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Current approach to diagnosing and treating necrotizing fasciitis

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ABSTRACT:

Introduction: Necrotizing fasciitis is an infrequent yet highly fatal bacterial infection characterized by widespread necrosis of fascia and subcutaneous fat tissue. Though initial symptoms resemble typical infection, necrotizing fasciitis progresses rapidly triggering acute phase response. Individuals with advanced age, chronically ill, immunocompromised, or abusing alcohol are especially susceptible to developing necrotizing fasciitis. In order to reduce mortality, early diagnosis and appropriate aggressive treatment are indispensable.

Aim of the Study: Aim of this study is through evaluating existing literature to outline the contemporary diagnostic strategies and emerging therapy options for necrotizing fasciitis.

Description of the State of Knowledge: Primary diagnostic methods involve clinical evaluation and surgical exploration, complemented by fresh frozen sections for rapid diagnosis and the finger test when imaging is inconclusive. Diagnostic imaging incorporates the use of magnetic resonance imaging, computed tomography and ultrasound. The treatment is mostly centered around surgical debridement and antibiotic therapy. Therapies that display potential efficacy include low-dose radiotherapy, hyperbaric oxygen therapy, and the use of intact fish skin grafts for tissue reconstruction after successful treatment. The emerging approach includes therapy targeting systemic inflammatory response syndrome, sepsis induced coagulopathy and critical illness related corticosteroid insufficiency.

Conclusions: The management of necrotizing fasciitis primarily depends on traditional methods. Fast identification and proper treatment are pivotal in reducing the mortality rate. Recognizing the significance of addressing the acute phase response in necrotizing fasciitis treatment introduces new possibilities for therapeutic interventions. Further research is vital to evaluate the existing approaches to necrotizing fasciitis management and explore new diagnostic and therapeutic alternatives.

KEY WORDS: Necrotizing fasciitis, Necrotizing fasciitis diagnosis, Necrotizing fasciitis treatment, Necrotizing soft tissue infections, Surgical debridement

INTRODUCTION

Necrotizing fasciitis is a rarely occurring, promptly exacerbating and highly lethal bacterial infection, often initially misdiagnosed by doctors as cellulitis. It belongs to the category of necrotizing soft tissue infections (NSTIs) and can be classified based on the bacteria causing it, the extent of infection and its location. **[1]** The prevalence of NF ranges from 0.4 cases per 100.000 in the UK to 15 cases per 100.000 in Thailand yearly, and mortality rate reaches

approximately 30%, mostly due to delay in identification as well as proper management of the disease. **[2]** Conditions such as diabetes, chronic illness, malnutrition, age above 60 years, immunosuppression, malignancy, obesity, kidney failure, liver cirrhosis and intravenous injected drugs use, drastically increase the risk of developing NF. **[3]** Bacteria inducing necrotizing fasciitis, rapidly invade the muscular fascia, leading to occlusion of small as well as medium diameter blood vessels, which subsequently results in liquefactive necrosis. **[4]** The clinical manifestation of NF initially includes local erythema and swelling accompanied by pain exceeding the level appropriate to the degree of inflammation. Within a very short period of time systemic symptoms of acute phase response occur. They encompass fever, sepsis, systemic toxicity and multiple organ dysfunction syndrome (MODS). **[1][2]** Prompt diagnosis, antibiotics administration, and surgical intervention play a crucial role in reducing mortality. **[5]** In this literature review, we display contemporary diagnostic strategies and treatment options used in combating NF.

METHODS

In order to perform the present systematic review we searched PubMed, Medline, Elsevier and Google Scholar to seek scientific literature covering recent diagnostic tools and treatment strategies available for necrotizing fasciitis. We used the keywords “necrotizing fasciitis”, “necrotizing soft tissue infection”, “necrotizing fasciitis diagnostics”,” necrotizing fasciitis treatment", "sepsis", “surgical debridement”. We picked only articles written in English. The studies were meticulously examined and involved due to applicability to the subject of this review.

NECROTIZING FASCIITIS

During the 5th centenary BC case corresponding to the description of necrotizing soft tissue infections was first reported by Hippocaretes of Kos. **[4]** In 1871 NSTIs were initially specified by Jones as “hospital gangrene”. **[3]** In 1883 Fournier described cases of necrotizing fasciitis in genital and perineal regions. **[4]** In 1924 Meleney reported patients from China where NF was described as “acute hemolytic streptococcal gangrene”. **[6]** In 1948 Lyons along with Mc-Cafferty used the term “suppurative fasciitis” in reference to NF. They insisted that in order to reduce fatality of the disease, prompt diagnosis and aggressive treatment are necessary. Finally in 1952 Wilson came up with the exact name “necrotizing fasciitis”. **[7]**

Necrotizing fasciitis is a sparse, rapidly advancing bacterial infection, with a significant fatality rate. It falls under the category of NSTIs alongside necrotizing forms of cellulitis and myositis. **[1]** The incidence of NF is relatively low in Western countries such as England, with a rate of 0.4 cases per 100.000 annually, while high in other world regions like Thailand, where there are 15 cases per 100.000 yearly. Delay in detection and the administration of proper treatment, have an impact on mortality rate that can reach up to 30%. **[2]** Individuals aged 60 and above, suffering from diabetes, chronic disease, malnutrition, malignancy, immunosuppression, obesity, alcoholism, liver cirrhosis, renal failure, paraplegia, those using nonsteroidal anti-inflammatory drugs, and those using intravenous injected drugs, are particularly susceptible to developing the infection. Necrotizing fasciitis primarily affects the muscular fascia and subcutaneous fat tissue.**[3]**

Myofascia consists of highly dense fibrous connective tissue that envelops the muscles. It provides connection between components of the muscular system and likely takes part in nociception along with proprioception **[8].** In the classification of fasciae based on their location, we can distinguish three groups: superficial, deep and visceral. Muscular fascia lies in the category of deep fasciae. **[9]** Necrotizing fasciitis leads to necrosis of myofascia and subcutaneous adipose tissue, sparing the muscles underneath. **[3][10]**

Often there is a history of trauma related skin integrity damage or prior surgical intervention. **[11]** As bacteria start to grow in the fascia, they induce inflammation by secreting toxins and enzymes facilitating further invasion. This process disrupts microcirculation, triggers thrombosis in small veins, resulting in ischaemia and subsequently liquefactive necrosis. NF can be categorized into the three stages. Initially, the skin surface may look unchanged. Stage 1 is characterized by inflammation of the overlying skin, marked by erythema, warmth, tenderness and swelling. Stage 2, occurring after a couple days, displays the formation of bullae and emphysema. In stage 3, which follows in the subsequent days, hemorrhagic bullae, necrosis and gangrene occur. At this point, the gangrene induced destruction of superficial nerves becomes evident, making pain less noticeable. Further progression gives rise to systemic symptoms. **[12][13]** When the body is severely damaged, it reacts with acute phase response. Infection promotes cell injury, leading to coagulation and inflammation. This process aims to halt bleeding and confine the bacteria. **[14]** Subsequently macrophages engulfs, kills and eliminates the bacteria. In NF bacteria escape the process of elimination causing exaggerated inflammatory response that may result in SIRS, and coagulopathic state,

that may lead to SIC. **[15]** Patients suffering from necrotizing fasciitis usually die as a result of SIRS and SIC by thrombosis, MODS and CIRCI. **[16]**

The disease manifests clinically with signs of an infection that can be easily overlooked. Symptoms encompass pyrexia, vomiting, crepitus, skin redness along with edema and pain. Aside from pain, erythema, swelling, presence of bullae and crepitus induced by emphysema, nothing distinctive may be present in superficial findings. The most typical symptom of necrotizing fasciitis is an excruciating pain, surpassing the level normally attributed to the degree of inflammation. **[1][4][13][17]**

NF can be classified in regards to its microbiology, extent of infection and location.

Based on bacteria causing necrotizing fasciitis, we can distinguish Type I and Type II covering the majority of cases (approximately 95%), and Type III along with Type IV acclaimed by some experts. Type I, polymicrobial, constitutes 70-80% of cases and results from aerobic and anaerobic bacteria infections. It affects mostly individuals of advanced age with an array of chronic diseases. The mortality depends on individuals' risk factors. Type II, monomicrobial, accounts for 20-30% of cases and results from group A β-haemolytic Streptococcus and Staphylococcus aureus infections. It is not assigned to any specific risk factors. The mortality rate is >32%. Type III is infrequent and primarily caused by Aeromonas hydrophila, Vibrio species, Klebsiella species. Contamination usually happens either through seafood ingestion or by contact between a wound and contaminated water. The mortality rate is 30-40%. Type IV is extremely rare, caused by Candida species, and mostly affects immunocompromised patients. The mortality rate is >47%. **[1][2][12][18]**

Based on location we can distinguish Ludwig angina in the submandibular space, Lemierre syndrome affecting the oropharynx, Fournier gangrene occurring in the perineal region.

Based on the extent of infection we can distinguish necrotizing adipositis, fasciitis and myositis. **[1][19]**

DIAGNOSTIC STRATEGIES

Early identification of necrotizing fasciitis is crucial in order to decrease the mortality rate. **[18]** A considerable number of individuals suffering from NF are often primarily incorrectly diagnosed with cellulitis. However unlike cellulitis, which occurs between the dermis and superficial fascia, NF develops at the adipose tissue and deep fascia level. Furthermore, the distinctive symptoms of NF include intense pain that is inordinate to the level typically expected for the degree of inflammation, and the formation of blisters and bullae. **[4][12]**

The primary diagnosis of necrotizing fasciitis is based on clinical evaluation, covering symptoms mentioned in the previous paragraph. **[20]** Subsequently**,** the gold standard method is surgical exploration along with tissue biopsy. If there is evidence of necrosis or disintegration of the fascia, small blood vessels thrombosis, nonappearance of bleeding, tissues are easily cut without resistance, and a presence of a gray fluid with characteristic foul fish-like pus odor, NF can be diagnosed. Alternatively transdermic needle aspiration can be performed at the advancing margin of the infection. **[4][10]** Blood cultures may yield positive results in 10-60% of individuals with Streptococcus infection. Biopsies and aspirates should be stained with Gram's method and cultured. For patients with immunosuppression, fungal cultures should be conducted. **[12][21]**

Fresh frozen sections proved to be beneficial for the rapid diagnosis of necrotizing fasciitis. This procedure can be conducted in the operating theater, the intensive care unit as well as the emergency room.**[13]** The process involves embedding a sample in a gel, freezing it to -20 degrees Celsius, cutting into 6 to 9 μm sections using a cryostat, staining with hematoxylin & eosin, and then analyzing by a pathologist. Presence of bullae, fascial inflammation, thrombosis or vasculitis, and necrosis may be indicative of necrotizing fasciitis. **[22]**

The finger test is taken under consideration, when there is a strong suspicion of NF and diagnostic imaging is either unavailable, negative or inconclusive. After administering local anesthesia, a small incision in the skin is made, reaching the deep fascia. Subsequently an index finger is inserted down the incision. If the tissues are disintegrated to the degree of dissecting with no resistance under finger pressure, there is no bleeding and a gray fluid with fish-like pus odor is present, the finger test is considered positive.**[23]**

In the blood count results may be present anemia as a consequence of fluid administration induced blood dilution, leukocytosis with a shift to the left, leucopenia, thrombocytopenia, coagulopathy, and decreased serum bicarbonate.
Blood chemistry tests often reveal elevated levels of creatine kinase (CK) and aspartate aminotransferase (AST) corresponding to muscle damage, ischaemia and circulating bacterial toxins. Hypocalcemia can be linked to adipose tissue necrosis and accumulation of calcium in the gangrene. Inflammation may lead to an elevation of C reactive protein (CRP).

Additional biochemical abnormalities may involve impaired kidneys and liver function, hyponatremia, hypoalbuminemia, metabolic acidosis, as well as increased serum lactate. **[1][12][24]**

In 2004, the Laboratory Risk Indicator for Necrotising Fasciitis (LRINEC) score was introduced by Wong in order to easily differentiate NF from other NSTI's. The variables taken under consideration encompass C-reactive protein, hemoglobin blood level, total leucocyte count, serum sodium, serum creatinine and blood glucose level. A score lower than 6 points indicates a low risk, a score between 6 and 7 points indicates intermediate risk, and a score higher than 8 points indicates high risk of necrotizing fasciitis. Several studies have suggested that LRINEC score may lack accuracy in differentiating NF from other NSTIs considering its low sensitivity. **[17][18][25][26]** In 2021 the scoring system was updated by Wu, leading to the development of a modified Laboratory Risk Indicator for Necrotizing Fasciitis (m-LIRNEC) score. Changes involved adding comorbid diabetes and comorbid kidney disease to the scoring, instead of CRP incorporating high-sensitivity C- reactive protein (hs-CRP), and altering the limit values of the cut-off for remaining four other factors. If the m-LRINEC score is above 17, the likelihood of the presence of NF is high. Further studies are necessary to validate the accuracy of this tool. **[27]**

Diagnostic imaging can serve a valuable role in eliminating diseases similar to necrotizing fasciitis and demarking margins of surgical debridement. **[28]**

Magnetic resonance imaging demonstrates a sensitivity of approximately 93% in identifying NF. It's a gold standard tool for comprehensive evaluation of NSTI's, enabling distinction between mild cellulitis and necrotizing fasciitis necessitating prompt and aggressive debridement. MRI reveals thickening of more than 3mm in the fascia and identifies involvement across multiple compartments of the deep fascia. Additionally, MRI is valuable in finding the margins of necrosis, swelling and inflammation. When combined with clinical evaluation, MRI assists in establishing the requirement and extent of potential surgical debridement. **[12][29][30]**

Ultrasound has a sensitivity of about 88% in detecting NF. It displays thickening and disintegration of the fascia, as well as the presence of gas and fluid accumulation in the

surrounding tissues. Ultrasonography is inexpensive, readily available and can be swiftly performed, providing an accurate view of the current situation. It enables fast surgical intervention, contributing to a reduction in mortality rate. Furthermore, USG can be beneficial in directing fluid drainage in the presence of fluid collection, and for excluding deep vein thrombosis. Therefore, ultrasound is proven to be a valuable tool in diagnosing NF. **[12][28][30][31][32]**

Computed tomography exhibits a sensitivity of around 80% in confirming NF. It depicts the disintegration of soft tissues, thickening of the deep fascia, as well as the presence of abnormal gas and fluid soft tissue collection with various contrast enhancement. The main limitation of CT is its diminished efficacy in revealing changes during the initial phases of necrotizing fasciitis. It proves more effective in identifying advanced stages. Thereby, CT is primarily used to rule out the urgency to perform immediate surgical intervention in individuals suspected of suffering from NF.**[12][30][33][34]**

Radiography (RTG) is employed to visualize emphysema and edema in the tissues. Sight of gas is characteristic of necrotizing fasciitis, though it doesn't occur frequently. Approximately 25% of patients with advanced necrotizing fasciitis type I may display emphysema in the deep fascia. Fluid accumulated in the tissues can indicate the presence of NF, but it can also be found in cellulitis and myositis. Consequently, radiography is not recommended for detecting NF as it can lead to oversight and delay in surgical intervention, ultimately increasing the mortality rate.**[31]**

TREATMENT OPTIONS

The management of NF primarily is based on traditional approaches involving surgical intervention and antibiotic therapy. However, recent studies have explored association of NF with the acute phase response. These findings have prompted investigations into potential treatment strategies to address SIRS, SIC and CIRCI. **[16]**

Surgical debridement of necrotic tissues should be performed promptly and aggressively. The sooner the intervention, the lower the risk of further infection, extensive tissue loss, potential amputation, and mortality. **[35]** It's crucial that the procedure is performed extensively, ensuring the removal of all disintegrated necrotic tissues. The optimal degree of tissue

excision remains unclear. Some researchers suggest that even seemingly normal tissues may already be affected by vasculitis and thrombosis. Therefore, the extent of debridement should be wider than initially suggested. Typically, the process of debridement is repeated multiple times.**[4]** Following an incision, the surgeon observes tissue disintegration, absence of bleeding, and the presence of gray fluid with characteristic odor. The following observations are indicative of liquefactive necrosis. Repeated surgical debridement, biopsy with staining and culture, and wound irrigation play a pivotal role in the treatment of NF. **[16]**

Reconstruction of the soft tissues is often required following successful surgical debridement and initial presence of granulation tissue. Typically primary closure cannot be performed. Tissue reconstruction must be conducted first, subsequently the wound is closed with a muscle flap. In cases where there is no sufficient amount of skin for grafting, artificial skin may be used. **[10]** Alternatively, recent studies have demonstrated potential in the use of intact fish skin grafts to induce wound granulation and pain relief. Further research is essential to confirm efficacy and safety of this treatment. **[36]**

Antibiotic therapy for NF should be selected based on antibiograms and administered as soon as possible. The recommended choice of antibiotics, determined by the result of Gram staining, is displayed in the table below (Table. 1). **[37]**

For patients with a penicillin allergy, alternatives include vancomycin 15 mg per kg intravenous twice daily **OR** linezolid 600 mg intravenous twice daily, **AND** aztreonam 1 - 2 g intravenous every 6 to 8 hours **OR** gentamicin 3 - 5 mg per kg daily intravenous **OR** ciprofloxacin 400 mg intravenous twice daily, **AND** Clindamycin 600 mg intravenous every 8 hours.

Individuals with methicillin resistant Staphylococcus aureus (MRSA) should receive vancomycin 1 g intravenous twice daily **OR** daptomycin 6 - 10 mg per kg daily **OR** linezolid 600 mg intravenous twice daily. **[10][37][38]**

Other antibiotics recently approved by the FDA for treating acute bacterial skin infections include dalbavancin, oritavancin and tedizolid. **[39]**

<table>
<tr><td>Gram positive cocci :</td><td>Gram positive rods :</td><td>Gram negative rods or Gram positive cocci mixed or in clusters :</td></tr>
<tr><td>Penicillin 1 - 4 million U intravenous every 4 hours
AND
Clindamycin 600 - 900 mg intravenous every 8 hours</td><td>Ampicillin with sulbactam 1.5-3 g intravenous every 6 hours</td><td>Ampicillin with sulbactam 1.5 - 3 g intravenous every 6 to 8 hours
AND
Clindamycin 600 - 900 mg intravenous every 8 hours
AND
Ciprofloxacin 400 mg intravenous every 12 hours</td></tr>
<tr><td rowspan="3">OR
Ampicillin with sulbactam 1.5 - 3 g intravenous every 6 to 8 hours

AND
Clindamycin 600 - 900 mg intravenous every 8 hours</td><td rowspan="3">OR
Clindamycin 600 mg intravenous every 8 hours</td><td>OR
Piperacillin with tazobactam 3.375 g intravenous every 6 to 8 hours
AND
Clindamycin 600 - 900 mg intravenous every 8 hours
AND
Ciprofloxacin 400 mg intravenous every 12 hours</td></tr>
<tr><td>OR
Imipenem with cilastatin 1 g intravenous every 6 to 8 hours</td></tr>
<tr><td>OR
Meropenem 1 g intravenous every 8 hours</td></tr>
</table>

		OR Ertapenem 1 g intravenous once daily
		OR Cefotaxime 2 g intravenous every 6 hours **AND** Metronidazole 500 mg intravenous every 6 hours

Table 1. Recommended antibiotic therapy options based on Gram staining results. **[37]**

Hyperbaric oxygen therapy is utilized in the treatment of various infections due to its capacity to eliminate anaerobic bacteria. Additionally, it enhances tissue perfusion, increases tissue oxygenation levels, promotes formation of new blood vessels, and inhibits toxins production. **[40][41][42]** HBOT therapy has also been applied in cases of mixed infections. Hyperoxia serves as a barrier, preventing the spread of infection in NF. **[43][44]** HBOT therapy can be combined with intravenous antibiotic therapy and surgical debridement. **[38]** According to recommendations on promoting global standards in skin and soft tissue infections (SSTIs), issued in 2022 by collaborative organizations including the World Society of Emergency Surgery, the Global Alliance for Infections in Surgery, the Surgical Infection Society-Europe, the World Surgical Infection Society, and the American Association for the Surgery of Trauma, the role of HBOT in NF remains unclear due to a lack of valid evidence and clinical trials. **[45]**

Low dose radiotherapy, ranging from 1 to 2 Gy, have the potential to enhance the immune response by polarizing macrophages into an anti-inflammatory M2 type. Thereby it can be considered a potential treatment for inflammatory conditions like necrotizing fasciitis. RT elicits the M2 phenotype by activating nuclear factor KB and protein-1, increasing TNF-β along with heme oxygenase, and reducing TNF-α, inducible nitric oxide synthetase, reactive oxygen species as well as adhesion of leukocytes to endothelial cells. Additional research is

required to assess the efficacy and safety of this approach, with an emphasis on the potential risk of cancer resulting from exposure to radiation. **[46]**

Therapy for systemic inflammatory response syndrome. In order to combat SIRS along with formed superantigens in NF, intravenous immunoglobulins (IVIG) can be employed. The immunoglobulins aid the body in disposing of pathogens and deactivating superantigens. **[16][47][48][49][50]** The recommended dosage is 2g per kg. **[48][51]** If additional dosing is indispensable, it should be administered no sooner than 24 hours after the previous dose. **[47]**

Treatment for sepsis-induced coagulopathy. Administration of antithrombin or thrombomodulin intravenously has demonstrated a reduction in mortality among individuals with SIC. Antithrombin acts as an inhibitor of thrombin, factor IXa and Xa, while thrombomodulin is a cofactor for protein C activation. **[52][53][54]** Alternative option for SIC therapy involves intravenous supplementation of vitamin K. Vitamin K acts as a cofactor and participates in the carboxylation of coagulation factors II, VII, IX and X. It's also involved in the action of protein C and protein S. **[55][56][57]**. Some studies have displayed beneficial outcomes with the use of vitamin K in patients with NF, with minimal side effects, making it a considered option in SIC treatment.**[58]** Platelet transfusions can also be administered due to their crucial role in the acute phase response. A decrease in platelets count is linked to worse outcomes. **[47][50][59]** Fresh frozen plasma (FFP) is another consideration, especially in patients with a PT-INR greater or equal 1.7. **[60][61]** It contains both anticoagulants and procoagulants, however is incapable of accommodating a total reinstatement of coagulation factors, thus its efficacy in critically ill individuals is varying. **[62][63]** Heparin works by inducing natural anticoagulants including antithrombin and protein C. Yet in SIC those are deficient and heparin is ineffective. **[52][64][65]**

Therapy for critical illness-related corticosteroid insufficiency. As a treatment for CIRCI in adults with septic shock, intravenous hydrocortisone is administered at a dosage of 400 mg daily for a duration of 3 days. In children, the dose is adjusted to 50 mg/m2 daily. Patients with sepsis without shock should not undergo this treatment. Monitoring cortisol levels is essential, as both extremely high and low cortisol levels are associated with worse outcomes. **[66][67]**

CONCLUSIONS

Despite advancements in management, necrotizing fasciitis remains a highly fatal bacterial infection. A comprehensive, multidisciplinary approach is necessary for combating NF. Early identification and appropriate treatment play a pivotal role in reducing mortality rate.

The primary diagnosis is based on clinical evaluation, surgical exploration, and tissue biopsy. Fresh frozen sections are beneficial in providing rapid diagnosis. Finger test is utilized when there is a strong suspicion of necrotizing fasciitis and imaging is either unavailable, negative or inconclusive. Laboratory findings typically include positive blood and tissue cultures, leukocytosis, hypocalcemia, increased CRP, elevated serum CK and heightened serum lactate. The m-LRINEC score is considered a potential diagnostic tool to distinguish NF from other NSTI's, however further research is required to determine its accuracy. Imaging in NF incorporates the use of magnetic resonance imaging, computed tomography and ultrasonography. Radiography is not recommended due to its limited accuracy.

NF management predominantly relies on traditional methods of repeated extensive surgical debridement and antibiogram-based antibiotic therapy. Recent FDA approvals include dalbavancin, oritavancin and tedizolid. Intact fish skin grafts offer potential in soft tissues regeneration after successful debridement. Hyperbaric oxygen therapy shows promise in combating NF, however further studies are needed to determine its effectiveness. Low dose radiotherapy might boost the immune response via polarizing the macrophages towards an anti-inflammatory M2 phenotype, still additional studies are required to evaluate its efficacy and safety. Emerging therapeutic approaches target the acute phase response. Therapy of SIRS is based on intravenous immunoglobulins. Treatment for SIC includes administration of antithrombin, thrombomodulin, supplementation of vitamin K, platelets transfusion and fresh frozen plasma. Heparin has not proved to be useful in the treatment of SIC. Therapy for CIRCI involves monitoring and stabilizing cortisol levels with intravenous hydrocortisone injections.

Further research is essential to evaluate current practices, explore new diagnostic and therapeutic options, and subsequently improve outcomes for individuals with necrotizing fasciitis.

Supplementary materials

Table 1. Recommended antibiotic therapy options based on Gram staining results. **[37]**

Author's contribution

Conceptualization, ŁC, MP, PJ, AK; methodology, ŁC, MP, PK, JF; software, MP, PK, PJ; check, PK, PJ, AK; formal analysis, ŁC, MP; investigation, ŁC, PJ, JF; resources, ŁC, MP, PK, JF; data curation ŁC, MP, PK, PJ; writing - rough preparation, ŁC, MP, AK; writing - review and editing, ŁC, MP, PK, PJ, AK, JF; visualization ŁC, MP, JF; supervision, ŁC;.
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