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A Review of Necrotising Fasciitis and Treatment Strategies

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[**]S M Sandhya, [1]Aranya K Sreekumar, [1]Jibin John, [1]Kavya Shyam, [1]Reshma S Reghu, [2]Prasobh G R, [3]Swathy S

*** Vice Principal, Head Of Department of Pharmaceutical Chemistry, Sree Krishna College of Pharmacy and Research Centre ,Thiruvananthapuram , Kerala , India*

1.Fifth year Pharm D, Sree Krishna College of Pharmacy and Research Centre, Thiruvananthapuram , Kerala , India.

2 Principal, Head Of Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, Thiruvananthapuram , Kerala , India .

3. Assistant Professor, Sree Krishna College of Pharmacy and Research Centre, Thiruvananthapuram, Kerala, India .

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ABSTRACT

Necrotizing fasciitis can be defined as infections of any of the layers within the soft tissue compartment that are associated with necrotizing changes. Bacterial growth within the superficial fascia releases a mixture of enzymes, endotoxins and exotoxins causing the spread of infection through this fascia. This process results in poor microcirculation, ischemia in affected tissues, and ultimately, cell death and necrosis. Diagnosis of NF is essentially clinical. The gold standard is surgical exploration and tissue biopsy. The treatment for NF is a combination of surgical debridement as well as appropriate antibiotics and optimal oxygenation of the infected tissues.

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INTRODUCTION

Necrotizing fasciitis (NF) or necrotizing soft-tissue infections (NSTIs)which are infrequently observed but highly complicated infections. It is defined as infections of any layer within the soft tissue compartment that are associated with necrotizing changes.It can affect any part of the body and is the most serious manifestation of necrotizing soft tissue infection (NSTI); it is a rare but potentially fatal condition. The speed of the spread is directly proportional to the subcutaneous layer. Necrtotizing fasciitis moves along the fascial plane. NSTIs are typically not associated with abscesses, although they can originate from man untreated or inadequately drained abscess. These infections were first explained by Jones [1] in 1871 and at the time were termed "hospital gangrene" that had a mortality of 46%. Shortly afterwards, Jean-Alfred Fournier [2] explained a type of soft tissue infection affecting the male perineal region, now known as Fournier's gangrene. This definition has been elaborated recently to include necrotizing infections of the perineum of men and women. Surgical debridement was performed for the first time by Meleney[3] in the early 1920s and has remained an integral part of current treatment. In 1951,Wilson[4] put forward the term"Necrotizing Fasciitis" to encircle as well as include many of these infections. At onset, necrotizing fasciitis can be difficult to differentiate from cellulitis and other superficial infections of the skin. Studies shows that only 15% to 34% of patients with NF have a precise admission diagnosis [5,6]. Only early diagnosis and aggressive surgical treatment can reduce mortality and morbidity. Family physicians are often the first point of contact for these patients, and a high index of suspicion is needed, as there is a paucity of initial signs. The current review focuses on presentation, early diagnosis, and management of Necrotizing Fasciitis[5-6].

CLASSIFICATION

Type I

Type I infections are the most common form of the disease. They are polymicrobial and wound tissue isolates identify on average four different organisms. Causative microbes include a combination of Gram-positive cocci, Gram-negative rods, and anaerobes. Type I infections most frequently occur in the perineal and trunk areas in immuno compromised patients, particularly diabetics and patients with peripheral vascular disease. Fournier's gangrene refers to NF affecting the perineal, perianal, and genital regions and is a relatively common presentation in the UK. chronic renal failure, HIV, alcohol abuse, abscess, i.v. drug

abuse, blunt or penetrating trauma, insect bites, surgical incisions, in dwelling catheters, chickenpox, vesicles, and (rarely) perforation of the gastrointestinal tract (e.g. carcinoma or diverticulitis)[7].

Type II

An infection caused by the group A streptococcus (Streptococcus pyogenes) either alone or in association with Staphylococcus aureus classically located on the extremities of the body but truncal involvement has also been reported. Group A streptococci can survive and replicate in macrophages thereby escaping antibiotic therapy even in those tissues that remain well perfused and considered amenable to antibiotic penetration.

Type II is the only NSTI associated with toxic shock syndrome. Type II is far less common than type I infection; however, this incidence is increasing, reflecting the rise in the incidence of community-acquired Methicillin Resistant S. aureus (MRSA) in some parts of the world. MRSA soft tissue infection has been reported particularly in i.v. drug abusers, athletes, and institutionalized groups. Type IINSTIs often occur in healthy, young, immunocompetent hosts, although frequently there is a history of recent trauma or operation to the tissue involved[7].

Type III

Type III is a Gram-negative monomicrobial NF. The most common Gram-negative responsible for the infection Vibrio spp., such as *V. damselae* and *V. vulnificus*. Type III is uncommon but carries a very high mortality of 30–40%, despite prompt diagnosis and aggressive therapy[7].

Type IV

Type IV describes fungal cases of Candida NF. These are very rare. Fungal invasion is most commonly observed in patients with traumatic wounds and burns and in those who are severely immunocompromised[7].

PATHOPHYSIOLOGY

Microbial invasion of the subcutaneous tissues occurs either through external trauma or direct spread from a perforated viscus (particularly colon, rectum) or urogenital organ. Bacterial growth within the superficial fascia releases a mixture of enzymes, endotoxins and exotoxins causing the spread of infection through this fascia[7],This process results in poor microcirculation, ischemia in affected tissues, and ultimately, cell death and necrosis. Thrombosis of small veins and arteries passing through the fascia causes profound skin ischemia. This skin ischemia is the fundamental process for the soft tissue presentation of NF as it progresses. Importantly, during the early pathological stages, an apparently normal looking skin is seen, despite extensive infection of the underlying fascia. Haemorrhagic bullae, ulceration, and skin necrosis subsequently manifest with further involvement of the deeper structures. The initial clinical skin findings underestimate the tissue infection present, although thrombosis of penetrating vessels to the skin is the key feature in the pathology of NSTI. Thrombosis of large numbers of dermal capillary beds must occur before skin changes suggestive of necrosis occur[8].

RISK FACTORS

Majority of patients who develop NF have pre-existing conditions that make them susceptible to infection[10], although it also occurs in young, previously healthy individuals [7,11]. The disease occurs more frequently in the elderly[10,12,13], diabetics[10,12-16] alcoholics [12-19], intravenous drug users[7,10,12,17],in patients with chronic liver disease [7], renal insufficiency [10,13,19], peripheral vascular disease[10,12,13], gout [19,18], underlying malignancy[10,12,13] or immunocompromised states[10,12]. Other factors which have been found to be associated with NF are obesity[10,12], malnutrition[10,12], chronic obstructive pulmonary diseases [13,15] and congestive heart failure [15]. Many NF patients are found to be taking non-steroidal anti-inflammatory drugs (NSAID) at the time of presentation to hospital [15,18,19],but its role remains unclear [20,21]. Usually, the disease is precipitated by some form of injury or local pathological condition [13]. Blunt or penetrating trauma [10].infections of the operation site[10],burn[10], ulcers[22], abscess[22] and even child birth[10] have been believed as the precipitating factors for NF. Independent markers of mortality from NF in order of severity are: streptococcal toxic shock syndrome, immunocompromise, and advanced age[23].

CLINICAL PRESENTATION

Necrotizing infections can occur anywhere in the body, although some anatomic locations are affected more commonly. Most necrotizing soft tissue infections occur in the extremities, abdomen, groin, and perineum. In a case series, these infections were discovered in the extremities (53 percent of cases), perineum or buttocks (20 percent), trunk (18percent), and head and neck (8.9 percent) [24].

Many patients with NF are initially misdiagnosed with cellulitis, delaying appropriate management and increasing morbidity and mortality. Despite some similarities in the clinical presentation of cellulitis and NF, it is very important to correctly identify symptoms and signs allowing the correct diagnosis. The most critical early distinctive symptom of NF is a disproportionate level of pain compared with physical findings. Unlike cellulitis where the infection begins at the junction between the dermis and superficial fascia, in NF, the infection starts at the level of subcutaneous fat and deep fascia. It is because of this sparing of the epidermal and dermal layers in the early stages of the disease that erythema and oedema of skin are not obvious[8]and so the extent of infection clinically is not clear. Lymphangitis is rare in NF. Blister or bulla formation is an important but late feature of necrotizing fasciitis. Blisters result from ischemia as the penetrating vessels that perfuse the skin are largely thrombosed due to the inflammatory process. In contrast, blistering and bullae are rare findings in cellulitis. The rate of progression of NF can vary from several days from presentation to, in contrast, a rapid decline and death within hours from presentation. Patients with NF in the later stages of the disease often show symptoms and signs of septic shock, toxic shock syndrome, and multiorgan- failure. Tachycardia, tachypnoea, fever or hypothermia, hypotension, cardiac arrhythmias, confusion, metabolic acidosis, abnormal renal and liver function, coagulopathy, and thrombocytopenia may occur[24].

These patients carry a high rate of mortality. Clinical dermatological features of NF can be classified into three stages:

Stage 1: defined with signs such as erythema, tenderness beyond the erythema, swelling, and hot skin.

Stage 2: defined by the formation of skin bullae, blister, and skin fluctuation.

Stage 3: manifests with haemorrhagic bullae, crepitus, skin necrosis and gangrene.

DIAGNOSIS

Diagnosis of NF is essentially clinical. The gold standard is surgical exploration and tissue biopsy. The presence of fascial necrosis and myonecrosis or loss of fascial integrity along tissue planes and frank evidence of muscle involvement are diagnostic. There is a lack of resistance to blunt dissection of the normally adherent superficial fascia, accompanied by a lack of bleeding and the presence of foul-smelling 'dishwater' pus[8].

Haematology:

Haematological changes in NF are consistent with any septic process. These changes include leucocytosis, leucopoenia, coagulopathy, and thrombocytopenia. Anaemia can be dilutional from fluid resuscitation or from haemolysis. Disseminated intravascular coagulation is not uncommon in any severe sepsis[8].

Biochemistry:

Raised serum creatinine kinase indicates myositis or myonecrosis, and the effects of circulating toxins or ischaemia[25]. Hypocalcaemia is a sign of fat necrosis and calcium deposit in necrotic tissues. Bacterial infection, inflammation, and necrosis cause raised C-reactive protein (CRP). As in severe sepsis, abnormal renal function, hypoalbuminaemia, hyponatraemia, abnormal liver function, metabolic acidosis, and high serum lactate concentrations may occur[25].

Microbiology:

Blood cultures are positive in 11–60% of the patients with NF caused by group A streptococci. Percutaneous needle aspiration of the advancing edge is useful but a tissue biopsy is the investigation of choice. Tissues and aspirates should be Gram stained and cultured. Fungal culture is recommended in high-risk immunocompromised patients[25].

Histology:

Deep incisional biopsies and frozen sections with Gram staining of tissues are all diagnostic of NF. Samples should include the advancing edge and central necrotic areas. It reveals the underlying thrombi, necrosis, polymorphonuclear infiltrates, microorganisms, and vasculitis[25].

Laboratory scoring systems for the prediction of NF:

The LRINEC (Laboratory Risk Indicator for Necrotising Fasciitis) scoring system was designed to distinguish NF from other soft tissue infections. A comparison of laboratory tests between these two groups of patients showed that the most reliable and significant indicators of the underlying NF rather than cellulitis were CRP, creatinine, haemoglobin, white cell count, sodium, and serum glucose[26].

PREVENTION

The following is the list of recommendations to prevent the Necrotizing fasciitis as reported by the CDC.

• Good handwashing will prevent the spread of Group A Streptococcus (GAS) infection, especially after coughing, sneezing and before preparing food or eating.

• Patients with strep throat should stay home at least 24hours after their last antibiotic dose.

•The skin should be kept intact.

• Wounds should be cleaned properly and monitored for signs of infection (redness, swelling, drainage, pain).

• Patients with an infected wound, sore throat and fever should seek medical care[30-32].

TREATMENT

The treatment strategies for NF comprises of surgical debridement along with appropriate antibiotics and optimal oxygenation of the infected tissues. Early diagnosis and treatment by debridement and antibiotics can prevent its fulminant course with a fatal outcome [27,28,29]. The priority is to proceed to radical surgical debridement and once NF is diagnosed in patients, they should be treated with immediate surgical debridement, and broad spectrum antibiotic combinations against the gram-negative and gram-positive bacilli, anaerobes that were changed to other antibiotic combinations as determined as per the culture sensitivity of the microbial isolates and clinical course of the patients. in the majority, the isolates were polibacterial of the patients with either idiopathic or secondary NF in some recent studies [30,31,32]. Therefore, the use of broad-spectrum antibiotics is essential in the treatment of these patients. Penicillin-clindamycin-gentamicin combination or nafcillin or cefazolin plus

metronidazole or ampicillin/sulbactam combination could be considered in the initial antibiotherapy of NF according to the physician's preference. If *Clostridium perfringens* is identified or suspected, aqueous penicillin G (18million units/day, if renal function is normal) was administered with or without hyperbaric oxygen-therapy.

Hyperbaric oxygen therapy (HBO) treatment increase tissue oxygenation in both infected tissue as well as healthy tissue [33-35]and was administered at 2.5 to 3.0 atmospheres for 90 minutes twice daily, following surgical debridement until no ongoing necrosis was seen in patients with clostridial infections. Critical care was given for patients with hemodynamic and ventilatory instability. Elderly patients with underlying DM that have suspicious clinical findings of NF without any causative factors (trauma or operation) should be carefully be examined for the presence of idiopathic NF. The mortality rates higher in NF due to the severe sepsis that necessitates other interventions to overcome sepsis-related mortality[33-35].

CONCLUSION

Necrotizing fasciitis can be defined as infections of any of the layers within the soft tissue compartment which are associated with necrotizing changes and bacterial growth within the superficial fascia releases a mixture of enzymes, endotoxins and exotoxins causing the spread of infection through this fascia. Diagnosis of NF is essentially clinical and the gold standard is surgical exploration and tissue biopsy. The disease occurs more frequently in the elderly diabetics, alcoholics, intravenous drug users, in patients with chronic liver disease, renal insufficiency, peripheral vascular disease, gout, underlying malignancy or immunocompromised patients. Other factors which have been found to be associated with NF are obesity, malnutrition chronic obstructive pulmonary diseases and congestive heart failure. Early diagnosis and treatment by debridement and antibiotics can prevent its fulminant course with a fatal outcome. Necrotising fasciitis should be treated with immediate surgical debridement and broad spectrum antibiotic combinations. Penicillin-clindamycin-gentamicin combination or nafcillin or cefazolin plus metronidazole or ampicillin/sulbactam combinations could be considered in the initial antibiotic therapy of NF according to the physician's preference. If *Clostridium perfringens* is identified or suspected, aqueous penicillin G (18million units/day, if renal function is normal) was administered with or without hyperbaric oxygen-therapy.

REFERENCES

[1] J. Jones, "Surgical memoirs of the war of the rebellion: investigation upon the nature, causes and treatment of hospital gangrene as prevailed in the Confederate armies 1861–1865," US Sanitary Commission, New York, NY, USA, 1871.
[2] N. Eke, "Fournier's gangrene: a review of 1726 cases," *British Journal of Surgery*, vol. 87, no. 6, pp. 718–728, 2000.
[3] F. Meleney, "Hemolytic streptococcus gangrene," *Archives of Surgery*, vol. 9, pp. 317–364, 1924.
[4] B.Wilson, "Necrotizing fasciitis," *The American Surgeon*, vol. 18, no. 4, pp. 416–431, 1952.
[5] A. F. Hefny, H. O. Eid, M. Al-Hussona, K. M. Idris, and F.M. Abu-Zidan, "Necrotizing fasciitis: a challenging diagnosis," *European Journal of Emergency Medicine*, vol. 14, no. 1, pp. 50–52, 2007.
[6] C.-H. Wong, H.-C. Chang, S. Pasupathy, L.-W. Khin, J.-L.Tan, and C.-O. Low, "Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality," *Journal of Bone and Joint Surgery A*, vol. 85, no. 8, pp. 1454–1460, 2003.
[7] Sarani B, Strong M, Pascual J, Schwab CW. Necrotising fasciitis: current concepts and review of the literature. J Am CollSurg 2009; 208: 279–88.
[8] Wong CH, Wang YS. The diagnosis of necrotising fasciitis. CurrOpin Infect Dis 2005; 18: 101–6
[9] Das DK, Baker MG, Venugopal K: Increasing incidence of necrotizing fasciitis in New Zealand: a nationwide study over the period 1990 to2006. J Infect 2011, 63:429–433.
[10] Hasham S, Matteucci P, Stanley PRW, Hart NB: Necrotising fasciitis. BMJ 2005, 330:830–833.
[11] Green RJ, Dafoe DC, Raffin TA: Necrotizing fasciitis. Chest 1996,110:219–229.
[12] Headley AJ: Necrotizing soft tissue infections: a primary care review.AmFam Physician 2003, 68:323–328.
[13] Taviloglu K, Cabioglu N, Cagatay A, Yanar H, Ertekin C, Baspinar I, OzsutH, Guloglu R: Idiopathic necrotizing fasciitis: risk factors and strategies for management. Am Surg 2005, 71:315–320.
[14] Bair M-J, Chi H, Wang W-S, Hsiao Y-C, Chiang R-A, Chang K-Y: Necrotizing fasciitis in southeast Taiwan: clinical features, microbiology, and prognosis. Int J Infect Dis 2009, 13:255–260.
[15] Tiu A, Martin R, Vanniasingham P, MacCormick AD, Hill AG: Necrotizing fasciitis: analysis of 48 cases in South Auckland, New Zealand. ANZ J Surg2005, 75:32–34.
[16] Salvador VBDG, San Juan MD, Salisi JA, Consunji RJ: Clinical and microbiological spectrum of necrotizing fasciitis in surgical patients at a Philippine university medical centre. Asian J 2010, 33:51–58.
[17] Frazee BW, Fee C, Lynn J, Wang R, Bostrom A, Hargis C, Moore P: Community-acquired necrotizing soft tissue infections: a review of 122 cases presenting to a single emergency department over 12 years.JEmerg Med 2008, 34:139–146.
[18] Nisbet M, Ansell G, Lang S, Taylor S, Dzendrowskyj P, Holland D:Necrotizing fasciitis: review of 82 cases in South Auckland. Intern Med J2011, 41:543–548.
[19] Zerr DM, Alexander ER, Duchin JS, Koutsky LA, Rubens CE: A case–control study of necrotizing fasciitis during primary varicella.[see comment].Pediatrics 1999, 103:783–790.
[20] Zerr DM, Rubens CE: NSAIDS and necrotizing fasciitis. Pediatr Infect Dis J 1999, 18:724–725.
[21] Forbes N, Rankin APN: Necrotizing fasciitis and nonsteroidal anti-inflammatory drugs: a case series and review of literature. N Z Med J2001, 114:3–6.
[22] Childers BJ, Potyondy LD, Nachreiner R, Rogers FR, Childers ER, Oberg KC, Hendricks DL, Hardesty RA: Necrotizing fasciitis: a fourteen-year retrospective study of 163 consecutive patients. Am Surg 2002,68:109–116.
[23] Golger A, Ching S, Goldsmith CH et al. Mortality in patients with necrotising fasciitis. PlastReconstrSurg 2007; 119: 1803–7
[24] T. L. Bosshardt, V. J. Henderson, and C. H. Organ Jr., "Necrotizing soft-tissue infections," *Archives of Surgery*, vol. 131, no. 8, pp.846–854, 1996.
[25] Morgan MS. Diagnosis and management of necrotising fasciitis: a multiparametric approach. J Hosp Infect 2010; 75: 249–57
[26] Wong CH, Khin LW, Heng KS. 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

[27] McHenry CR, Piotrowski JJ, Petrinic D, Malangoni MA: Determinants of mortality for necrotizing soft-tissue infections. *AnnSurg*1995, 221:558-65.
[28] Elliott DC, Kufera JA, Myers RA: Necrotizing soft tissue infections: risk factors for mortality and strategies for management.*AnnSurg*1996, 224:672-83.
[29] Taviloglu K, Gunay K, Ertekin C, Gencosmanoglu R, Turel: Necrotizing fasciitis: therapeutical modalities (in Turkish). *Turk J Surg*1996, 12:128-33.
[30] Childers BJ, Potyondy LD, Nachreiner R, Rogers FR, Childers ER, Oberg KC, Hendricks DL, Hardesty RA: Necrotizing Fasciitis: a fourteen-year retrospective study of 163 consecutive patients. *Am Surgeon* 2002, 68:109-16.
[31] Elliott D, Kufera JA, Myers RAM: The microbiology of necrotizing soft tissue infections. *Am J Surg*2000, 179:361-6.
[32] Nothwang J, Ulrich C: Necrotising fasciitis-cryptogenic infection following posttraumatic immunopathy. *Arch OrthopTrauma Surg*1998, 118:167
[33] Korhonen K: Hyperbaric oxygen therapy in acute necrotizing infections. With a special reference to the effects on tissue gas tensions. *Ann ChirGynaecol*2000, 214:7-36.
[34.] Him M: Hyperbaric oxygen in the treatment of gas gangrene and perineal necrotizing fasciitis. A clinical and experimental study. *Eur J SurgSuppl*1993, 570:1-36.
[35] Mindrup SR, Kealey GP, Fallon B: Hyperbaric oxygen for the treatment of Fournier's gangrene. *J Urol*2005, 173:1975-7.

Image *Author -1*	*S M Sandhya* Vice Principal, Head Of Department of Pharmaceutical Chemistry, Sree Krishna College of Pharmacy and Research Centre ,Thiruvananthapuram , Kerala , India
Image *Author -2*	*Aranya K Sreekumar* Fifth year Pharm D, Sree Krishna College of Pharmacy and Research Centre, Thiruvananthapuram , Kerala , India.
Image *Author -3*	*Jibin John* Fifth year Pharm D, Sree Krishna College of Pharmacy and Research Centre, Thiruvananthapuram , Kerala , India.
Image *Author -4*	*Kavya Shyam* Fifth year Pharm D, Sree Krishna College of Pharmacy and Research Centre, Thiruvananthapuram , Kerala , India.
Image *Author -5*	*Reshma S Reghu* Fifth year Pharm D, Sree Krishna College of Pharmacy and Research Centre, Thiruvananthapuram , Kerala , India.