had no statistical difference between two groups. (Table 2). Clinical data revealed that pain out of proportion to other physical findings was the most predominant clinical manifestation in addition to a combination of tenderness, and skin discoloration. Hard clinical signs showed significant statistical difference between the two groups except skin necrosis that was variable but without significant difference. Eighteen cases (69.2 %) in group A performed plain x ray , 6 of them (33%) showed soft tissue gaseous shadow, while 24 patients (17.7%) in group B performed plain x ray, only one patient (4%) revealed gaseous soft tissue shadow (p=0,001).

(Table 2). Laboratory studies showed that elevated WBCs >15.4 $\times 10^9$ /L was found in 18 patients (69%) of group A and 11 patients (8%) of group B with significant p value=0.0001. Band form leucocytes percentage > 10% was observed in 6 patients (23.08 %) of group A and 9 patients (6.61%) of group B (P=0.001). Also, serum Na < 135 mml /L was observed in 22 patients (85%) in group A and in 14 patients (10%) only in group B (p=0.0001). Preoperative diagnosis of NF was doubtful in 2 patients (8%) because none of them had significant hard clinical signs or laboratory findings on admission. Diagnosis was discovered incidentally during surgery and confirmed by histopathological study. Early and aggressive debridement was done to all cases in group A. On the other hand, surgical debridement was performed only to 32 patients (24 %) of group B and treatment of the remaining cases varied from simple drainage to conservative treatment in cases of cellulities.

Wide surgical debridement after initial resuscitation was done to 22 patients of group A that was repeated to all of them whether in the operating theater or at bed side. The remaining 4 cases were submitted to major extremity amputations. Concomitant surgical procedures e.g. colostomy and reconstructive maneuvers were shown in table (3). The overall mortality was 27% (7 patients) for group A (NF group) versus zero% for group B (non-NF group) (p<0.0001). The mortality rate was related to the initial time of surgical intervention. Among patients underlying early surgical debridement within 12 hours from admission (n=17), there was 3 deaths (18%) in comparison to 4 deaths out of 9 patients (44.4%) with delayed operation (p<0.05) after 12 hours from admission. The cause of death in group A was septic shock in 5 patients, hepatorenal failure in one and the last one due to severe pneumonia

a b

**Figure 1. Post traumatic necrotizing fascitis of left thigh. (a), (b) before and after debridement**



**A** **B** **C**

**Figure 2. Diabetic patient with necrotizing fascitis. (a) before management, (b) after surgical debridement, (c) Limb reconstruction by split thickness skin graft**

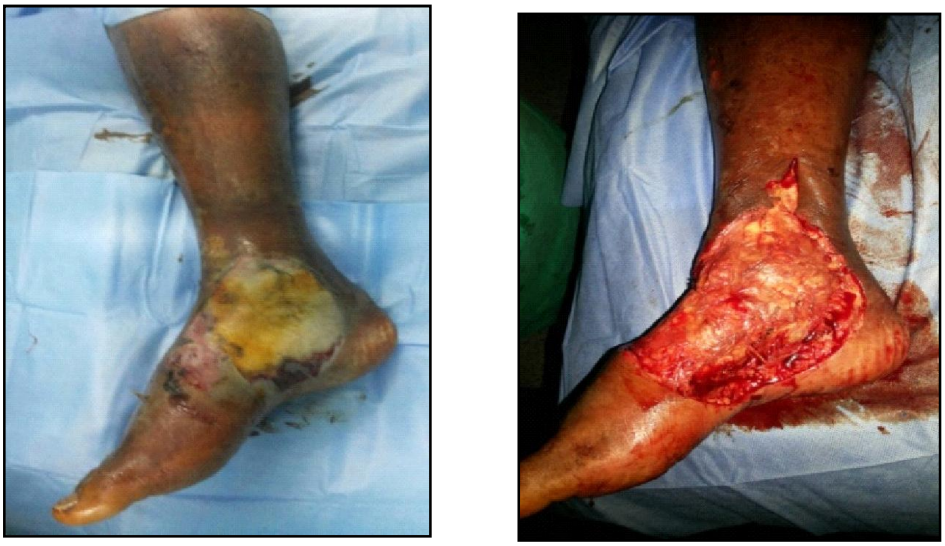



**Figure 3. Chronic renal failure patient with NF over medial aspect of right foot and ankle (a) before, (b) after treatment**

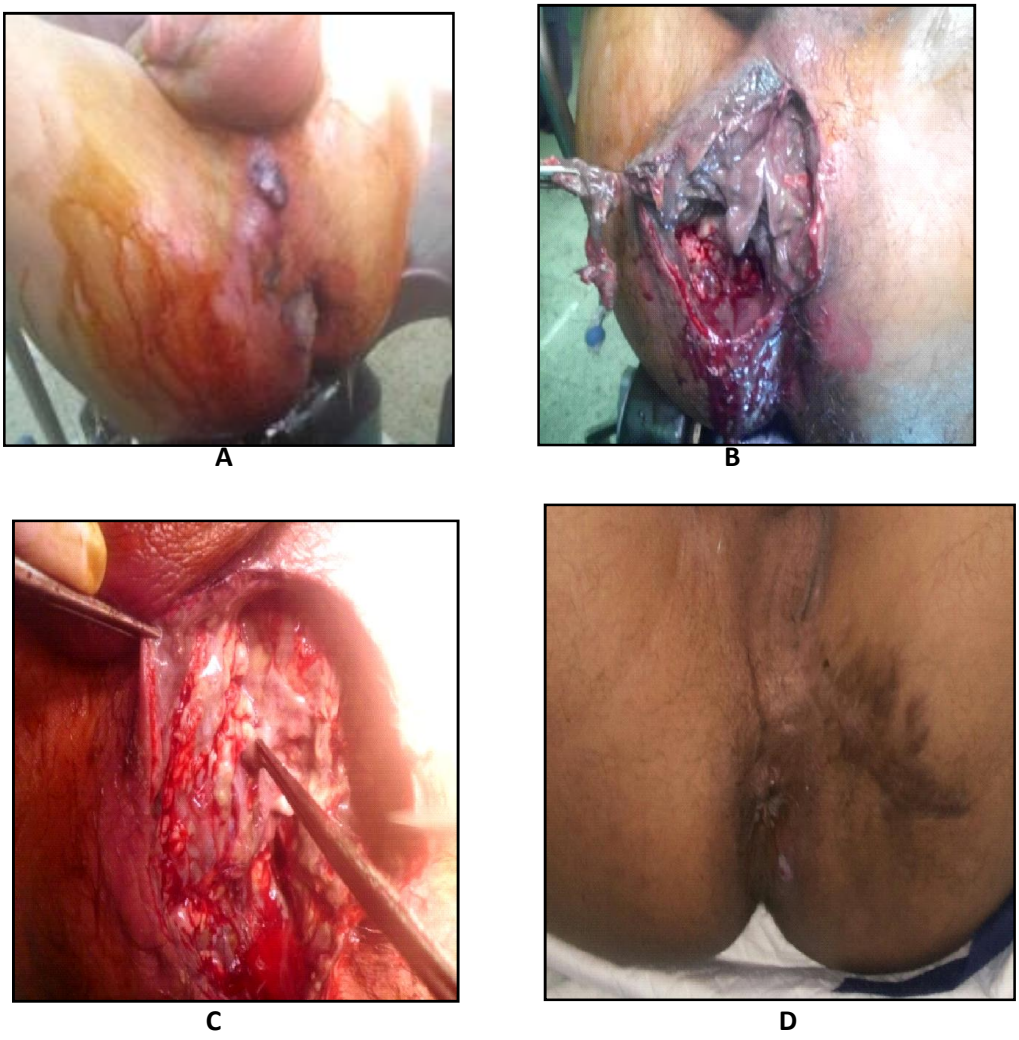



**Figure 4. Fournier Gangrene (a) before management, (b & c) during intraoperative debridement, (d) after reconstruction by rotational flap**

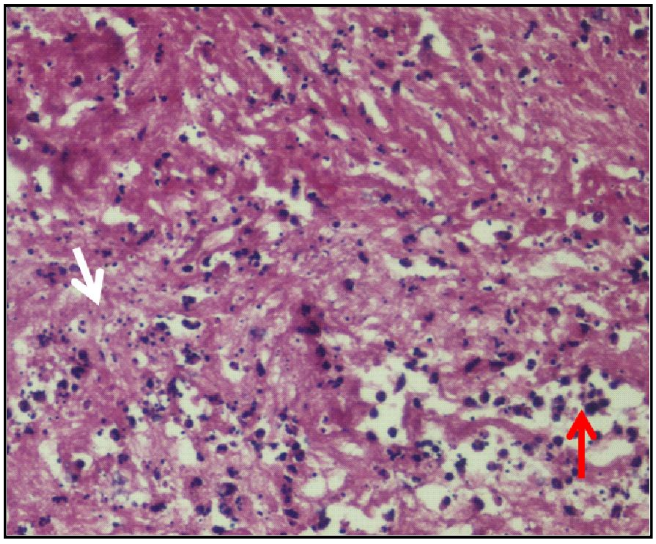


**Figure5. Necrotizing fasciitis showing necrotic area of the deep fascia (white arrow) and infiltration by neutrophiles and pus cells (red arrow); H&E x400**

## DISCUSSION

Necrotizing fasciitis is extremely rare clinical entity with an estimated 1000 cases annually in United States; however it appears that this incidence has been increasing. (Salcido, 2007) This rarity prevents most physicians from maintaining sufficient clinical suspicion for establishing the diagnosis early and subsequently initiating appropriate treatment. In addition, early symptoms and signs of NF are quite similar to those seen with cellulitis or abscesses potentially making difficulties in reaching the correct diagnosis. (Hakkarainen *et al.,* 2014) Wong *et al,.* (Wong *et al.,* 2004) had noted in his series that early diagnosis was missed in 85% - 100% of cases in large published series and it was reported as the single cause of fatal outcomes. Necrotizing fasciitis can occur anywhere all over the body but is commonly seen in extremities, perineum and genitalia with fewer cases arising on chest or abdomen. (Childers *et al.,* 2002). This was agreed with this study as NF occurred in 65.3 % (17 cases) in peripheral extremities and in 15.3 % (4 cases) in perineum.

**Table 1. Demographic data and patients criteria**

| | **Group A** No.(26) | **Group B** No. (136) |
|---|---|---|
| Age (mean) | 46.18 | 38.26 |
| Sex M/ F | 15/11 | 72/64 |
| Underlying predominant disease : | | |
| - Diabetes Mellitus | 15 (57.69%) | 52 (38.24%) |
| - Peripheral vascular disease | 3 (11.54%) | 12 (8.82%) |
| - Hepatic insufficiency | 2 (7.69%) | 18 (13.24%) |
| - Renal insufficiency | 1 (3.85%) | 7 (5.15%) |
| - Ambulance user | 1 (3.85%) | 11 (8.09%) |
| -Malignancy | 1 (3.85%) | 4 (2.94%) |
| -No underlying medical disease | 3 (7.69%) | 32 (23.53%) |
| -Site of infection: | | |
| -Lower extremity | 12 (46.15%) | 63 (46.32%) |
| -Upper extremity | 5 (19.23%) | 20 (14.71%) |
| - Perineum | 4 (15.38%) | 15 (11.03%) |
| - Abdomen | 2 (7.69%) | 19 (13.97%) |
| - Head and neck | 1 (3.85%) | 10 (7.35%) |
| - Multiple sites | 2 (7.69%) | 9 (6.62%) |
| Mechanism of infection: | | |
| - Traumatic wound | 10 (38.46%) | 46 (33.82%) |
| - Ulceration | 6 (23.08%) | 16 (11.76%) |
| - Surgical wound | 2 (7.69%) | 27 (19.85%) |
| - Hematogenous spread | 8 (30.77%) | 47 (34.56%) |

**Table 2. Clinical findings and laboratory studies**

| Physical signs | Group A No. (26) | Group B No. (136) | P- value |
|---|---|---|---|
| Admission vital signs : | | | 0.001 |
| - Mean systolic BP(mmHg) | 95 100 | 120 | 0.007 |
| - Mean heart Rate (beat/ minute) | 22.2 | 95 | NS |
| - Mean respiratory rate (breath/ min) | 39.2 | 18.4 | NS |
| - Mean temperature | | 38.6 | |
| Admission " hard" clinical manifestations: | | | |
| - Pain out of proportion to other criteria | 23 ( 88.46%) | 52 (38.24%) | 0.04 |
| - Tense oedema | 6 (23%) 5 | 7 (5%) | 0.01 |
| - Bullae | (19%) 5 | 4 (3%) | 0.032 |
| - Purplish skin discoloration | (19%) 3 | 2 (1.5%) | 0.023 |
| - Skin necrosis | (12%) 4 | 8 (6%) | NS |
| - Crepitation | (15%) | 2 (1.5%) | 0.045 |
| Soft tissue gas on x –ray | 6/18(33%) | 1/24(4%) | 0.001 |
| Admission laboratory values: | | | |
| -W.B.C >15.4 × $10^9$ /L | 18 (69%) | 11(8%) | 0.0001 |
| - Band leucocytes percentage > 10 % | 6 (23.08 %) | 9 ( 6.61%) | 0.001 |
| - Serum Na < 135 mml/ L | 22(85%) | 14(10%) | 0.0001 |

**Table 3. Surgical results of both groups**

| | Group A No. (26) | Group B No. (136) | |
|---|---|---|---|
| Early surgical treatment <12hours | 17 (65%) | 82 (60%) | NS |
| Late surgical treatment >12hours | 9 (35%) | 54 (40%) | NS |
| Surgical procedures: | | | |
| - Debridement | 22 (85%) | 32 (24%) | 0.0001 |
| - Amputation | 4 (15%) | 0 | 0.0002 |
| Concomitant procedures: | | | |
| - Colostomy | 2 (8%) | 0 | |
| Mean time of hospital stays(days) | 26.3 | 3.2 | 0.0001 |
| Reconstructive surgery : | | | |
| - Local tissue flap | 6 (23%) | 4(3%) | |
| - Skin grafts | 5 (19%) | 5(4%) | |
| - Abdominal wall reconstruction | 1 (4%) | 9(7%) | |
| Mortality: | | | |
| - In early surgical treatment <12hours | 3/17 (18%) | 0 | Early & late surgical |
| - In late surgical treatment >12hours | 4/9 (44.4%) | 0 | intervention ($p<0.05$) |
| - Overall mortality | 7/26 (27%) | 0 | A & B 0.0001 |

Diabetes mellitus and peripheral vascular disease represented the highest risk factors among group A patients (57.69%) and (11.54%) respectively. This was agreed with other studies that confirmed the importance of diabetes and peripheral vascular disease as medical co morbidities affecting the incidence of NF. (Bellapianta *et al.,* 2009; Lee *et al.,* 2011; Singh *et al.,* 2002) In this study, traumatic wound was the most common etiology of infection (10 cases, 38.46%), 6 cases (23.08%) had ulceration ,two cases (7.69%) had previous surgical wounds, while 8 cases (30.77%) had no obvious wound that could be identified. This was matched with Singh *et al*,. (Singh *et al.,* 2002) who reported that the etiology of necrotizing fasciitis is still not fully clear because, in many cases, no identifiable causes could be found. Joshy and his collegues (Joshy *et al.,* 2006) had reported that although hard signs are typical and specific, they are observed in only 10% - 40% of patients and quickly can progress within 1-2 days especially when NF is caused by *Streptococcus* species. Hsiao *et al*,. (Hsiao *et al.,* 2008) had reported in his series that presence of hemorrhagic bullae is an independent negative predictor of mortality which means that patients with hemorrhagic bullae may have better outcome and less deaths. He supposed his results on that the hemorrhagic bullae had a strong correlation with early diagnosis of NF and consequently, early management soon after diagnosis. In this study, we tried to obtain early diagnosis by comparing the objective criteria on admission of NF (group A) and non-NF (group B). First, considering the so called hard clinical manifestations alone (crepitation, skin necrosis, purplish skin discoloration, tense edema and presence of bullae). Our results showed that there was a significant statistical difference between group A and group B as regards the presence of hard clinical manifestations except the occurrence of skin necrosis. These findings agreed with that reported in other series. (Lancerotto *et al.,* 2012; Dufel and Martino, 2006; Lee *et al.,* 2011; Davies, 2001) Furtherly, by adding the most predictive laboratory values e.g. WBCs $>15.4\times10^9$/L, and/or serum Na <135mmol/L, it was appeared that there was marked statistical difference between group A and group B (P =0.0001). These results were roughly consistent with that reported by others. (Lancerotto *et al.,* 2012; Wall *et al*., 2000). Wall and his colleagues (Wall *et al*., 2000) reported in their series that the higher WBCs count in admission is indicative of intense local and systemic infection and lower Na level may reflect intravascular volume depletion secondary to third spacing of fluid around the edematous infected area. Also, Davies (Davies, 2001) had noticed that increased WBCs and decreased Na have been suggested as useful parameters to identify NF cases but are not exclusive. Band form leucocytes percentage more than 10% was observed in 23.08 % (6 patients) of group A which was matched with Hsiao *et al,* (Hsiaoe *et al.,* 2008) who reported in his series that this percentage of band form was noticed in 17.2 % among patients with NF. In this study, plain x-ray was done only in 18 cases in group A and in 24 patients in group B. X ray suggestive finding was presence of soft tissue gases in 6 cases (33 %). Green and his colleagues (Green *et al.,* 1996) found that gas in subcutaneous tissues on X-ray or CT was reported only in 17% - 29% of patients and therefore he considered that there was very specific but not very sensitive finding in patients with NF. In addition, Wall and his colleagues (Wall *et al.,* 2000) reported that frozen section tissue biopsy and magnetic resonance imaging are useful aids for early diagnosis but they were not available all the time. Surgical exploration remains the gold standard and specific parameter to confirm or exclude NF.

Detection of gray necrotic tissue, gross fascial edema, thrombosed vessels, foul-smelling pus, non contracting muscles and easily dissecting the subcutaneous tissue off the deep fascia with minimal resistance should be considered as highly suggestive criteria. (Childers *et al.,* 2002) In this study, surgery was performed as soon as possible even in doubtful cases. In addition, postoperative histopathological examination was performed for more confirmation. Our decision was matched with Kaul *et al,*. (Kaul *et al.,* 1997) who considered that surgical debridment was mandatory and life-saving procedure. Also, Goode *et al,*. (Goode *et al.,* 2004) had confirmed that increased time from admission to debridement and inadequacy of initial debridement had been associated with increased mortality.

Initial empiric antibiotic therapy in this study included coverage of gram-positive, gram-negative and anaerobic coverage as prescribed by Hakkarainen *et al*. (2014) until culture and sensitivity test was performed. Because of a significant local incidence of MRSA infection, Andreasen

*et al*. (2001) appreciated vancomycin for empiric coverage and advised penicillin G because of its significant activity against streptococcal and clostridial species.

The overall mortality was 27% (7 patients) for group A versus zero% for group B ($p$<0.0001). The cause of death in group A was septic shock in 5 patients (19.23%), hepatorenal failure in one patient (3.85%) and severe pneumonia in the last case. Singh *et al,*. (Singh *et al.,* 2002) had reported in his series that mortality rate of NF remains high with reported mortality rate varying from 6% - 76%. Also, mortality rates reaches 25% - 35% in recent series (Wong *et al.,* 2004; Wall *et al.,* 2000; Hakkarainen *et al.,* 2014; Tillou *et al.,* 2004) Tillou *et al,*. (Tillou *et al.,* 2004) noticed that patients who die due to necrotizing fasciitis had higher leucocytic counts on admission but it is not an independent predictor of mortality. Inversely, Tsai *et al.* (Tsai *et al.,* 2004) found that patient with leukopenia (WBC ≤ 5200) had a significantly higher mortality rate. Also, he noticed that band form WBCs percentage ≥ 10% was an independent factor of mortality. In our study, it was noticed that the mortality rate was related to the time interval between operative intervention and admission. Among patients underlying early debridement within 12 hours of admission (n=17), there was 3 deaths (18%) versus 4 deaths (44.4 %) were recorded in patients with delayed operation (P< 0.05). This is in consistence with other studies (Lancerotto *et al.,* 2012; Wong *et al.,* 2004; Voros *et al.,* 1993; Elliot *et al.,* 1996; Boyer *et al.,* 2009; Holena *et al.,* 2011) who stated that early surgical interference is associated with better surgical outcome and improved survival. Inversely; Hsiao and his colleagues (Hsiao *et al.,* 2008) reported in their series that surgical interference is not a predictor of mortality and this may be related to virulence of the causative microorganism.

**Conclusion**

NF is a potentially fatal disease. Early diagnosis of NF remains the cornerstone in achieving reasonable surgical outcome. In patients with clinical suspicious, laboratory parameters on admission including WBCs >$15.4\times10^9$/L, serum Na < 135 mmol / L and band form leucocytes percentage ≥ 10% may be helpful in early diagnosis.

## REFERENCES


Andreasen, T. J., Green, S. D., Childers, B. J. 2001. Massive infectious soft-tissue injury: diagnosis and management of necrotizing fasciitis and purpura fulminans. *Plast Reconstr Surg.,* 107:1025–1035.

Bellapianta, L. M., Ljungquist, K., Tobin, E., *et al.,* 2009. Necrotizing fasciitis. *J. Am. Acad. Orthop. Surg.,* 17:174-182.

Boyer, A., Vargas, F., Coste, F., *et al.,* 2009. Influence of surgical treatment timing on mortality from necrotizing soft tissue infections requiring intensive care management. *Intensive Care Med.,* 35(5):847–853

Callahan, T. E., Schecter, W. P. and Horn, J. K. 1998. Necrotizing soft tissue infection misleading as cutaneous abscess following drug injection. *Arch. Surg.,* 133:812-818.

Childers, B. J., Potyondy, L. D., Nachreiner, R., *et al.,* 2002. Necrotizing fasciitis:A fourteen-year retrospective study of 163 consecutive patients. *Am. Surg*., 68:109-116.

Davies, H. D. 2001. Flesh-eating disease: a note on necrotizing fasciitis. *Can. J. Infect. Dis.,* 12:136 –140.

Dufel, S. and Martino, M. 2006. Simple cellulitis or a more serious infection *J. infection. Fam. Pract.,* 55:396-400.

Elder, D. E., Elenitsas, R., Johnson, B. L., *et al.,* 2005. Bacterial diseases In Lever`s histopathology of the skin, Ninth ed Lippincott Williams and Wilkins, pp 553-4.

Elliot, D., Kufera, J. and Myers, R. 1996. Necrotizing soft tissue infections: risk factors for mortality and strategies for management. *Ann. Surg.,* 224:672

File, T. M., Jr, Tan, J. S. and Dipersio, J. R. 1998. Diagnosing and treating the "Flesh Eating Bacteria Syndrome." *Clev. Clin. J. Med.,* 65:241–249.

Fustes Morales, A., Gutierrez-Castrellon, P., Duran-McKinster, C., *et al.,* 2002. Necrotizing fasciitis :report of 390 pediatric cases. *Arch. Dermatol.,* 138:893–899.

Goodell, K., Jordan, M., Graham, R., Cassidy, C., *et al.,* 2004. Rapidly advancing necrotizing fasciitis caused by Phytobacterium (Vibrio) damsela: a hyperaggressive variant. *Crit Care Med*., (1):278–281.

Green, R. J., Dafoe, D. C. and Raffin, T. A. 1996. Necrotizing fasciitis. *Chest.,* 110: 219–229.

Hakkarainen, T. W., Burkette Ikebata, N., Bulger, E., *et al.,* 2014. Necrotizing soft tissue infections: Review and current concepts in treatment, systems of care, and outcomes Current Problems in Surgery, 51;344–362.

Hidalgo-Grass, C. 2004. Effect of a bacterial phenomone peptide on host chemokine degradation in group A streptococcal necrotizing soft-tissue infections. Lancet 363:696-703.

Holena, D. N., Mills, A. M., Carr, B. G., *et al.,* 2011. Transfer status: a risk factor for mortality in patients with necrotizing fasciitis. *Surgery,* 150(3):363–370.

Hsiao, C. T., Weng, H. H., Yuan, Y. D., *et al.,* 2008. Predictors of mortality in patients with necrotizing fasciitis. *American Journal of Emergency Medicine,* 26, 170–175.

Joshy, S., Haidar, S. G. and Iossifidis, A. 2006. Necrotising fasciitis of the shoulder following muscular strain. *Int. J. Clin. Pract.,* 60:856–857.

Kaul, R., Mc Geer, A., Low, D. E., *et al.,* 1997. 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.

Lancerotto, L., Tocco, I., Salmaso, R., *et al.,* 2012. Necrotizing fasciitis: classification, diagnosis, and management. *J. Trauma Acute Care Surg.,* Mar; 72(3):560-6.

Lee, C. Y., Kuo, L. T., Peng, K. T., *et al.,* 2011. Prognostic factors and monomicrobial necrotizing fasciitis: gram-positive versus gram-negative pathogens. *BMC Infectious Diseases*, 11:5, 2-8.

Salcido, R. S. 2007. Necrotizing fasciitis: reviewing the causes and treatment strategies. *Adv. Skin Wound Care*, 20 (5):288-293.

Sarani, B., Strong, M., Pascual, J., *et al.,* 2009. Necrotizing fasciitis: current concepts and review of the literature. *J. Am. Coll. Surg.,* 208:279-288.

Singh, G., Sinha, S. K., Adhikary, S. *et al.* 2002. Necrotising infections of soft tissues.a clinical profile. *Eur. J. Surg.,* 168(6):366-71.

Tillou, A., St Hill, C. R., Brown, C. *et al.* 2004. Necrotizing soft tissue infections: improved outcomes with modern care. *Am. Surg.,* 70(10):841-4.

Tsai, Y. H., Hsu, R. W., Huang, K. C. *et al.* 2010. Laboratory indicators for early detection and surgical treatment of vibrio necrotizing fasciitis. *Clin. Orthop. Relat. Res.,* 468:2230-2237.

Tsai, Y. H., Hsu, R. W., Huang, K. C., Chen, C. H. *et al.* 2004. Systemic Vibrio infection presenting as necrotizing fasciitis and sepsis. A series of thirteen cases. *J. Bone Joint Surg. Am. Nov.,* 86- A (11):2497-502.

Urschel, J. D. 1999. Necrotizing soft tissue infection. *Postgrad. Med. J.,* 75 (889):645-9.

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

Wall, D. B., de Virgilio, C. and Black, S. 2000. Objective criteria may assist distinguishing necrotizing fasciitis from non - necrotizing soft tissue infection. *Am. J. Surg.,*179:17-21.

Wong, C. H., Khin, L. W., Heng, K. S. *et al.* 2004. 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.

*******