World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

Contemporary strategies for diagnosis and management of necrotizing soft tissue infections: A review

Constantinos Avgoustou *

Department of Surgery, General Hospital of Nea Ionia "Constantopoulion-Patission (Aghia Olga)", Athens, Greece.

World Journal of Advanced Research and Reviews, 2023, 17(01), 489–500

Publication history: Received on 03 December 2022; revised on 10 January 2023; accepted on 13 January 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.17.1.0057

Abstract

The necrotizing soft tissue infection (NSTI) is an uncommon but rapidly progressive destructive disease associated with high mortality. In this study, we review basic knowledge and emphasize contemporary perspectives in diagnosis and treatment of adult NSTI.

The mainstays of management of NSTI that can modify outcomes are the awareness for early detection and that all aspects of multidisciplinary treatment should be started promptly and simultaneously. Surgical debridement entails aggressive approach with extensive, and, if required, repeat necrectomies to completely control advancing sepsis in soft tissues. There is general agreement that the principles of damage control surgery should be applied on deranged NSTI patients. Continuous supportive care and scheduled management of residual open wounds are considered as extremely important. It has also been recognized that relative clinical guidelines and recommendations are growing in number and may vary widely in quality. Notably, the compliance of therapists to given guidelines differs among studies, and variations in aspects of clinical practice exist. Many studies comprise small numbers of patients, making evaluation of proposed novel techniques or adjuncts unreliable.

Concluding, NSTI diagnosis should be promptly established, surgery should never be delayed so that sepsis remains reversible, and supportive care should be continuous. Novel therapeutics are required to combat this persistently lethal disease, thus, the next research steps should focus on determining if optimization of modifiable predictors would improve outcomes. Stronger well-conducted studies and wider dissemination of developed evidence-based instructions, while ensuring the strict compliance of daily clinicians' practices, are required to further improve outcomes.

Keywords: Necrotizing soft tissue infection; Necrotizing fasciitis; Resuscitation; Surgical debridement

1. Introduction

Necrotizing soft tissue infection (NSTI) includes a heterogeneous group of potentially lethal infections of the soft tissue compartment (dermis, subcutaneous fat, superficial and deep fascia, and/or muscle), characterized by rapid spread though fascial planes, progressive tissue destruction due to toxins released from virulent bacteria, and causing systemic toxicity [1-7]. Initially, local signs can be minimal and become more prominent only as the disease progresses [3].

The NSTI has been recognized very early, with reports dating back to notations by Hippocrates [8]. Genital and perineal NSTIs were referred to as "Fournier gangrene" since the late 1800s after a series of five male patients presented in 1883 and 1884 by the French dermatologist and venereologist Jean Alfred Fournier [9]. The first large-scale description of NSTIs came from Confederate Army surgeon Dr. Joseph Jones during the American Civil War who reported 2642 cases

*Corresponding author: Constantinos Avgoustou

with a mortality rate of 46%[10]. Although a reduced incidence has been recently reported, there are still approximately 3800-5800 cases annually in the United States, with complication and fatality rates of nearly 50% and up to 10% respectively [2]. Necrotizing fasciitis (NF), the worst and most fulminant form of the NSTIs, has a reported incidence of 0.4 cases per 100000 adults every year[1]. Unfortunately, a stagnant and high and unacceptable average mortality rate of around 20% has been recorded worldwide over the past 20 years [3,7,11-15]. The interval between the onset of symptoms and initiation of treatment has been recognized as the crucial determinant for outcome [4,6]. Relative data are nearly incontrovertible that delay, particularly in operative debridement, is associated with increased risk of death [4].

The basic principles of improved awareness for timely diagnosis, the synchronous intensive resuscitation/supporting, the prompt administration of broad-spectrum antimicrobial therapy, and the aggressive surgical debridement (necrectomy), which basically is a damage control surgery (DCS), as well as the required secondary surgical procedures, remain unchanged for the last decades, and they are still the pillars of therapy, aiming at reducing morbidity and mortality [2,4,6]. However, better compliance of physicians with the existing guidelines as well as innovative therapeutics are still needed to combat this persistently lethal disease [4,7].

In this study, we review basic knowledge and the new options relevant to different aspects of the NSTI disease, and list contemporary perspectives of diagnosis and management. Intentionally, the MEDLINE database using PubMed was used to collect the most recent English language articles regarding adult NSTI.

2. NSTI disease: overview and current concepts

NSTI encompass a group of destructive soft tissue bacterial necrotic disease processes, which can involve skin, subcutaneous fat, fascia(s) and/or muscle(s), associated with rapid spread along tissue planes, systemic toxicity and potentiality for high mortality [11,12,16-22].Although NSTIs have some common clinical features, various entities have been recognized, such as streptococcal gangrene, gas gangrene (clostridial myonecrosis), synergistic necrotizing cellulitis and progressive bacterial synergistic gangrene [5]. Subtle differences may distinguish one entity from another, but the clinical approach to diagnosis and treatment is similar. The disease includes also “subtypes”, based on the tissue layers affected (NF, necrotizing myositis, necrotizing cellulitis), and on the anatomic region (Fournier’s gangrene, Ludwig’s angina) [7,18,19].

2.1. Pathophysiology - Mechanisms of evolution of the disease

Two distinct pathogenesis pathways have been described regarding the evolution of NSTI: (i) with a recognizable portal of bacterial entry (i.e. injure, scrape), where the organisms enter the soft tissue causing local infection, or (ii) occurring when a non-penetrating tissue injury (i.e. hematoma, muscle sprain) is infected by transient bacteremia, usually originating from the gastrointestinal or genitourinary tract [5,17,20,22,23]. A secondary infection by the host’s own indigenous aerobic or anaerobic microflora usually leads to polymicrobial infection [4-6,14,16].

Once the pathogenic organisms reach the soft tissue, bacteria proliferate and release into the systemic circulation particularly destructive endotoxins causing acute inflammatory reactions(systemic inflammatory response syndrome, SIRS), that include increased permeability of the micro-vasculature (capillary leak syndrome), emigration of the leucocytes, and cytokine production by leukocytes[1,5,20]. The initiation of the cytokine cascade is directly associated with the vascular endothelial damage (toxin-induced platelet and leukocyte aggregation ,dermal capillary occlusion) and the development of fascial ischaemic necrosis [5,14,20]. The coagulation cascade of thromboplastin is activated resulting in disseminated microthrombosis of the feeding fascial vessels. High-protein fluid exudates out of the blood vessels into the soft tissue and accumulates along the deep fascia [1,20]. Hypoxia and ischaemic destruction of the subcutaneous tissue and the deep fascia ensues as the process progresses, resulting in extensive necrosis and liquefaction of the fascias and the surrounding tissues [1,14,20].The most prominent affected skin areas might be in discrepancy with the position of the fascial necrosis [3].Typically, the disease is characterized by sudden onset, spreads along existing fascial planes, and deteriorates rapidly[22,23]. It is not associated with an abscess, but if an abscess is left untreated or is inadequately drained, it may transition to progressive necrotizing infection [4].

According to the causative organisms, NSTIs have been traditionally classified in three basic categories: a) Type I-polymicrobial, mixture of aerobic and anaerobic bacteria (55%-75% of NSTIs); b) Type II-monomicrobial, caused by Group A *Streptococcus* (GAS) or in association with community-associated methicillin-resistant *Staphylococcus aureus*(CA-MRSA) ; and c) Type III-monomicrobial, *clostridial* infections [4,5]. Bacteria commonly identified include *hemolytic Streptococci (GAS, peptostreptococci)*, *Staphylococci (aureus, hemoliticus), Enterobacteriaceae (Escherichia coli,*

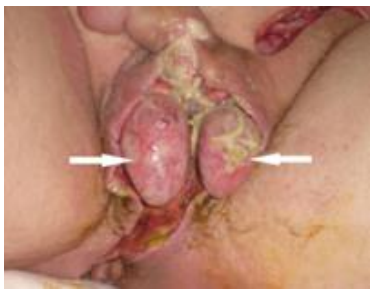
Klebsiella sp., Proteus mirabilis), Pseudomonas aeruginosa, Acinetobacter sp., Bacteroides sp., Clostridium perfringens, Fusobacterium sp. and *Citrobacter freundi*[1,3-6,16,23].

2.2. Clinical presentation and diagnostic evaluation

Any part of the body can be affected, but perineum, external genitalia, extremities and trunk appear to be the most common areas; various predisposing pathologic conditions, such as untreated chronic soft tissue abscesses, have been implicated [14,21,22]. Risk factors for the development of NSTIs include diabetes mellitus, obesity, malnutrition, congestive heart disease, peripheral vascular disease, chronic pulmonary disease, chronic alcoholism, advanced age (>60 years), intravenous drug use and immunocompromised states such as steroid use, HIV infection/AIDS and malignancy or transplantation under therapy [4, 14,16,22].

Diagnosis in the early stages can be challenging, as differentiation from the much more common non-NSTIs (i.e. common cellulitis) may be very difficult because the minimal initial local signs become prominent only as the disease progresses .For this reason, various algorithms for the diagnosis and treatment of NSTIs have been proposed [3,5,14]. NSTI should be suspected in those patients with a detected soft tissue infection with sudden onset who rapidly deteriorate [3,14,23]. It cannot be overemphasized that in clinical practice, time to surgical intervention decreases and outcome improves when awareness is increased and more timely referral of the patient is achieved [24,25].

Figure 1 NSTI presenting as Fournier's gangrene extended to lower abdominal wall-scrotum-penis (skin)-perineum (55-year-old man, own material)



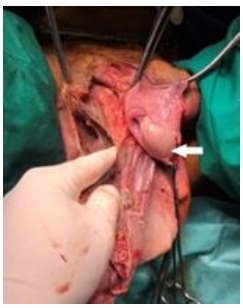


Figure 2 Index surgical debridement, residual large surgical wounds involving: a) scrotum and perineum (left/65-year-old man, own material), b) scrotum, perineum and lower abdominal wall (right/87-year-old man, own material). Denuded testicles (arrows) are spared

Patient's presentation may range from subtle physical findings to systemic signs of sepsis [5,17,18]. In the early phase, the spread and extent of infection that takes place under the skin into the subcutis do not correspond with the overlying skin changes, frequently resulting in ambivalent clinical diagnosis or in underestimation of the seriousness of the disease in progress, leading to delays in diagnosis and treatment, with the most dire concequences [1,3,5].Moreover, preadmission treatment with antibiotics or non-steroidal antiiflammatory drugs can modify the initial clinical picture and often mask the severity of the underlying infection [5,16]. Thus, early stages of the disease may present only minimal erythema or skin discoloration, tense edema beyond the erythematous area, local warmth or induration or numbness, and disproportional pain(Figure 1) [14,23]. Once the infection progresses, "hard signs" can be seen, including severe pain or local anaesthesia, local blistering and hemorrhagic bullae, purulent collections, foul odor, skin sloughing or necrosis, crepitous/soft tissue emphysema, compartment syndrome, as well as systemic manifestations of sepsis such as fever, hypotension, leukocytosis and acidosis [5,21,22]. The hallmark symptoms of prolonged NF, especially on the perineum-external genitalia and the extremities, include intense pain and tenderness over the involved skin and underlying muscles [1].In incisional biopsies, classical signs indicative for NF are swollen tissue, dull grey necrotic tissue, grey fascia, small vessel thrombosis, lack of bleeding, "dishwater" pus, non-constructing muscle fibres, and a positive "finger test" (see below) [3,4]. Systemic manifestations are a common feature of the prolonged untreated disease: SIRS, septic shock or multiple organ dysfunction syndrome (MODS) and multiple organ failure (MOF), that could lead to death [22]. Notably, the pathophysiological triad of coagulopathy, metabolic acidosis and hypothermia is called "lethal triad" [6,24]. Furthermore, the patients may present late, as a consequence of the rapid spread of the pathological process in deep tissues along the fascias, the lack of impressive skin changes over the infectious focus, and the limited or even absent significant subjective sensations due to the destruction of the subcutaneous nerves (i.e. NF), all leading to the underestimation of the severity of the disease [14,22,25]. NSTI patients, especially those in shock or with severe comorbidities, should be admitted in Intensive Care Unit (ICU) or High Dependency Unit (HDU) [3,4,6,20].

The diagnosis of NSTI/NF relies on clinical findings and can further be supplemented and supported by several diagnostic adjuncts, including common laboratory tests, plain x-rays (to detect air in soft tissues), the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) scoring system (proposed score $\geq$6 for NF), the Fournier's Gangrene

Severity Index, ultrasonography (US),enhanced computed tomography (CT) and magnetic resonance imaging (MRI) at the site of infection, and fascia biopsy[4-6,14,18-20,26-28]. Special imaging is important in diagnosis in equivocal cases as well as for the assessment of the infectious extent and severity [1,4,14,27].

Expected simple laboratory testing results include leukocytosis with a left shift (leukopenia in immunocompromised patients),elevated C-reactive protein, marked hyperglycemia (especially among diabetics), uremia (due to dehydration), elevated creatinine (in cases with kidney injury), elevated creatine kinase (in cases complicated with myositis), and hypocalcemia due to deposition to necrotic subcutaneous fat [4, 5,20]. Moreover, the biochemical tests can also be used as diagnostic adjuncts when it is difficult to distinguish between NSTI and severe cellulitis [20].Furthermore, in order to determine the degree of sepsis/septic shock in prolonged cases /critically ill patients, a comprehensive laboratory work-up and calculation of the SOFA and APACHE II scores using arterial blood gas and other variables is essential, and contributes to choose optimal treatment [4,6,22].

The 2018 World Society of Emergency Surgery (WSES) /Surgical Infection Society Europe (SIS-E) consensus conference guidelines for the management of skin and soft tissue infections suggested that incisional biopsy and Gram stain may be an important adjunct in early stages of suspected NSTI patients (recommendation 1C) [3,18,20]. However, this adjunct may be difficult to obtain under emergency conditions in many instances; for example, a pathologist may not always be immediately available for frozen section interpretation, and waiting for the results should not be a possible option [4-6,13,25]. Reported series on bedside tissue biopsy with frozen section have shown this method to be reliable or promising but the related experience is limited [4]. On the other hand, the use of intraoperative diagnostic modalities, such as the frozen section or Gram stain, has been accused to cause treatment delay, and it has been recommended to use them only if indicated: in ambivalent cases to prevent unnecessary debridements in non-NSTI cases or prevent delay and/or abregnation of debridement due to less evident macroscopic findings in NSTI cases [6,18,20]. However, this strategy has not yet been validated by a well-conducted clinical study [6,18].

The US- or CT-guided infectious fluid aspiration before the administration of empiric antibiotic therapy for Gram stain and culture, along with the blood cultures, may provide valuable information regarding the infective organisms spreading through the deep fascia[4,5,20]. Current studies also showed that other variables, such as the value of lactate dehydrogenase (LDH), lactate, albumin, total protein and pH of the infectious aspirate have an excellent diagnostic accuracy for NSTI [20]. Percutaneous biopsy and examination of a frozen section has been argued to be subject to sampling error and that is not a good substitute of open surgical inspection and biopsy [5].

2.3. Outcome: Morbidity and Mortality

NSTIs remain associated with a heavy mortality and significant morbidity despite the improvement in clinical care, usage of broad spectrum and targeted antibiotics, and the aggressive surgical debridement [12,14,19,22,28]. Average mortality rates remained high (around 20%) over the past 20 years [3,7,11-15,19]. However, the mortality appears recently to be declining, which should be attributed to increasing awareness, improved recognition and earlier institution of more effective therapies [11,12,14,28]. One should not forget, though, that survival after NSTI or NF attack invariably means prolonged hospital stay, increased financial burden and need for collaboration of many specialties [4].

Poor prognostic factors include the delayed or inadequate index surgery, the degree of dysfunctioning organs on admission (MODS), the presence of severe concomitant illness (i.e. immunosuppression, diabetes mellitus), the advanced age, and the high virulence of certain bacteria [1,14,16,17,29-31] .The relative risk of death was 9 times greater when index debridement was delayed more than 24 hours in the study of Wong et al [16], and it was 7.5 times greater with improper primary surgery in the study of Mock et al [30]. Independent predictive factor of mortality ($p=0.004$) was the extension of the gangrene beyond the perineum in the multivariate analysis in the series of Jerraya et al [31], as it was observed in our study [14] with 14 cases of perineal and/or scrotal gangrene among 24 NSTI patients. Diabetics are notably more susceptible to the disease, that is often characterized by delayed presentation, significant extension (especially, beyond the perineum), and at risk for a more unfavourable outcome [14,31].

Only a few recent studies have investigated the association between early/delayed initial surgery or reduced /prolonged operative time and the outcome. Delay to treatment has been identified as a determinant cause of mortality and is probably the only modifiable parameter [12,25,29,30] .A recent meta-analysis indicated that, early surgical debridement is vital for lowering mortality rates, since surgery within six hours after presentation lowered the mortality rates of NSTIs to almost 50%[13] . Similarly, a recent systematic review and pooled analysis/meta-analysis comprising of 66 observational studies, showed that the likelihood of complications increased significantly with prolonged operative duration, approximately doubling with operative time exceeding two or more hours, and then increasing by 14% for every 30 minutes of additional operative time [24]. In a recent multicenter cohort study

comprising of 160 NSTI patients, a linear multivariable analysis showed that the greater estimated total body surface area affected, the higher American Society of Anaesthesiologists (ASA) classification, and the longer operative time were associated with prolonged ICU and hospital stay, and higher mortality [3, 6].In the same study, as well as in other studies [18,20], the use of intraoperative diagnostics, such as frozen section or Gram stain, has been accused to cause treatment delay [6] .

It is well established in severe trauma and emergency surgery (for acute complicated disease),that prolonged operating times potentially lead to higher postoperative complication rates [6,24].Therefore, the DCS principles should be applied in critically ill NSTI patients with physiological derangement to provide timely, effective, and rapid infectious source control, in order to prevent and/or reverse the aforementioned" lethal triad" [6,22,24].

Recent studies, such as an animated interactive survey study [7] and a systematic review comprising of 20 studies and case series [32], investigated whether different approaches of surgical debridement in NSTI case, the classic *en block* approach in contrast to novel skin-sparing approach, may influence the long-term quality of life. Both studies concluded that current available evidence is of insufficient quality to support a certain approach.

Research and evidence-based approach to relative medical literature shows that, (i) a large number of studies (either cohort or not) and case series can be classified as poor based on Chambers criteria for case series; some recommendations are based on a small number of studies that often have insufficient power to draw well-supported conclusions [11,32-34] ; (ii) it is difficult for clinicians to keep up with the growing number of clinical practice guidelines and ,moreover, these guidelines can vary widely in quality; and (iii) extensive variation in current practice in some aspects concerning diagnosis and/or treatment is seen, despite guideline recommendations [7] . Adherence to or noncompliance with the medical guidelines is a known issue ,and it remains under debate whether clinical practice guidelines can be sufficiently detailed and clear, and always directly improve clinical practice [7,33] .While randomized controlled trials in emergencies or life-threatening conditions to detect the value of different approaches may be ethically or practically not feasible, the need for conducting better clinical studies, in order to achieve evidence for the superior approach, is always required.

2.4. Treatment strategies for NSTI: Practice guidelines and contemporary dilemmas

The management of NSTI requires aggressive resuscitation, intravenous administration of antibiotic agents, complete surgical debridement, and supportive care. All aspects of treatment should be started promptly and simultaneously [3-5,14,26,35,36]. Based on the most recent available literature reports and our own hospital experience, we propose a useful algorithm, as shown in Table I.

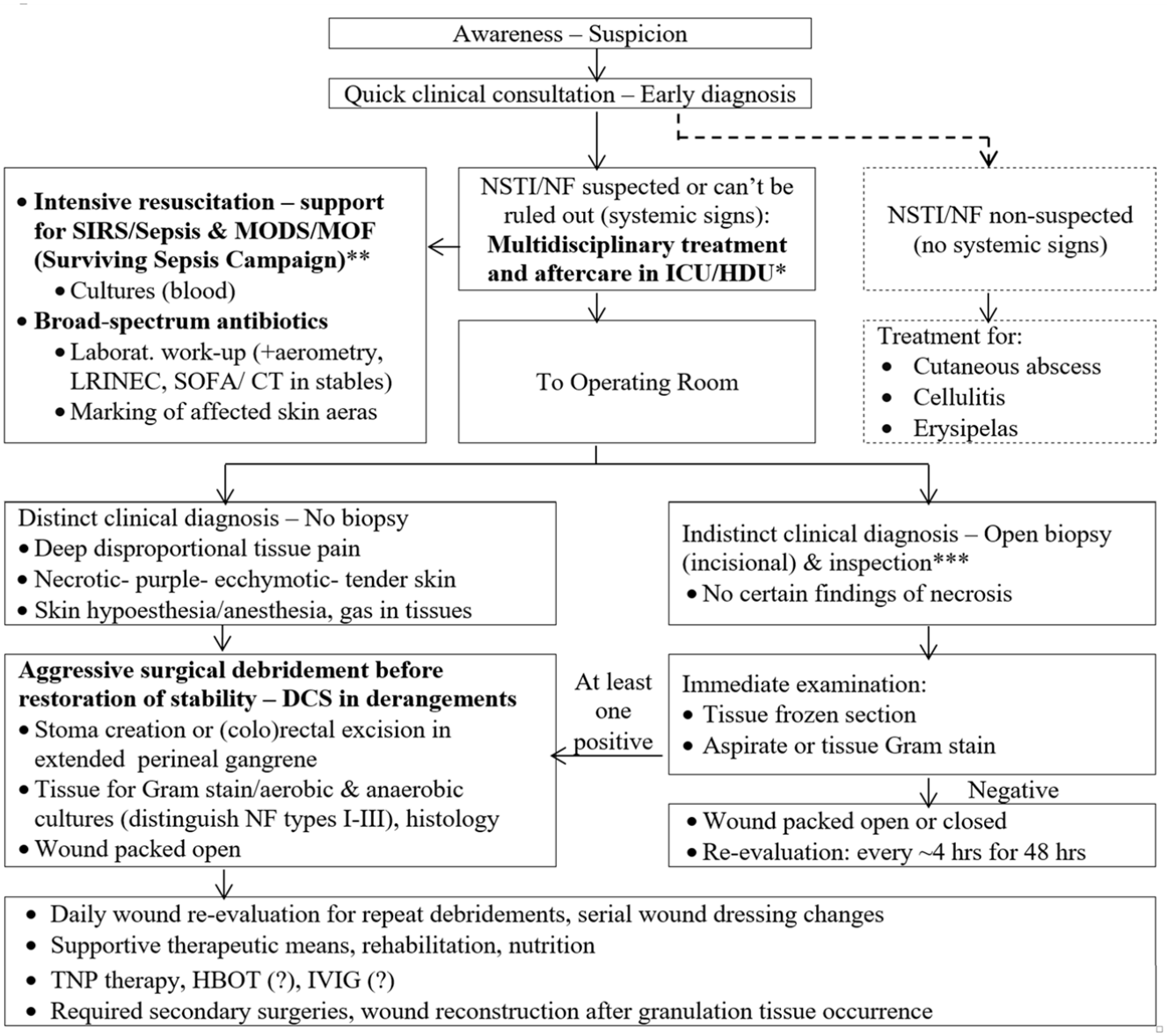
2.4.1. Medical means

A worldwide international panel of experts developed evidence-based guidelines for management of the NSTIs. Already since 2005, the Infectious Diseases Society of America (IDSA) practice guidelines for the diagnosis and management of NSTIs supported prompt and aggressive surgical excision of infected tissues accompanied by appropriate antibiotic therapy [5,26]. The same basic suggestions for the treatment of NSTIs have been included as guidelines in the reports of Surgical Infection Society (SIS)[11] , World Society of Emergency Surgery (WSES) [17],and the 2018 WSES/SIS-E Consensus Conference [18,20]. The Eastern Association for the Surgery of Trauma also contributed with a systematic review/ meta-analysis in 2018 [25], providing practice management guidelines for the NSTIs .It is unanimously accepted that sepsis must be treated immediately, and that is confirmed by the Surviving Sepsis Campaign (SSC) guidelines [35, 36].Especially for patients with systemic toxicity, a comprehensive laboratory work-up is essential [6]. Intentionally, the multifaceted nature of the NSTIs implies the collaboration among general and emergency surgeons, intensivists, infectious disease specialists and plastic surgeons, as well as nutritionists and physical therapists in a complex multidisciplinary approach[1, 4, 14, 17, 18, 26] .

Immediate crystalloid fluid resuscitation, with consideration of the addition of albumin, begins as soon as the diagnosis is suspected [5, 35, 36]. It targets to provide adequate end-organ perfusion and tissue oxygenation, taking into account the individual patient's physiologic status [4]. Aggressive initial fluid resuscitation will help restore intravascular volume (the goal should be to maintain a mean arterial pressure (MAP) 65 mm/Hg or higher, a central venous pressure of 8-10 cm H_2O and diuresis greater than 0.5ml/kg/h) in hypovolemic patients, who often have acute kidney injury, and will limit the adverse affects of end-organ failure [4, 35, 36]. If the aggressive fluid administration is not adequate to achieve a MAP of at least 65 mm/Hg, vasopressors, such as norepinephrine, epinephrine, dopamine and dobutamine should be initiated [35]. This is the definition of septic shock; in this case, guidelines recommend also intravenous administration of hydrocortisone (50mg/6h) [35, 36]. For patients in shock or suffering from severe comorbidities, such as cardiac or pulmonary disease, monitoring in ICUs or HDUs is warranted [3, 4, 6, 14, 20, 26]. For the critically ill patient,

the hematocrit may be a better indicator of the need for transfusion than the hemoglobulin level because bacterial hemolysis causes striking and rapid reduction in the hematocrit value in the absence of disseminated intravascular coagulopathy [5].Effort to correct any existing coagulation disorder is also of great importance in order to minimize blood loss during the following surgery [4]. Intubation and mechanical ventilation may be required in sepsis patients with severe refractory hypoxemia due to acute respiratory distress syndrome (ARDS). Some patients may need continuous hemofiltration or intermittent hemodialysis [23, 35].Deep vein thrombosis and stress ulcer prophylaxis are also essential [3, 35].Blood cultures are obtained before antibiotic therapy and imaging studies are performed promptly and concurrently to confirm the focus and extent of a potential source of infection[20, 35, 36].

Table 1 Algorithm for the diagnosis and treatment of NSTI/NF



* Labelling in bold letters reflects the major aspects of treatment that start promptly and simultaneously;
** References 35,36;
***CT/US guided biopsy is point under discussion

Initial intravenous antibiotic spectrum should be broad enough to cover various possible causative agents, including Gram positive and negative, aerobic and anaerobic bacteria[4, 12, 21, 35]. In many studies, including ours, the polymicrobial type of infection is the most common cause of either the NSTI or NF [4, 14, 27]. Empiric antibiotic regimens, based on the estimated individual patient's risk factors, should be administered without any delay (bolus doses independently of renal function within 1 hour of recognition of septic shock) and re-assessed daily [20, 35]. Combinations of antibiotics (commonly three drugs) are used, including penicillin G, ampicillin/sulbactam, piperacillin-tazobactam, 3rd or 4th generation cephalosporins, ceftazidime/avibactam, ceftolozane/tazobactam, carbapenems, aminoglycosides, quinolones, colistin, tygecyclin, clindamycin or metronidazole, vancomycin, daptomycin, linezolideetc [4]. As soon as the antibiograms are obtained, antibiotic regimens should be adjusted (de-escalation to targeted antibiotic therapy)[4,14,20,35]. Antibiotics should be administered at least for 3 to 5 days after resolution of the systemic signs and symptoms and most of the local signs of the soft tissue infection. What is the most effective drug combination, whether antifungal therapy is reasonable or what is the proper duration of therapy are contemporary questions not yet clearly answered [4,37].

2.4.2. Specific surgical management, relative adjuncts and supportive care

For patients with aggressive NSTIs or those with mild infection associated with evidence of systemic toxicity there is universal agreement that early debridement is the cornerstone of therapy. However, the definition of the starting point to surgery is not standardized in published data, although it should be. The starting point for measuring the time to surgical intervention varies among studies, with some of them using the time from hospital admission, some using the time from initial recognition of the infection, and others using the time from establishment of a definitive diagnosis [5].

The single most important aspect of managing NSTI/NF is the complete surgical excision of necrotic and infected tissues [4,5,12,26]. Operative debridement should never be delayed in the effort to restore hemodynamic stability before anaesthesia induction, because sepsis will never reverse unless all of the necrotic and infected tissues have been completely removed [4,25].

All necrotic/severely infected fascias and probably muscles, as well as the overlying fat and non-viable skin,should be excised to healthy bleeding tissue excision margins [4]. The dull gray appearance of fascias that are easily separated with blunt dissection ("finger test") and the brownish-tan odorous weeping from the affected tissues are highly suggestive of NF, and help to determine the extent and depth of excision[3,4]. Tissue planes should be opened, cleansed and drained[23]. This radical excision follows the DCS principles, thus the surgical approach is a staged procedure directed to a) only removing damaged tissues and packing the wounds open, avoiding any definite repair or wound closure (fashioning a simple colostomy when required), and b) keeping operative time as limited as possible [4,6,17,25,37,38]. A recent systematic review/meta-analysis [24] concluded that prolonged operative time is associated with an increase in the risk of complications. At the time of radical debridement, tissue specimen and fluid aspirates are obtained for immediate Gram stain, as well as for aerobic and anaerobic cultures and histology [14].

Particularly, in those patients with extended perineal gangrene, which is mostly obscure in nature, frequently fulminant in course, and associated with higher mortality, it is required to perform either a laparotomy for Hartmann's colostomy for involved distal colon/rectum or a diverting colostomy to control contamination of a wide residual perineal wound [14,22]. Radical resection in this area usually leaves extensive tissue defects in perineum, gluteal region, upper thighs and lower abdomen; scrotal skin and sac are excised, but the testicles are usually spared owing to their independent blood supply (Figure 2) [4,14]. Compartment syndrome can be a common complication of lower extremities NF and requires urgent opening of the muscle fascial sheath for decompression and examination of the muscles' viability [21]. Notably, sacrifice of the infected limb is sometimes inevitable if there is residual extensive tissue loss preventing any reasonable functional recovery or if there is destruction of the major nerves and blood vessels ("guillotine" type amputation)[4,37].

An important issue for current debate is the size of the defect and the final scar after the surgical debridement in the acute phase (index surgery). Traditionally, *en block* debridement is the favourable approach, in which all skin above the affected underlying fascia is excised, resulting in both effective source control and extensive residual skin defects [7].More recently, an innovative approach called skin-sparing debridement (SSd) was proposed, in which all potentially viable skin above the affected fascia (even, including blue/cyanotic discolored skin) is preserved, in order to decrease the final scar size and the related problems (scar tightening, deformity, pain) [7,32,39] .A systematic review comprising of 10 studies, 1 cohort study and 9 case-series with NSTI patients treated with SSd [32], and an animated interactive online survey study from Netherlands asking how to treat presented NSTI cases and based on the answers of 232 general surgeons and plastic surgeons [7], proponents and opponents, concluded that, there is currently no definite evidence for the clear superiority of either of these approaches. It is well-known that blue discolored skin indicates

cyanosis of the skin, which may be, but not necessarily, irreversible. Besides, there is a strong thesis that resecting non-necrotic skin does not improve source control, while it does increase morbidity [7,39]. The SSd approach has been adapted as the preferred approach in the Dutch guidelines on NSTI management ("only remove non-vital skin and preserve all vital or unsure skin") [32,39]. However, the problematic adherence to medical guidelines is another well-known issue, and it remains under discussion whether guidelines and recommendations directly improve clinical practice [7].

After index surgery, the wounds should be re-explored within 24 hours in the operating room, under general anaesthesia, in intubated patients and those whose clinical condition continues to deteriorate [4,14,22] . If either the initial debridement was inadequate or the necrotic infection has spread even further, all identified necrotic tissues should be aggressively excised on re-exploration [4,22]. Further limited debridements or new excisions should possibly be required during the next few days until definite control of sepsis [4]. Generally, closed wound care, namely serial dressing changes and frequent evaluations of surgical wounds and tissue viability twice or more daily, are required for the first 72 hours [22]. However, accurate practice guidelines for the best management of NSTI/NF after the index surgery do not exist [1,4,37].

Once surgical debridement is no longer required, meticulous wound care can be performed at the bedside [4]. Perineal wounds are particularly difficult to manage, because soilage of the wound is frequent; fecal diversion by means of colostomy is rarely required though. In general, open wounds are better irrigated with hydrogen peroxide and saline, and covered with dry dressings [4,14,22]. Use of topical antimicrobial therapy, povidone iodine or silver nitrade/silver sulfadiazine, possibly does not add substantial benefit [4]. When the wound is clean, a topical negative pressure (TNP) device can be used to extract wound exudates, improve tissue perfusion, induce granulation, and reduce wound surface (Figure 3) [4,5,14,15,22]. However, a vacuum wound dressing might not be an option for extended perineal defects due to technical problems of application.

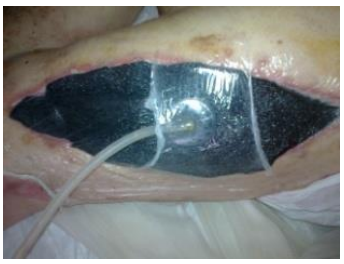


Figure 3 Aftercare reconstruction: Use of TNP in 64-year-old diabetic man (own material) with treated femoral NSTI/NF associated with compartment syndrome (20th postoperative day)

Hyperbaric oxygen treatment (HBOT), administration of intravenous immunoglobulin (IVIG) and the blood purification (plasmapheresis, plasma exchange) have been proposed as novel adjunctive therapies for critically ill NSTI patients, despite of their high cost and relative unavailability [2-5,14,15,19]. Direct bactericidal activity, enhanced innate immune function and improved tissue healing have been considered as underlying beneficial biologic mechanisms in the use of HBOT(i.e. for type I infection) [2-5,15]. HBOT has been incorporated into some published guidelines for the management of NSTIs, in spite of the lack of well conducted trials for proof of its efficacy [4,14,19]. The rationale for the use of (polyclonal) IVIG is that antibodies can neutralize the circulating streptococcal exotoxins, reducing this way the toxin-induced tissue necrosis, and may also have an effect on the cytokine cascade, thereby controlling SIRS (i.e. in streptococcal type IINSTIs) [3-5]. Studies showing a potential benefit from the use of IVIG in NSTI are limited and of a relatively low cohort size [4-6,19]. There are risks associated with the use of both of the above adjuncts (HBOT: grand mal seizures, barotrauma/ IVIG: allergic reactions, acute kidney injury) ,although contemporary studies suggest that these events are rare [4]. A final adjunct, the blood purification (plasmapheresis, plasma exchange, hemoperfusion associated with polymixin B), incorporates a group of interventions aimed at removing mediators purported as causative agents in the pathophysiology of sepsis/severe sepsis/septic shock and NSTI [4]. Whether the specific use of blood purification in severely ill NSTI patients has a possible beneficial effect on reducing the risk of death is also under debate. Concluding, available evidence is of insufficient quality to evaluate these adjuncts, as it is for some specific novel surgical techniques [4,5,19]. Additional studies are required before these treatments can be recommended for routine use.

Intensive supporting care of the NSTI patients is extremely important. The radical excision of necrotized infected tissues usually involves significant blood loss, that has to be corrected [4]. Surgically treated patients are also at risk for hypothermia, because a large surface is often exposed after the debridement [4]. Moreover, a protocolized approach to

blood glucose management is essential, and protocols for weaning and sedation after surgery have to be applied [34] . Nutritional support should be started as soon as the patient can tolerate it, and it is provided after calculating caloric and protein requirements for patients with extensive open wounds and in hypermetabolic state [4,14] . If the patient is able to take food by mouth, this is the preferred route [4]. If the patient remains intubated or is unable to obtain adequate caloric intake orally, enteral feeding via nasogastric or nasoduodenal feeding tube is preferred over parenteral nutrition [4,14,35,36]. Appropriate vitamins, such as vitamins A and D, and minerals, such as zinc, should be administered to patients with large open wounds to facilitate wound healing [4,14]. Rehabilitation should be started as soon as possible [4] .

After initial surgical control and resuscitation, when the patient is medically stable and the wound is free from any sign of infection, secondary surgical interventions are required to perform reconstruction and definitive wound closure [4,6,22]. Instead of waiting for granulation tissue to fill the entire wound bed for split thickness skin grafts, early coverage of the wound is superior in that it will decrease both the pain associated with dressing changes and the metabolic demands [4,22]. In practice, closure of the residual tissue defects and covering of denuded organs is guided by the individual patient's requirements, and it can be a scheduled procedure during the same admission or at planned re-admissions. For the majority of the wounds, closure is achieved with simple split thickness skin graft(s), or by repeated mobilization of wound edges and sectional suturing at week intervals [4,14,22]. More complex wounds should be managed with the formation of new granulation tissue, better in conjunction with the plastic surgery team [4,14,22]. Several reconstruction methods have been described, including the creation of advancement flaps, the component separation technique with restoration of abdominal wall function, and the use of bioprosthetic mesh[22]. Especially for a small perineal wound that involves the scrotum, the delayed primary closure is the most efficient method [4]. If such a wound is too large for primary closure, techniques to prevent contracture deformity of the scrotum have been described, including fashioning of musculocutaneous or fasciocutaneous flaps from the thigh(s) and abdomen, direct split thickness skin graft over the denuded testicles, placement of the testicles in subcutaneous pockets in the thigh, and some temporary coverage permitting future reversal with other reconstructive method [4].

Abbreviations

- APACHE: Acute Physiologic Assessment and Chronic Health Evaluation
- SOFA: Sequential Organ Failure Assessment

3. Conclusion

A soft tissue infection with sudden onset, spreading and deteriorating rapidly, accompanied or not by systemic signs, should set the suspicion of NSTI. Although the morbidity and mortality rates after the integrated and multidisciplinary management of patients with life-threatening NSTIs continue to be high, better outcomes have been achieved during the last two decades, attributable to improved diagnosis and treatment. Strong agreement exists among a large cohort of international therapists regarding many basic recommendations for the best care of NSTI patients. Thus, successful management of NSTIs involves high index of suspicion, early recognition after careful clinical examination, appropriate antibiotic coverage, and prompt delivery of more effective therapies such as the synchronous intensive resuscitation and supporting of the critically ill patient, and the aggressive surgical debridement, which should be repeated if needed. Surgery should never be delayed, because the reversal of the septic state requires all necrotic and infected tissues to be timely removed. Contributors for favourable outcome are the close wound care, the adjustment to targeted antibiotic therapy after culture results, the nutritional support, the appropriate rehabilitation and the specific plastic surgical interventions to cover denuded organs and reconstruct residual tissue defects. Broader studies on specific topics or with a particular clinical question, and relevant systematic reviews meeting higher standards should be conducted in order to have better clinical practice guidelines. The strict compliance of daily clinician's practices is also required to further improve outcomes.

Compliance with ethical standards

Acknowledgments

The author is thankful to Dr. Elena Avgoustou for her help in preparing and submitting the final manuscript.

Disclosure of conflict of interest

No conflicts of interest exist.

Statement of informed consent

Informed consent was obtained from individual participants included in the study; a close relative has signed in the case of an intubated patient who died.

References

[1] Roje Z, Roje Z, Matić D, Librenjak D, Dokuzović S,Varvodić J .Necrotizing fasciitis: literature review of contemporary strategies for diagnosing and management with three case reports: torso, abdominal wall, upper and lower limbs. World J Emerg Surg. 2011;6: 46. doi: 10.1186/1749-7922-6-46.

[2] Psoinos CM, Flahive JM, Shaw JJ, et al. Contemporary trends in necrotizing soft-tissue infection in the United States. Surgery. 2013; 153:819-827. doi:10.1016/j.surg.2012.11.026.

[3] Hietbrink F, Bode LG, Riddez L, Leenen LPH, van Dijk MR. Triple diagnostics for early detection of ambivalent necrotizing fasciitis. WorldJ Emerg Surg. 2016; 11: 51-62. doi: 10.1186/s13017-016-0108-z.

[4] Cocanour CS, Chang P, Huston JM, et al. Management and novel adjuncts of necrotizing soft tissue infections. Surg Infect. 2017;18:250 -272.doi: 10.1089/sur.2016.200.

[5] Stevens DL, Bryant AE. Necrotizing soft –tissue infections. New Engl J Med.2017; 377:2253-65. doi: 10.1056/NEJMra1600673.

[6] Nawijn F , van Heij lM , Keizer J , van Koperen PJ , Hietbrink F. The impact of operative time on the outcomes of necrotizing soft tissue infections: a multicenter cohort study. BMC Surg. 2022;22:3. doi: 10.1186/s12893-021-01456-0.

[7] Suijker J , Hofmans FAC , van Zuijlen PPM , Cense HA , Bonjer HJ , Meij-de Vries A. Approaches to surgical debridement in necrotizing soft tissue infections: Outcomes of an animated, interactive survey. World J Surg. 2022; 46:1051-1058. doi: 10.1007/s00268-022-06470-8.

[8] Descamps V, Aitken J, Lee MG. Hippocrates on necrotizing fasciitis. Lancet. 1994; 344:556.

[9] Fournier JA. Etude Clinique de la gangrene foudroyante de la verge. Semaine Med.1884; 4:69-70.

[10] Jones J. 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.New York: U.S.Sanitary Commission; 1871.

[11] May AK, Stafford RE, Bulger EM, et al. Treatment of complicated skin and soft tissue infections. Surg Infect (Larchmt).2009;10:467-99. doi: 10.1089/sur.2009.012.

[12] Ustin JS, Malangoni MA. Necrotizing soft-tissue infections. Crit Care Med. 2011;39:2156-2162. doi: 10.1097/CCM.0b013e31821cb246.

[13] Nawijn F, Smeeing D, Houwert R , Leenen L, Hietbrink F. Time is of the essence when treating necrotizing soft tissue infections: a systematic review and meta-analysis. World J Emerg Surg. 2020; 15:4.doi: 10.1186/s13017-019-0286-6.

[14] Avgoustou C, Constantinou P, Avgoustou Ch, Karampas V, Sioula M. Necrotizing soft-tissue infection and necrotizing fasciitis in adults of a single center: review, current concepts and challenges. Surgical Case Reports. 2021;4: 2-9. doi:10.31487/j.SCR2021.02.13 .

[15] Mladenov A, DiehlK, Müller O, von Heymann C, Kopp S, Peitsch WK. Outcome of necrotizing fasciitis and Fournier's gangrene with and without hyperbaric oxygen therapy: a retrospective analysis over 10 years. World J Emerg Surg. 2022; 17:43. doi:10.1186/s13017-022-00448-6.

[16] Wong CH, Chang HC, Pasupathy S, et al. Necrotizing fasciitis: clinical presentation, microbiology and determinants of mortality. J Bone Joint Surg Am. 2003; 85:1454-1460. PMID: 12925624.

[17] Sartelli M, Malangoni MA, May AK, et al. World Society of Emergency Surgery (WSES) guidelines for management of skin and soft tissue infections. World J Emerg Surg. 2014; 9:57.doi:10.1186/1749-7922-9-57.

[18] Sartelli M, Guirao X, Hardcastle TC, et al.2018WSES/SIS-E consensus conference: recommendations for the management of skin and soft-tissue infections. World J Emerg Surg. 2018; 13: 58. doi:10.1186/s13017-018-0219-9 .

[19] Pelletier J, Gottlieb M, Long B, Perkins JC Jr. Necrotizing soft tissue infections (NSTI): Pearls and pitfalls for the emergency clinician. J Emerg Med.2022;62:480-491. doi:10.1016/j.jemermed.2021.12.012.

[20] Wu K-H, Wu P-H, Chang C-Y , et al . Differentiating necrotizing soft tissue infections from cellulitis by soft tissue infectious fluid analysis: a pilot study. World J Emer Surg. 2022; 17: 1. doi:10.1186/s 13017-022-00404-4.

[21] Gibson D, Chow O, Seth I, Siu AHY, Kwei J. Compartment syndrome as a novel complication of extended spectrum beta lactamase Escherichia coli necrotising soft tissue infection – A case report. Int Surg Case Rep. 2022; 99:107574 .doi:10.1016/j.ijscr.2022.107574.

[22] Kline BP, Jeganathan NA. Necrotizing soft tissue infections of the perineum. Clin Colon Rectal Surg. 2022; 35: 237-243. doi: 10.1055/s-0041-1740102.

[23] Avgoustou C, Avgoustou Ch. Necrotizing soft-tissue infections: current concepts and challenges. Clin Surg.2021; 6: 3039(Editorial). Citation: Avgoustou C, Avgoustou Chr. Necrotizing Soft-Tissue Infections: Current Concepts and Challenges. Clin Surg. 2021;6:3039. http://clinicsinsurgery.com/

[24] Cheng H, Clymer JW, Chen BP-H, et al . Prolonged operative duration is associated with complications: a systematic review and meta-analysis.J Surg Res. 2018; 229: 134-144. doi:10.1016/j.jss.2018.03.022.

[25] Gelbard RB, Ferrada P, Yeh DD, et al. Optimal timing of initial debridement for necrotizing soft-tissue infection: A Practice Management Guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2018; 85: 208-214. doi:10.1097/TA.0000000000001857.

[26] Stevens DL, Bisno AL, Chambers HD,et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections.Clin Infect Dis. 2005; 41:1373-1406.doi: 10.1086/497143.

[27] Kwee RM,Kwee TC. Diagnostic performance of MRI and CT in diagnosing necrotizing soft tissue infection: a systematic review. Skeletal Radiol. 2022;51: 727–736 .doi:10.1007/s00256-021-03875-9.

[28] van Stigt S, Knubben M,Schrooten T,Tan E. Prognostic factors for mortality in 123 severe cases of necrotizing fasciitis in 5 hospitals in the Netherlands between 2003 and 2017.Eur J Trauma Emerg Surg.2022; 48: 1189–1195 .doi:10.1007/s00068-021-01706-z.

[29] McHenry CR, Piotrowski JJ, Petrinic D, Malangoni MA. Determinants of mortality for necrotizing soft-tissue infections. Ann Surg. 1995; 221: 558-563. doi: 10.1097/00000658-199505000-00013.

[30] Mock MY, Wong SY, Chan TM, et al. Necrotizing fasciitis in rheumatic diseases. Lupus. 2006;15:380-383.doi: 10.1191/09612033061u2314cr.

[31] Jerraya H, Fehri H, Khalfallah M, Abdesselem MM, Dziri C. Predictive factors of mortality in Fournier's gangrene. Tunis Med. 2015; 93:800-803. PMID : 27249392.

[32] Suijker J, Zheng KJ, Pijpe A, et al. The skin-sparing debridement technique in necrotizing soft-tissue infections: a systematic review. J Surg Res. 2021; 264: 296-308. doi:10.1016/j.jss2021.03.001.

[33] Fletcher RH, Fletcher SW. Evidence-based approach to the medical literature. J Gen Intern Med. 2003; 12: 5-14.https://doi.org/10.1016/j.1521497.12.s2.1.x.

[34] Chambers D, Rodgers M, Woolacott N. Not only randomized controlled trials, but also case series should be considered in systematic reviews of rapidly developing technologies. J Clin Epidemiol. 2009; 62:1253-1260.e4. doi:10.1016/j.jclinepi.2008.12.010.

[35] Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup Surviving sepsis campaign international guidelines for management of severe sepsis and septic shock: 2012.Crit Care Med. 2013; 41:580-637. doi: 10.1097/CCM.0b013e31827e83af.

[36] Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017; 43:304-377. doi: 10.1007/s00134-017-4683-6.

[37] Faraklas I, Yang D, Eggerstedt M , et al. A multi-center review of care patterns and outcomes in necrotizing soft tissue infections.Surg Infect (Larchmt). 2016;17:773-778. doi: 10.1089/sur.2015.238.

[38] Benz D,Balogh Z J.Damage control surgery: current state and future directions. Curr Opin Crit Care. 2017;23:491-497.doi: 10.1097/MCC.0000000000000465.

[39] Tom LK, Wright TJ, Horn DL, et al. A skin-sparing approach to the treatment of necrotizing soft-tissue infections: thinking reconstruction at initial debridement. J Am Coll Surg. 2016; 222: e47-60. doi:10.1016/j.jamcollsurg.2016.01.008.

Author's short Biography

Avgoustou Constantinos is graduate of Medical School of Athens-Greece. He is Director of Surgery in Athens, since 2010. He has been trained in specific topics: thoracic, laparoscopic, and pelvic surgery. His main areas of interest are colon/pelvic, hepatobiliary/gastric and thyroid surgery. He has participated in Congresses as Keynote Speaker. He is author of a Medical Book and of 13 Chapters in Medical Books. He has 133 medical publications. He is reviewer in Medical Magazines.