



CLINICAL FINDINGS AND PHARMACOTHERAPY MANAGEMENT OF A NECROTIZING FASCIITIS FOR IMPROVEMENT OF PATIENT'S QUALITY OF LIFE AND FINANCIAL STATUS

S. M. Biradar^{1*}, Bharathi M.¹, Mounika M. V.¹, Meghana P.¹, Pournamy¹, Virupanagouda P. Patil¹, Akram Naikwadi², Vijaykumar Warad² and N. V. Kalyane¹

¹Department of Clinical Pharmacy Practice (Pharm D), BLDEA's SSM College of Pharmacy and Research Centre Vijaypur-586103 Karnataka, India.

²Department of Medicine and Pharmacology, Shri B.M. Patil Medical College Hospital and Research Centre, Vijaypur-586103. Karnataka, India.

*Corresponding Author: Dr. S. M. Biradar

Department of Clinical Pharmacy Practice (Pharm D), BLDEA's SSM College of Pharmacy and Research Centre Vijaypur-586103 Karnataka, India.

Article Received on 06/11/2017

Article Revised on 27/11/2017

Article Accepted on 17/12/2017

ABSTRACT

Background and objective: Necrotizing fasciitis (NF) is a rare and life-threatening infection that involves deep soft tissue; it is characterized by widespread fascial necrosis, with a mortality rate of 25-73%. The current research explores the early diagnosis of necrotising fasciitis and its beneficial outcomes. **Materials and Methods:** A prospective and observational study was conducted for a period of 6 months in the Department of Surgery at Shri B.M. Patil Medical College Hospital and Research Centre. A total of 80 patients were enrolled to extract the necessary data. Major factors contributing to the development of Necrotizing fasciitis were analyzed and the micro-organisms involved were provided. **Results:** The NF was affected in geriatric patients, in the age group of 60-70 years. The clinical symptoms of NF were fever, swelling, pain and pus discharge. Early diagnosis of disease is useful for determining the causative organisms involved and establish the specific antibiotic therapy, which further curtail the severity of infection and length of the hospital stay. Supportive therapy is essential component of treatment regimen in order to improve the quality of life of a patient and symptomatic management. **Conclusion:** Early diagnosis and specific antibiotic therapy with supportive symptomatic management improve the quality of life of a patient and reduce the financial burden.

KEYWORDS: Necrotizing fasciitis; Microorganism; Pharmacotherapy; supportive therapy; Quality of life; financial status.

INTRODUCTION

Necrotizing fasciitis (NF) is a flesh eating bacterial infection which is rapidly progressive soft tissue necrosis that usually involves the muscular fascia and subcutaneous tissue but can also affect the muscle and skin (Fig. 01). Necrotising soft tissue infections are classified as myositis, fasciitis and cellulitis.^[1] Necrotizing fasciitis is also known by some other names they are Synergistic Gangrene or Meleney's Gangrene, Necrotizing Cellulitis, Streptococcal Myositis, Clostridial Cellulitis, Fournier's Gangrene.^[2] Non soft tissue infections (NSTIs) are an exceedingly rare clinical entity, with an estimated 1000 cases annually in the United States; however it appears that this incidence has been increasing.^[3] NF may develop at the site of a skin biopsy, laceration, insect bite, needle puncture (particularly delineated in users of illicit drugs), herpes zoster, surgical wound, skin abscess, or areas affected with a chronic venous leg ulcer. The symptoms of NF

which include pain, diarrhoea, nausea, fever, confusion, dizziness, weakness, general malaise and dehydration. Risk factors for the development of NF include diabetes mellitus, old age, surgery, trauma, chronic skin infection and immune system impairment predispose patients to polymicrobial NF.^[4] NF is of four types, according to microbiological findings. The most common is Type I, also known as the polymicrobial type, Type II, otherwise known as monomicrobial, Type III includes monomicrobial infections involving the *Clostridium* species or Gram-negative bacteria, Type IV is the result of fungal infections. Laboratory risk indicators for necrotising fasciitis (LRINEC) score which includes six different variables helps to differentiate between necrotising and non-necrotising soft tissue infections. Laboratory risk indicators for Necrotising fasciitis (LRINEC) Scoring Scale - Low ≤ 5 Points, Moderate 6-7 Points, Severe ≥ 8 Points. This disease is diagnosed by using various tests like laboratory tests, surgical

diagnosis which includes finger test, frozen section evaluation and examination techniques like MR imaging and CT. The most important and commonest for diagnosing NF is culture sensitivity test used to identify the causative organisms like aerobic and anaerobic bacteria. The NF is primarily treated with broad spectrum antibiotics and culture sensitivity test is performed to identify the causative organism and specific antibiotics are given according to the organism involved. In severe cases surgical management should be performed like hyperbaric oxygen therapy, amputation etc. According to Centre for disease control (CDC), NF can be prevented by the following recommendations, are wounds should be cleaned and monitored for signs of infection, patients with sore throats should be seen by a doctor, Patients with strep throat should stay home until 24 hours after their last antibiotic dose, keeping the skin intact is important factor in preventing of NF.^[2]

MATERIALS AND METHODS

Study design and settings: A Prospective and observational study was conducted for a period of 6 months from October, 2016 to March, 2017 in the Department of surgery of shri B M. Patil Medical College Hospital and Research Centre, Vijaypur, after obtaining the Institutional Ethical Committee Clearance. The Hospital provides primary and specialized health care facilities to people in and around Vijaypur district. The patients admitted to the surgery ward were screened according to inclusion and exclusion criteria and 80 patients were finally selected for the study.

Inclusion criteria

- Provisionally diagnosed inpatients of NF.
- Both the genders, irrespective of ages.
- Patients willing to participate.

Exclusion criteria

- OPD patients.
- Incomplete documented patients.
- Against medical advice cases were excluded.

Source of data: In-patient case files (including patient's specific information, drug therapy and laboratory investigations).

Data collection: Data from each patient was collected from patient's case files and personal interview. The collected data was documented and evaluated for the study parameters. The entire enrolled patients were followed on a daily basis from the date of admission to the date of discharge. Past medication and medical history were also reviewed by extracting data from patients/care takers (relatives). Laboratory investigation and treatment data were collected to assess the severity and management of NF patients.

Statistical analysis

The data were analyzed statistically using student test and Microsoft excel. Values were expressed as

Mean±Standard Errors (S.E.M). P<0.05 is considered as significant and P>0.05 were considered as non-significant. Statistical comparisons were performed by Student Paired test with the help of Graph Pad Prism version 5.0, U.S.A. sample size was calculated by the following formula with the help of statistician.

$$n = \frac{Z^2 \times P \times (1-P)}{d^2}$$

Where, n is sample size, Z is Level of significance, P- Proportion value, d-10% absolute error.

RESULTS

Out of 80 subjects enrolled for the study 54 (67.5%) were male and 26 (32.5%) were female (Table 1). In the present scenario the prevalence of NF increases with advanced age. Age wise categorisation was done and it was found that the patients from age group of (61-70) comprising about 32.5% contributed to the maximum number, followed by age group of (51-60) comprising about 25%, with the least percentage of age group(21-30) comprising about 3.75% of the total subjects enrolled in the study (Table 2).

The commonest presenting symptom was fever 74 (92.5%), followed by swelling 69 (86.25%), pain 63 (78.75%) and pus discharge were 35 (43.75%) (Table 3). To determine the diagnosis of NF, early debriment test was performed for 37 patients (46.25%) and late debriment was performed for 43 patients (53.75%) (Table 4). Based on the extremities affected by NF, it was classified as upper extremities (neck, hands check etc.) and lower extremities (foot, legs etc.) (Table 5). A maximum of 54 (67.5 %) patients were observed with type-2 NF followed by type-1, 26 (32.5%) (Table 6).

Based on causative organism involved in necrotizing fasciitis, *Klebsiella* and *Pseudomonas* species were predominantly high when compared with other species. (Table 7). Patients received different Antibiotics based on organism involved, Out of 80 patients, 57 (71.25%) received metronidazole, ceftriaxone 41 (51.25%), Amoxicillin + Clavulanic acid and Amikacin were 36 (45%). The least prescribed antibiotics were Cefixime (06) and Ciprofloxacin (06) (Table 8).

All the patients received supportive therapy based on their individual conditions. Out of 80 patients enrolled in the present study, all the 80 (100%) were prescribed with Pantoprazole followed by Aceclofenac+Paracetamol (Zerodol-P), 74 (92.5%). Ascorbic acid was least prescribed, only in 30 patients of the study population (Table 9).A maximum of 55 (68.75%) patients were observed to have no co-morbidities. A number of 8 (10 %) were presented with co-morbidities of type -2 DM followed by HTN 4 (5%) (Table 10). According to LRINEC score, it was categorised as mild, moderate and severe. Assessment of severity as a major contributor, it was observed that a higher number of patients were included in moderate, 31 (38.75%) in comparison with severe 30 (37.5%) and mild were just 19 (23.75%).

Length of hospital stay as a consideration, it was observed that 21 patients stayed for about 10-15 days followed by 20 patients for 7-10 days, and 7 patients were observed with maximum length of hospital stay for more than 30 days (Table 12). A group of people where a late- debriment test was performed, significantly ($P<0.0001$) increases the length of hospital stay in comparison with group where early debriment test was done (Fig. 02).



Fig. 01. Necrotizing fasciitis affected lower extremity.

Effect of Debriment Test on length of Hospital stay

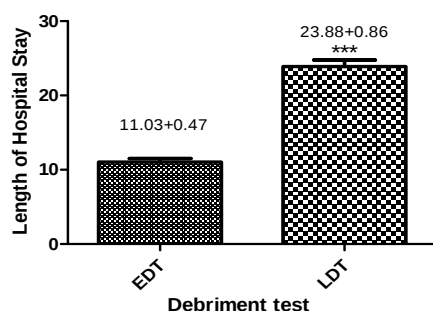


Fig. 02: Effect of Debriment test performed on length of hospital stay.

Table 4: Early diagnosis of NF patients.

Test for diagnosis	No. of patients n = 80	Percentage (%)	Advantages/	Disadvantages
Early Debriment performed	37	46.25%	Specific antibiotic therapy, Curtail severity and hospital stay	-
Late Debriment performed	43	53.75%	-	Emperical therapy, prolonged wound healing and hospital stay.

Table 5: Extremities affected by NF, where n=80

Extremities	No. of patients n=80	Percentage (%)
Upper	08	10
Lower	72	90

Fig. 02. EDT (Early debriment test) group consists of Average number of patients 11.03 ± 0.47 whereas, LDT (Late debriment test) group consists of average of patients 23.88 ± 0.86 . Values are Mean $\pm$ S.E.M. LDT is considered as significant, *** $P<0.0001$ compared to EDT. $P>0.05$ is considered as non significant.

Table 1: Gender wise distribution of NF.

Gender	No. of patients (n = 80)	Percentage
Male	54	67.5%
Female	26	32.5%

Table 2: Age wise distribution of NF.

Age	No. of Patients (n = 80)	Percentage (%)
01-20	04	05.00
21-30	03	03.75
31-40	07	08.75
41-50	09	11.25
51-60	20	25.00
61-70	26	32.50
71-80	05	06.25
≥ 80	06	07.50

Table 3: Evaluation of clinical symptoms.

Symptoms	No. of patients n = 80	Percentage (%)
Fever	74	92.5
Swelling	69	86.25
Pain	63	78.75
Pus discharge	35	43.75
Blackish discolouration	7	8.75
Blisters	6	7.5

Table 6: Classification based on organism involved.

Types	No. of patients n = 80	Percentage (%)
Type 1 (Poly bacterial)	26	32.50
Type 2 (Mono bacterial)	54	67.50

Table 7: Causative organisms involved in NF patients.

Name of the organisms	No. of patients n = 80
<i>Klebsilla pneumonia</i>	11
<i>Pseudomonas auregenosa</i>	11
<i>E.Coli</i>	10
<i>Enterococcus species</i>	09
<i>Streptococcus aureus</i>	06
<i>Staphylococcus aureus with Enterococcus species</i>	04
<i>Enterococcus species with Pseudomonas auregenosa</i>	03
<i>Staphylococcus aureus</i>	03
<i>Staphylococcus species with Pseudomonas auregenosa</i>	02
<i>Citrobacterfrundi</i>	02
<i>Pseudomonas auregenosa with Klebsiellaoxytoca</i>	02
<i>Klebsiella pneumonia with E.coli</i>	02
<i>Citrobacterfreundi with Pseudomonas auregenosa</i>	02
<i>Acenobacter with Klebsiellaoxytoca with itrobacterkoseri</i>	02
<i>Klebsiellaoxytoca with Acenobacter species</i>	01
<i>Coagulase negative stephylococci with Klebsiellapnemonia</i>	01
<i>E.coli with Pseudomonas auregenosa</i>	01
<i>Enterococcus species with E.coli</i>	01
<i>Klebsiella pneumonia with Citrobacterkoseri</i>	01
<i>Klebsiellaoxytoca with Pseudomonas auregenosa</i>	01
<i>Staphylococci with Cynobacterfruendi</i>	01
<i>Coagulase negative staphylococcus</i>	01
<i>Citrobacterfreundi with Klebsiella pneumonia</i>	01
<i>Citrobacterkoseri</i>	01
<i>Staphylococcus aureus with E.coli</i>	01

Table 8: Antibiotics prescribed in NF.

Antibiotics	No. of patients	Percentage (%)
Metronidazole	57	71.25
Ceftriaxone	41	51.25
Amoxicillin + Clavulanic acid	36	45.00
Amikacin	36	45.00
Tazobactam	19	23.75
Gentamycin	17	21.25
Linezolid	16	20.00
Cefixime	06	07.50
Ciprofloxacin	06	07.50

Table 9: supportive therapy in NF patients.

Supportive therapy	No of patients n=80	Percentage (%)
Pantoprazole	80	100
Aceclofenac+Paracetamol	74	92.5
B-Complex	50	62.5
Chymoral forte	42	52.5
Tramadol	36	45
Diclofenac sodium	35	43.75
Ascorbic acid	30	37.5

Table 10: Co-morbidities of NF patients

Co-morbidities	No.of patients n = 80	Percentage (%)
None	55	68.75
DM type 2	08	10.00
HTN	04	05.00
Haemopoiesis	03	03.75
DM& HTN	03	03.75
Asthma	03	03.75
IHD	02	02.50
Asthma & TB	02	02.50

Table 11: Severity assessment by LRINEC score,

Severity	No. of patients n= 80	Percentage (%)
Mild	19	23.75
Moderate	31	38.75
Severe	30	37.50

Table 12: Length of hospital stay

Length of stay	No. of patients n = 80	Percentage (%)
07-10	20	25.00
10-15	21	26.25
15-20	10	12.50
20-25	08	10.00
25-30	14	17.50
≥30	07	8.75

DISCUSSION

Necrotising fasciitis is a flesh eating bacterial infection which comprises a wide spectrum of disease entities that are categorised by extensive, rapidly progressive soft tissue necrosis that usually involves subcutaneous tissue and muscular fascia and can also affect muscle and skin.¹ Specific antibiotic therapy based on culture sensitivity test and proper pharmaceutical care may drastically suppress the severity of infection. Early diagnosis is a key source to a favourable outcome. The incidence rate of necrotising fasciitis is observed to be high in male when compared to females with a male-to-female ratio of 2:1. The mortality may be high in necrotising fasciitis despite use of modern powerful antibiotic therapy and intensive care for critically ill patients. The current research focuses on major contributing factors, organisms involved and effect of early diagnosis of NF on quality of life and financial burden of a patient.

In the present study males patients were predominantly high when compared to female patients, which correlates to the study conducted by Magala John et al.,^[5] had showed that maximum number of male patients were predominant over female patients. As per his results, male to female ratio were 3:1 where as in our study it was found to be 2:1. The study showed that predominance of male gender was affected with NF, as the definite incidence remains unclear.

The patients with necrotising fasciitis are in age group above 50 years (geriatrics) which is similar to a study conducted by Magala John et al.^[5] The elderly patients are more likely to be affected when compared to younger. Geriatrics are probably affected due to low immunity and with the history of current or past injected drug usage. Considering the age as a key factor, the elderly patients are usually associated with comorbidities, due to which multiple drug therapy (polypharmacy) may be a leading cause to necrotising fasciitis.

The hallmark clinical presentation of NF are fever, swelling, pain and Pus discharge, which is similar to the study conducted by Shaikh Nissar et al.,^[6] the symptoms may be due to active participation of bacterial involvement in the skin and soft tissue infection.

The diagnosis of disease play an important role in reducing the severity of disease and curtain the risk of life threatening developments. Early debriment test

performance is useful for determining the specific causative organism, based on which specific antibiotic therapy may be prescribed that contributes to the beneficial outcomes.

The patients affected with lower extremities were more when compared with upper extremities which is similar to the study conducted by Changchien C H et al.,^[7] has revealed that the patients affected with lower extremities were high, tailed by the patients affected with upper extremities. The common predisposing factor for extremities may be due to drug abuse and multiple needle perforations in the affected sites of upper and lower extremities. It can also be affected by severe skin ulcers, and thorn prick, wounds caused by metals, trauma, and post-operative wound infections.

In the present study, we have analysed that more number of patients were affected with Type 2 NF (mono microbial) tracked by Type 1 NF (poly microbial) respectively based on the organism involved, which is similar to a study conducted by Jabbour Gaby et al.,^[8] revealed that predominance of Type 2 NF (mono microbial) when compared to Type 1 NF (poly microbial). As the results reveals most of the times NF may be involved with mono bacterial (Type 2), the Type 1 may be developed due to hospital infected and length of stay in the hospital. Due to poly microbial infection (Type 1), multiple antibiotics are prescribed which may develop the antibiotic resistance, which may be contributing factor for severity of infection.

In the present study, the most common organisms involved in NF were *Klebsiella* and *Pseudomonas* species were predominantly high when compared with other species, which is contrary to the study conducted by Magala John et al.,^[5] had showed that *E.coli* was common organism when compared to other species. Some cultured organism were found to have extended spectrum beta-lactamase activities such as *E.coli* and *Klebsiella pneumonia*, which are sensitive to antibiotics such as Imipenem and Amikacin.^[16] Similarly, a study conducted by Changchien H C et al.,^[7] had showed that MRSA has high incidence when compared to other species in Taiwan which is contradictory to our study.

The highly prescribed antibiotic in NF patients was Metronidazole, followed by Ceftriaxone, Amoxicillin + clavulonic acid and Amikacin. Moderately prescribed antibiotics were Tazobactam, followed by Gentamycin and Linezolid. Rarely prescribed antibiotics were Cefixime and Ciprofloxacin as observed in our hospital which is contrary to the study conducted by Shaikh Nissar et al.,^[6] had showed that highly prescribed antibiotics were Tazocin, moderately prescribed antibiotics were metronidazole and rarely prescribed antibiotics were Vancomycin. It is true that the indication of antibiotics may be varied based on evidence based practice of a medical practioner and individual patients sensitivity to the antibiotics.

All the patients were received with supportive therapy based on their individual medical conditions; supportive therapy is essential component of treatment regimen in order to improve the Quality of life of a patient and symptomatic management of patient condition.

In the present study most of the patients were have no co-morbidities (Table 10), indicates that, co-morbid condition may not be a trigger factor for the development of NF. However, some co-morbidities were found in some of the patients such as diabetes mellitus Hypertension, Haemoperisis and Diabetes mellitus and hypertension, which is adjacent to the study conducted by Jabbour Gaby. *et.al.*,^[8]

In the present study LRINEC score was used as a key source to assess the level of severity of NF in patients. Which revealed that, a higher number of Patients were included in moderate to severe which is contradictory to the study conducted by Misiakos P. Evangelos *et.al.*,^[5] where as mild were less. Based on the length of hospital stay during the treatment period, it was observed that 21 patients stayed for about 10-15 days and no mortality rate was observed, which is contradictory to the study conducted by Mulla Z D *et.al.*,^[20] which showed mortality rate of 11.1%. The severity of NF and length of stay in hospital may be depend on the many factor such as early diagnosis, specific antibiotic therapy and medication adherence etc, hence there is lots of scope for clinical pharmacist in these aspects.

CONCLUSION

Patient centered care as a focal point by every health care system to provide optimal treatment regimen for the betterment of patient's quality of life. Early diagnosis and specific antibiotic therapy based on culture sensitivity tests as an obligate by health care professionals ensures a higher probability of survival. The study also enlightens severity assessment based on LRINEC Score, supportive therapy for symptomatic management, on-time surgery and implementation of clinical pharmacist services may be beneficial outcomes that can exponentially curtail the mortality rates. Instructive alertness should be incorporated about NF and its fatal consequences may be curtailed through clinical pharmacy services.

SIGNIFICANCE STATEMENT

The current study enabled that the patients with NF should be early diagnosed to curtail its severity and mortality rate. Specific antibiotic therapy based on culture sensitivity tests and supportive treatment regimen for symptomatic management should be strictly adopted to improve the patient's quality of life and maintain the economical status of a patient by reducing the length of the hospital stay.

ACKNOWLEDGEMENT

Authors are thankful to the Principal and staff of BLDEA's SSM College of Pharmacy and Research

Centre and Shri Basanagouda Mallangouda Patil Medical college, Hospital and Research Centre, Vijayapur, India for providing the necessary facilities and timely support in order to complete the research work.

REFERENCES

- McHenry C R, Piotrowski J J, Petrinic D, Malangoni M A. Determinants of Mortality for Necrotizing Soft-Tissue Infections. *Annals of surgery*, 1995; 221(5): 558-565.
- Vijayakumar A, Pullagura R, Thimmappa D. Necrotizing fasciitis: Diagnostic challenges and current practices. *ISRN Infectious Diseases*, 2014; 1-8.
- Hakkarainen T W, Kopari N M, Tarn N, Evans H L. Necrotizing soft tissue infections: Review and current concepts in treatment, systems of care, and outcomes. *Curr Probl Surgery*, August, 2014; 51(8): 344-362.
- Kihiczak G G, Schwartz R A, Kapila R. Necrotizing fasciitis : a deadly infection. *European Academy of Dermatology and Venereology*, 2006; 20: 365-369.
- Magala J, Makobore P, Makumbi T, Kaggwa S, Kalanzi E, Galukande M. The clinical presentation and early outcomes of necrotizing fasciitis in a Ugandan tertiary Hospital- a prospective study. *BMC research notes*, 2014; 7(476): 1-6.
- Shaik N, Khawaiter J, Al-Thani H. Necrotizing fasciitis a surgical and medical emergency. *Surgical science*, 2012; 3: 518-525.
- Changchien C H, Chen Y Y, Chen S W, Chen W L, Tsay J G, Chu C. Retrospective study of necrotizing fasciitis and characterization of its associated Methicillin resistant *Staphylococcus aureus* in Taiwan. *BMC Infectious Diseases*, 2011; 11(297): 1-11
- Jabbour R. El-Menyar A, Al-Thani H. Pattern and predictors of mortality in necrotizing fasciitis patients in a single tertiary hospital. *World journal of Emergency Surgery*, 2016; 11(40): 1-10.
- Taviloglu K, Yanar H. Necrotizing fasciitis: strategies for diagnosis and management. *World Journal of Emergency Surgery*, 2007; 2(19): 1-3.
- Hadeed GJ, Smith J O, Keefe T, Kulvatunyou N, Wynne JL, Joseph B, Friese RS, Wachtel TL, Rhee PM, El-Menyar A, Latifi R. Early surgical intervention and its impact on patients presenting with necrotizing soft tissue infections: A single academic center experience. *Journal of Emerg Trauma Shock*, 2016; 9: 22-27.
- Misiakos E P, Bagias G, Papadopoulos I, Danias N, Patapis P, Machairas N, Karatzas T, Arkadopoulos Toutouzas K, Alexakis N, Konstantoulakis M N, Zografos G, Smyrniotis V, Kouraklis G, Machairas A. Early diagnosis and surgical treatment for necrotizing fasciitis: A multicenter study. *Frontiers in Surgery*, 2017; 4(5): 1-7.
- Misiakos E P, Bagias G, Patapis P, Sotiriopoulos D, Kanavidis P, Machairas A. Current concepts in the

- management of necrotizing fasciitis. *Frontiers in Surgery*, 2014; 1(36): 1-10.
13. Anaya D A, Dellinger P. Necrotizing Soft-Tissue Infection:Diagnosis and Management. *Clinical Infectious Disease*, 2007; 44: 705-710.
 14. Puranendran R, Huey J C M, Pasupathy S. Clinical review on necrotizing fasciitis. *Canadian family physician*, 2009; 55: 981-987.
 15. Naqvi G A, Malik S A, Jan W. Necrotizing fasciitis of the lower extremity:a case report and current concept of diagnosis and management. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, 2009; 17(28): 1-7.
 16. Schmid M R, Kossmann T, Duewell S. Differentiation of Necrotizing fasciitis and Cellulites using MR imaging. *AJR*, 1998; 170: 615-620.
 17. Elliott D C, Kufera J A, Myers R A.M. Necrotizing soft tissue infections –Risk factors for mortality and strategies for management. *Annals of Surgery*, 224(5): 672-683.
 18. Mulla Z D, Gibbs S G, Aronoff D M. Correlates of length of stay, cost of care, and mortality among patients hospitalized for necrotizing fasciitis. *Epidemiol. Infect*, 2007; 135: 868–876.
 19. Wong C H, Khin L W, Heng K S, Tan K C, Low C O. 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(7): 1535-1541.
 20. Miller L G, Remington F P, Rieg G, Mehdi S, Perlroth J, Bayer A S, Tang A W, Phung T O, Spellberg B. Necrotizing Fasciitis Caused by Community-Associated Methicillin-Resistant *Staphylococcus aureus* in Los Angeles. *New England Journal of Medicine*, 2005; 352: 1445-1453.
 21. Goh T, Goh L. G., Ang C. H., Wong C. H. Early diagnosis of necrotizing fasciitis. *BJS*, 2014; 101: 119–125.
 22. Cheng N C, Tai H C, Chang S C, Chang C H, Lai H S. Necrotizing fasciitis in patients with diabetes mellitus: clinical characteristics and risk factors for mortality. *BMC Infectious Diseases*, 2015; 15(417): 1-9.
 23. Nischal N, Babu G R, Manjunath B D, Santhosh C S. Clinico - Microbiological Profile of Necrotizing Fasciitis in a Tertiary Care Hospital. *Int J Sci Stud*, 2015; 3(5): 95-98.
 24. Oud L, Watkins P. Necrotizing Fasciitis Associated with Pregnancy: a Population-Based Cohort Study. *Infect Dis Ther.*, 2014; 3: 307–320.
 25. Chen J L, Fullerton K E, Flynn N M. Necrotizing Fasciitis Associated with Injection Drug Use. *CID*, 2001; 33: 6-15.