Review Article

Necrotizing Soft-tissue Infections: An Orthopaedic Emergency

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Abstract

Necrotizing soft-tissue infections are caused by a variety of bacterial pathogens that may affect patients at any age or health status. This orthopaedic emergency initially presents with nonspecific signs such as erythema and edema. As the disease progresses, classic signs such as bullae, cutaneous anesthesia, ecchymosis, tense edema, and gas can be seen. A high level of suspicion is needed to properly identify and treat in a timely manner. Pain out of proportion to presentation and rapid progression even with appropriate antibiotic treatment should heighten suspicion of a necrotizing soft-tissue infection. The mainstay of management is extensive débridement and decompression of all necrotic tissue and broad-spectrum antibiotics. Débridements are repeated to ensure that disease progression has been halted. Early surgical débridements should take precedent over transfer because of the high rate of limb loss and mortality as a result of surgical delay.

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Hippocrates astutely described what we now know as necrotizing soft-tissue infection (NSTI). He called it a "malignant case of erysipelas" where "fatal cases were many." He noted a precipitating event as a "trivial accident or very small wound" that progressed to "abscessions ending in suppurations" or where "flesh, sinews and bones fell away in large quantities." In addition, the hallmark dishwater purulence was described as "flux . . . not like pus but . . . a different sort of putrefaction with a copious and varied flux." He saw that in cases that did not have discrete abscess formation with frank drainage "there were many deaths."[1] This account describes the common presentation, progression, and natural history of untreated NSTIs. For reasons that are not agreed on, this disease process has a high morbidity and mortality despite medical advances and necessitates that surgeons have a high degree of suspicion to diagnose and make a decisive move to treat once a diagnosis of NSTI is confirmed or highly suspected.

NSTIs are not uniform in presentation or extent of involvement. NSTIs include any or all soft-tissue layers (ie, skin, subcutaneous fat, fascia, muscle). Necrotizing fasciitis, a subset of this broad disease entity, is the most common manifestation of NSTI; however, one must be aware of other presentations as well (ie, necrotizing adipositis, pyomyositis). The general diagnosis and management principles for necrotizing fasciitis and other specific forms hold true for all NSTIs and therefore will be discussed broadly in the context of this review.

Unfortunately, NSTIs fall on a spectrum of clinical severity. Unlike nonnecrotizing soft-tissue infections, NSTIs cannot be managed with antibiotics alone because these infections commonly occur in the extremities. Orthopaedic surgeons are often involved in the early management of

Table 1

Common Bacteria in Necrotizing Soft-tissue Infections

Polymicrobial	
Anaerobes	*Bacteroides*, *Clostridium*, Other anaerobes
Enterobacteriaceae	*Escherichia coli*, *Enterobacter*, *Klebsiella*, *Proteus*
Monomicrobial	Predominantly group A *Streptococcus*
	Other β-hemolytic *Streptococcus*
	Community-acquired MRSA
	Vibrio (with exposure)
	Aeromonas (with exposure)
	Prevotella
	Fungal

MRSA = methicillin-resistant *Staphylococcus aureus*

this pathology as consultants and therefore have a critical role in raising the possibility of and potentially diagnosing NSTI.[2] In its most virulent form, an NSTI can be rapidly progressive and quickly fatal without intervention. Awareness is crucial in preventing this outcome, and a current review of the relevant literature is presented to raise awareness.

Epidemiology and Risk Factors

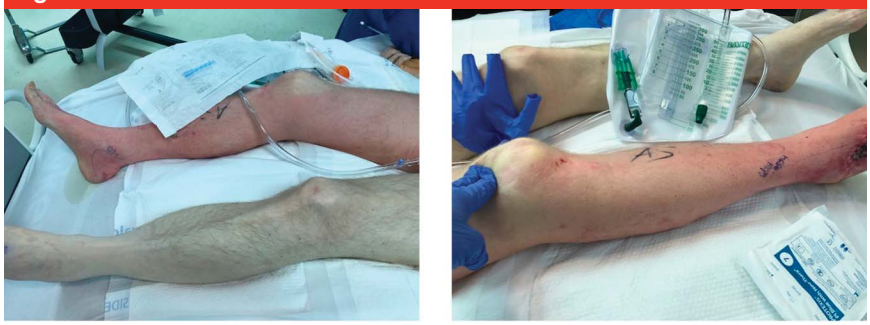
NSTIs are a heterogeneous group of rare, limb, and life-threatening processes caused by a variety of bacterial pathogens that may affect patients at any age or health status. An estimated 1,000 cases per year occur with an increasing incidence in the United States.[3] In an analysis of Centers for Disease Control and Prevention data of invasive group A *Streptococcus*, a common infecting agent in NSTIs, an estimated 10 to 13,000 cases occur each year with a mortality of 29% in cases that involve NSTI.[4] NSTI has a predilection for the aging, infirm population, but all age ranges can be infected. However, up to 40% of patients have no known risk factors.[5,6] Diabetes mellitus is the most prevalent risk factor and is present in up to 71% of infections.[6-11] Intravenous drug abuse is another common predisposing factor in as many as 43% of patients with NSTI.[11] Other associations include smoking, trauma, prior methicillin-resistant *Staphylococcus aureus* (MRSA) infection, chronic hepatitis C, HIV/AIDS, chronic illness, increasing age, NSAID use, and exposure to persons infected with invasive group A *Streptococcus*.[6,8,11-14] Using the National Surgical Quality Improvement Program data, a risk calculator found that seven independent variables correlated with mortality including age greater than 60 years, functional status, requiring dialysis, American Society of Anesthesiologists class 4 or higher, emergent surgery, septic shock, and low platelet count.[15]

The infections can be grouped broadly into polymicrobial and monomicrobial subtypes. Polymicrobial NSTIs account for approximately 75% of cases making it the most common presentation.[16,17] These polymicrobial infections are commonly associated with risk factors such as diabetes, peripheral vascular disease, recent surgery, trauma, or immunocompromised hosts. These infections tend to be a combination of aerobic and anaerobic bacteria. A variety of bacterial isolates have been cultured from this type, which tends to arise from a chronic source such as a diabetic foot ulcer.[18] Table 1 lists common organisms cultured in the polymicrobial subtype. The remainder of infections are monomicrobial in nature.

These monomicrobial infections are primarily caused by group A streptococcal infection, other β-hemolytic strep, MRSA, and in the fresh water setting *Aeromonas hydrophila*. Clostridial species are the most prevalent single organism infecting agents and account for a higher incidence of limb loss and mortality.[16] In cases of saltwater or consumption of oysters/cirrhosis Vibrio vulnificans.[19] These patients presenting with monomicrobial infections may not have the same identifiable risk factors as those described with polymicrobial infections. In the setting of the monomicrobial infection, group A streptococcal infection is likely related to skin injury or hematogenous strep from pharyngeal infection or colonization.

All NSTIs begin with an inoculum of bacteria at the site of infection. Bacteria may be transferred from direct contacts or via skin or nasopharyngeal colonization.[6,14] Wounds ranging from small skin abrasions to large traumatic lacerations may serve as a point of entry. Individuals can be asymptomatic carriers on the skin or mucosal surfaces where transient bacteremia distributes the pathogen to a source of tissue damage to initiate an infection. Cases of NSTI being caused by skin breakdown in a poorly padded splint, external-fixation pin sites, and IV sites are reported.[12,13] Once the infecting agent has gained access into the host, the disease is perpetuated by bacterial virulence factors that facilitate rapid spread and systemic toxicity. Although the exact mechanisms of rapid spread and tissues destruction likely vary between species and are not fully characterized, these factors are theorized to contribute to local tissue progression through tissue ischemia, enzymatic degradation, cell lysis, and a systemic response by the release of

Figure 1



A B

Photographs showing the (**A**) nonspecific erythema and (**B**) edema presentation of necrotizing fasciitis in a patient with no erythema or proximal edema on physical examination just 6 hours before.

Figure 2

Radiograph showing gas in the soft tissue.

toxins into the circulation.[18,20,21] Bacterial inoculation causes the secretion of local cytokines which activates platelets. In the presence of activated white cells, the platelets clump leading to microvascular occlusion. This occlusion in turn disrupts the cutaneous blood supply and lymphatic channels inciting a local hypoxia and cytokine release resulting in cellular dysfunction and death. The local ischemia and subsequent necrosis limits access of antibiotics and humoral response to the affected region and leads to progressive cutaneous nerve damage causing severe pain early in the disease to local anesthesia when nerve endings have died.[21] Invasive group A *Streptococcus* has a high expression of one such factor called exotoxin that is seen in most strains that produce invasive infections.[20,21] Another common infecting pathogen, MRSA, produces panton-valentine leukocidin, a toxin commonly seen in necrotizing infections that causes muscle necrosis.[8] Toxin production and the host's response to the toxins are potential targets for intervention in patients with these difficult infections.

Presentation

Presenting features of necrotizing soft-tissues injuries can be vague and nondescriptive. There may be no features that initially distinguish necrotizing soft-tissue infections from nonnecrotizing soft-tissue infections. Close monitoring with interval examination is necessary because NSTIs can progress quickly, and seemingly benign presentations may become clearly defined over interval examinations (Figure 1, A and B).

A thorough history should be performed assessing for risk factors discussed earlier. In addition, potential sources of exposure and sites of inoculation should be elicited. In approximately 50% of cases, no site of entry is found. Exposure to household cohabitants infected with group A *Streptococcus* raises the risk of infection to 2000 times that of the general public, and such exposures should be determined.[6,22] Healthcare workers caring for patients with these highly virulent infections are at increased risk as well.[14] Pain out of proportion to examination is the most common finding and should raise one's suspicion for a more aggressive process.

Physical examination findings can be initially benign. The most common findings are erythema, edema/swelling/induration, and pain, although skin changes may not be present early.[7,10,18,23] Erythema can progress from red to purple/red as subcutaneous vessels are effaced and then to blue gray as superficial layers begin to necrose. As the disease progresses, the pain may abate because cutaneous nerves are obliterated by the infection resulting in anesthesia of the skin. Bullae may appear signifying tissue loss and are highly specific for an NSTI. (Figure 2) Finally, palpable crepitance in the tissues around the focus of infection, indicative of subcutaneous gas formation, is highly suggestive of an NSTI because of anaerobic bacteria. These so-called hard signs (ie, anesthesia, ecchymosis/bullae, gas in tissue) are present up to 44% of the time.[7,18,24] Importantly, the presence of gas in tissue that is identified with clinical examination or radiograph (Figure 2) is found only in infections from species that can grow under anaerobic conditions producing non–carbon dioxide gases, and these gases are present in less than 50% of cases. Up to 83% of patients present in clinical duress with signs consistent with a systemic inflammatory response syndrome, sepsis, or septic shock.[23]

Diagnosis

Early diagnosis confirmation is often delayed because of the underestimation or confusion with cellulitis. As mentioned previously, hard signs of NSTI are present in a minority of

Table 2

Laboratory Risk Indicator for Necrotizing Fasciitis Score (Scoring System to Predict Necrotizing Soft-tissue Infections)

Laboratory Parameter, Units	LRINEC Points
CRP, mg/L	
<150	0
≥150	4
Total WBC, k/mm^3	
<15	0
15-25	1
>25	2
Hb, g/dL	
>13.5	0
11-13.5	1
<11	2
Sodium, mmol/L	
≥135	0
<135	2
Creatinine, mg/dL	
≤1.6	0
>1.6	2
Glucose, mg/dL	
≤180	0
>180	1

LRINEC = Laboratory Risk Indicator for Necrotizing Fasciitis

patients, and thus a high index of suspicion and ongoing vigilance are needed to prevent potentially fatal progression.[3] No one finding or a group of findings has been prospectively validated as a highly sensitive and specific means of confirming the presence or lack of NSTI, and therefore, all objective findings must be considered in the context of the patient's clinical course.[25]

Laboratory Evaluation

Additional laboratory evaluation is useful to stratify presenting findings. Initial workup of a suspected necrotizing infection should include a measure of white blood cell count with differential, platelet count and hemoglobin, sodium, creatinine, blood glucose, albumin, and C-reactive protein (CRP) levels. Blood cultures should be obtained when concern for systemic involvement is raised because this can direct early antibiotic therapy and confirm presence of virulent pathogens. Studies have shown low sodium level, elevated creatinine level, and high white blood cell count were sensitive at predicting NSTI.[24,26] These findings were used along with laboratory values found to be predictive of NTSI in a multivariate regression to develop a scoring system for prediction of necrotizing infections[27] (Table 2). Although this Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score has not been validated in a prospective trial, the components of the score are still useful in addition to the overall assessment and as a prognostic tool.[9,19,28] A study retrospectively comparing a cohort of patients with severe erysipelas subsequently diagnosed with either cellulitis or NSTI found that the overall clinical presentation for each was similar; however, NSTI patients were more likely to have higher pain scores, a higher CRP level, and a higher LRINEC score[29] (Table 2). Another series analyzing vibrio NSTI found severe hypoalbuminemia, thrombocytopenia, and bandemia as a predictor of mortality and suggested that these values be used to direct early surgical intervention.[19] Because of the variability of laboratory data indicative of NSTIs, the use of the LRINEC is surgeon dependent and has never been prospectively validated.

Imaging

Radiographic evaluation may or may not assist in diagnosis of NSTI. Imaging findings are often nonspecific and may not manifest until substantial disease progression has occurred. Further, advanced imaging may delay time to surgical débridement and it should be used judicially in evaluation of equivocal cases. Gas dissecting in facial planes on plain radiograph (in the absence of an open wound) is a hard sign indicative of NSTI although this finding is present in a minority of cases. CT and MRI are advanced imaging techniques that may be considered in the stable patient with nonfocal disease to assess for signs of necrotizing fasciitis (thickening of deep fascia) or deep abscess or necrotic area.[30] MRI is more sensitive at detecting subtle changes in the fascia and deep edema, but acquisition time in most hospitals is longer than that of a CT scan; so again, a thoughtful approach is needed to optimize data gathering while preventing lengthy delay in definitive management. Advanced imaging can be useful to direct surgical approach if no superficial manifestations are present.

Presence of hard signs of NSTI makes diagnosis more certain. Clinical decompensation or progression of infection despite broad antibiotic management with increasing serum lactate, CRP >150 mg/L, or leukocytosis >25,000/mm^3 are indications for urgent surgical intervention. Diagnosis is formally confirmed with growth of microorganism from cultures taken from deep tissue intraoperatively as discussed later. Diagnosis is confirmed on intraoperative inspection of deep structures. These findings include necrotic tissue and dusky gray appearance of fascia. Microbiologic diagnosis is confirmed with deep tissue cultures with deep tissue samples being submitted to histopathology to aid in confirmation of diagnosis and focused antibiotic management.

Management

Management of NSTIs is best carried out by a multidisciplinary team with

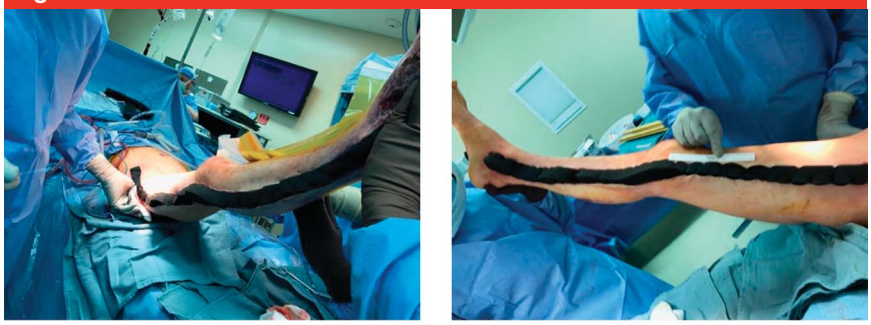
experience treating large soft-tissue wounds. However, initial management should be done by the first surgeon who recognizes and diagnoses this potentially lethal infection. The mainstay of management is expeditious, soft-tissue decompression and débridement of the necrotic tissue with first broad-spectrum antibiotic management and then focused systemic antibiotic management.[31] Repeat débridements are done to ensure disease progression has halted and to remove unviable tissue. As many patients present with a systemic response or progress to systemic toxicity, intensive care unit admission with critical-care team resuscitative support is mandatory. Adjunctive management may be considered in special cases.

Surgical Débridement

When NSTI is diagnosed or is suspected based on the progression of symptoms in spite of antibiotic management, surgical intervention should take precedence. Surgery should not be delayed for imaging assessment, and resuscitation and antibiotic administration should be ongoing concomitantly in preparation for surgery.[32] Broad decompression and débridement of the infected tissue helps to halt progression and allows for antibiotics to take effect and for the host's immune system to respond.[3] Débridement should begin with a longitudinal incision over the nidus of infection (ie, entry site, site of abscess, site of original erythema/necrosis). In the early phase, a simple skin and subcutaneous incision down to fascia and extended proximally until uninvolved tissue is encountered is required. If the underlying muscle is involved or notable muscle swelling is present, the underlying fascia should be incised as in a compartment release. Often, dual incisions are required on the extremities to ensure adequate decompression is attained as in compartment syndrome. Devitalized tissue should be removed in all affected layers (eg, skin, subcutaneous fat, fascia, muscle, bone) until healthy tissue margins are reached (Figure 3, A and B). Multiple deep tissue cultures should be collected for microbiologic analysis. Débridement should proceed with no regard for late reconstruction because this may bias a surgeon to leave disease-burdened tissue. Amputation is required if the progression of the infection is so rapid that débridement alone would not be adequate, the limb is not salvageable because of notable tissue loss or if the condition of the patient does not allow repetitive débridements. Guillotine amputations above the level of progression are the most direct form of amputation and should be considered at the extreme end of the surgical algorithm. In less progressive cases, small ladder incisions may be used to assess more proximal sites of progression. If diagnosis is equivocal, a smaller incision can be made to assess for deep fluid or tissue plane disruption (finger test). Once a thorough débridement is complete, wounds are dressed according to their location and practical application. Moist gauze packing is the simplest dressing and may be useful early when frequent débridements are ongoing. Vacuum-assisted closure can be used and aids in preparing wounds for subsequent closure, graft, or flap.[33] Early surgical débridement is so important to limb salvage and patient survival in which initial débridement should be considered before transferring a patient to a higher level of care for intensive care and reconstruction. The initial débridement is not complicated or technically difficult and should be treated similarly to compartment syndrome where initial surgical débridement can be done by any surgeon and then transfer the patient if needed for extended care.

The reason for the success of a simple incision over the area involved is not completely clear. Surgical incision and débridement decreases the source and bacterial load, but the condition of the skin and subcutaneous tissue improves quickly after the skin incision is extended proximally into healthy tissue. The decompression seems to halt the bacteria that spread in the fascial layers and lymphatic system. The incision may allow decompression and abort the cycle of local tissue inflammation and edema that drive the proximal spread of the disease process.

Figure 3



A **B**

Photograph showing (**A** and **B**) extensive dual incision fasciotomy with negative pressure wound therapy placement. Immediately after fasciotomy, notable decrease in erythema is seen.

Early surgical re-exploration is recommended within 24 hours of initial débridement and has been shown to decrease mortality and rate of acute kidney injury compared with repeat débridements done at greater than 48 hours.[17] The same principles apply to subsequent débridements as to the initial débridement. The average number of surgical procedures in the management of NSTI in large series ranges from 2 to 5 times.[10,26,28,34,35]

When the clinical course has improved and no signs of progression of disease have manifested for several days, reconstruction procedures can be pursued. The sooner the decompression is done, the less the necrotic tissue needs to be removed and allows wounds to undergo primary closure or skin grafting although occasional local or free soft-tissue transfers are necessary, and nearly half of all patients will need some form of coverage.[32-34] One large retrospective study reported an average of 1.2 reconstructive procedures in each case of NSTI.[26]

Antibiotics

Antibiotic administration complements the surgical débridement as a means to further decrease infective load. Broad-spectrum empiric antibiotics should be administered on presentation based on the presenting history, patient risk factors, and possible exposures. Most hospitals will have an infectious disease protocol for empiric antibiotic treatment in the critically ill based on local virulence patterns and antibiogram. A broad-spectrum, synergistic penicillin (ie, piperacillin/tazobactam, ampicillin/sulbactam) with clindamycin or carbapenem is included in most recommendations for empiric coverage. Because of the possibility of community acquired MRSA, vancomycin or linezolid should be added to broaden the antibiotic scope.[31,33] Blood cultures and tissue cultures further direct bacteria-specific treatment based on susceptibilities and local policies. Antiribosomal agents are recommended to (1) limit toxin production and (2) enhance the effectiveness of cell wall antimicrobial agents in setting of high bacterial burden. For gram-positive pathogens, the antiribosomal agent is most commonly clindamycin.[22] Linezolid may have similar effects on protein synthesis and has been reported as an antibiotic supplement in the management of NSTI.[36]

If gram stains of the excised tissue demonstrate the presence of gram-negative pathogens such as Tularemia, agents in the tetracycline class should be considered.

No specific, evidence-based guidelines directing antibiotic selection, mode of delivery, or duration are available. Consultation with an infectious disease specialist with experience in treating soft-tissue infections may aid in directing long-term antibiotic management.[31]

Adjuncts

A number of adjunctive management have been attempted to supplement management of these devastating NSTIs. Given the heterogeneity of this disease process and the relatively rare occurrences, high-quality evidence of therapies used in addition to débridement and antibiotics is limited.

Adjuncts have been sought to attenuate the systemic response to disease. Intravenous immunoglobulin (IVIG) offers theoretical benefit in blunting the host's response to bacterial toxins.[20] Pooled immunoglobulins from donors previously infected with toxin-producing bacteria are thought to neutralize circulating toxins and lessen the systemic response. However, data are conflicting on the utility of this treatment with studies showing no change and notable change in outcomes.[22,37] This change may be because not all IVIG infusions contain the same proportion of antitoxin immunoglobulins. In a similar pursuit of immunomodulation, the only randomized controlled trial involving NSTIs evaluated the drug AB103, a substance that acts on T cells to decrease the immune response to toxins. Unfortunately, the authors found no changes when the novel therapeutic was compared with the placebo.[35] Corticosteroids have a similar, albeit less specific effect on the immune response to bacterial toxins have been used as an adjunct in patients with NSTI and toxic shock syndrome.[38]

Hyperbaric oxygen treatment is theorized to aid in the prevention of the progression of tissue loss and therefore morbidity and mortality. However, in a Cochrane review, no literature worth of analysis was found, and no summation of data was suggested.[39] Hyperbaric oxygen treatment may be considered if it does not interfere with access to surgical and antibiotic treatment.

Outcomes

The morbidity and mortality associated with NSTIs are substantial. Mortality caused by this disease has been reported in as many as 33% of cases with an average mortality of 22.6%.[2,4,5,10,11,16,22,23,26,28,34,40,41] Risk factors for increased mortality are similar to risk factors for acquiring an NSTI. Surgical delay or factors indirectly resulting in surgical delay such as transfer from an outside hospital is the single most important modifiable factor contributing to mortality.[5,10] Nonmodifiable risk factors include increasing age, multiple comorbidities, chronic illness, and immunosuppression.[4,5,9,18,23,31,41,42] Other predictors of mortality are related to the systemic effect, how far the disease has progressed, at the time

of admission (ie, creatinine, sepsis status, elevated lactate, amount of tissue involved).[42]

If one survives the initial management of an NSTI, morbidity can be expected from enduring the treatment. Surgical sequela may limit function if substantial muscle or skin is lost. Peripheral circulatory issues or lymphatic problems may also occur secondary to surgery. Extensive scarring and stigmata of reconstruction are also prevalent cosmetic changes. Disease resulted in amputation in 18% to 28% of cases.[10,26,41]

Outcomes in the last decade are improving with decreased overall mortality likely secondary to earlier diagnosis, increased awareness of surgical urgency, improved antibiotic coverage, and involvement of multidisciplinary providers.[40]

Summary

Necrotizing soft-tissue infections have been present and documented since the time of Hippocrates. This disease process continues to have a high morbidity and mortality with approximately one third of patients undergoing amputation or death. Early diagnosis and surgical intervention is critical to minimize the severity of illness. Orthopaedic surgeons are commonly asked to differentiate cellulitis from a more aggressive necrotizing soft-tissue infection. We need to have a high index of suspicion and follow the progression of disease to identify when surgical intervention is critical. Resuscitation, broad empiric antibiotic therapy, and surgical débridement are required. Surgical débridement is time sensitive and similar to compartment syndrome because of its acuity which makes transfer of patients with a diagnosis of an necrotizing fasciitis challenging. Adjunct treatment in "toxic patients" may include IVIG or short-term high-dose corticosteroids.

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