Necrotizing soft tissue infection is a life-threatening condition, characterized by extensive necrosis of skin, subcutaneous, fascia and muscle. 82% of patients exhibit some of the risk factors, such as diabetes mellitus, obesity and alcoholism, smoking, immunodeficiency, malnutrition or low socioeconomic status. The necrotizing soft tissue infection is initially diagnosed by a clinical examination. The use of imaging, particularly computed tomography, represents a golden standard; the CT exam usually shows the presence fluid collections, abscess, adipose tissue degeneration and subcutaneous emphysema. The treatment of necrotizing soft tissue infection involves surgical debridement, drainage, wide incisions of the affected area, tissue decompression and application of broad-spectrum antimicrobial therapy. Despite existing modern methods of treatment, or the so-called principle of “source control”, the mortality is still up to 51%. Necrotizing soft tissue infection is a very dangerous infection we should always be aware of, and treat it as early as possible.

Key words: Necrotozing soft tissue infection; Necrotizing fasciitis; Fournier’s gangrene; perianal region; perineal region

INTRODUCTION

Necrotizing soft tissue infection (NSTI) is a life-threatening condition, characterized by widely spread necrosis of the skin, subcutaneous, fascia and muscle tissue. In literature, it is also called a necrotizing fasciitis (NF), or Fournier’s gangrene, which is basically only one of the forms of a necrotizing infection of soft tissues. The incidence of NSTI in the United States is estimated to be 500–1500 cases per year. A recent study established the incidence of soft-tissue infection, using insurance databases from various states of the US, determined the incidence of NSTI to be 0.04 cases per 1000 person-years. The infection is mainly caused by mixed bacterial flora, dominantly by E coli, Staphylococcus aureus, Clostridium, beta-hemolytic streptococcus and Bacteroides. Aside from bacteria, the possible cause could be fungi of the genus Candida albicans and glabrata.

In relation to the origin of spread, we can divide NSTI in two ways: (1) NSTI originating from surface-type A infection (surgical interventions, injection sites, injuries etc.); and (2) NSTI originating from deep structures-type B infection (most often hematogenous or lymphogenous dissemination, injuries, ruptures or perforations of the gastrointestinal or urogenital tract). Infections type A are usually easy to diagnose and treat, while the B type is commonly characterized by the a delayed diagnosis, complex treatment and high mortality.

The history of NSTI dates back to the fifth century BC, at the time of Hippocrates, who thought that the infection occurred as a complication of erysipelas. French author Buirrene published the first paper in 1795. However, Joseph Jones, surgeon of the Confederate Army, gave a more detailed description of 2642 soldiers injured during the American Civil War in 1871. The reported mortality of 46% was caused by the so called “hospital gangrene”. In 1883, Jean Alfred Fournier, a famous French dermatovenereologist from Paris, described fulminate infection of the subcutaneous tissue and fascia of the scrotum, penis and perineum in young men. Later on, all combined perineal and urogenital infections were named after him. In 1924, a well-known surgeon from Columbia Frank Meleny University described 20 patients in a hospital in Beijing suffering from “hemolytic gangrene” caused by Streptococcus pyogenes, at the time also known as “flesh-eating bacteria” or the “killer bug”. Its modern name, NF, was given to it by Wilson, who described it in 1952.
Regardless of the type of infection (A or B), the beginning of NSTI is characterized by a fulminant inflammatory response, leading to the obliterate endarteritis of cutaneous and subcutaneous blood vessels, and subsequent necrosis. In cases with Clostridia infection, we have the presence of gas, toxemia and extensive edema with massive necrosis of soft tissue. The present alpha exotoxin damages cell membrane, causes hemolysis, fascia and muscle necrosis. Infection penetrates the tissue (Type A infection), from the epidermis through to the muscles, in the form of erysipelas, impetigo, folliculitis, cellulite, necrotizing fasciitis and myonecrosis, causing increased morbidity, i.e., mortality, of up to 76%. The high mortal-

TABLE 1

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sex</th>
<th>Patient (n)</th>
<th>Cause of NSTI</th>
<th>Complication</th>
<th>Clinical manifestation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khwaja et al</td>
<td>f</td>
<td>1</td>
<td>diverticulitis sigmoid colon</td>
<td>perforation of divertikulum</td>
<td>infection of the front abdominal wall</td>
<td>survived</td>
</tr>
<tr>
<td>Pecie et al</td>
<td>m</td>
<td>1</td>
<td>blunt abdominal trauma</td>
<td>coecal rupure</td>
<td>infection of the front abdominal wall</td>
<td>died</td>
</tr>
<tr>
<td>Banzahf et al</td>
<td>m</td>
<td>1</td>
<td>diverticulitis sigmoid colon</td>
<td>perforation</td>
<td>infection of the front abdominal wall</td>
<td>died</td>
</tr>
<tr>
<td>Dewire et al</td>
<td>m</td>
<td>1</td>
<td>Ca sigmoid</td>
<td>perforation in inguinal hernia</td>
<td>Fourinier's gangrene</td>
<td>survived</td>
</tr>
<tr>
<td>Gerber et al</td>
<td>m</td>
<td>2</td>
<td>I. Appendicitis acuta. II. Diverticulitis perforation</td>
<td>Fourinier's gangrene</td>
<td>Fourinier's gangrene</td>
<td>survived</td>
</tr>
<tr>
<td>Gould et al</td>
<td>m</td>
<td>1</td>
<td>Ca sigmoid</td>
<td>perforation</td>
<td>Fourinier's gangrene</td>
<td>died</td>
</tr>
<tr>
<td>Gamagami et al</td>
<td>m</td>
<td>1</td>
<td>Ca rectum</td>
<td>perforation</td>
<td>intraabdominal infection</td>
<td>survived</td>
</tr>
<tr>
<td>Veljkovic et al</td>
<td>m</td>
<td>1</td>
<td>Ca colon</td>
<td>perforation</td>
<td>sournier's gangrene</td>
<td>survived</td>
</tr>
<tr>
<td>Groth&amp;Henders on</td>
<td>f</td>
<td>1</td>
<td>appendicitis acuta</td>
<td>perforation</td>
<td>infection of the front and side abdominal wall</td>
<td>survived</td>
</tr>
<tr>
<td>Lawrentschuk et al</td>
<td>m</td>
<td>1</td>
<td>Ca rectum</td>
<td>perforation</td>
<td>intraabdominal infection</td>
<td>survived</td>
</tr>
<tr>
<td>Ku et al</td>
<td>f</td>
<td>1</td>
<td>Ca transversum</td>
<td>perforation</td>
<td>infection of the front abdominal wall</td>
<td>survived</td>
</tr>
<tr>
<td>Fu et al</td>
<td>m</td>
<td>1</td>
<td>Clisma</td>
<td>perforation of rectum</td>
<td>infection of thigh end leg</td>
<td>survived</td>
</tr>
<tr>
<td>Saldua et al</td>
<td>m</td>
<td>1</td>
<td>Condition after rectal radiation</td>
<td>perforation of small intestine</td>
<td>thigh subcutaneous emphysema</td>
<td>survived</td>
</tr>
<tr>
<td>Agaba et al</td>
<td>m</td>
<td>1</td>
<td>diverticulitis sigmoid</td>
<td>perforation</td>
<td>infection the front abdominal wall</td>
<td>survived</td>
</tr>
<tr>
<td>Kearnay et al</td>
<td>m</td>
<td>1</td>
<td>Diverticulitis sigmoid (Systemic LE)</td>
<td>perforation diverticulum</td>
<td>fourinier's gangrene</td>
<td>survived</td>
</tr>
</tbody>
</table>

**PATHOPHYSIOLOGY OF NSTI**
ity rate is explained by the dominant influence of proinflammatory cytokines such as: tumor necrosis factor alpha (TNFα) Interleukin 1(IL-1) Interleukin 6 (IL-6), which cause the systemic inflammatory response (SIRS), increased level of reactive oxygen and oxygen radicals with the consequent development of multi-organ insufficiency7. Recently, attention has been paid to the so-called extracellular high mobility group box 1 (HMGGB1), highly conserved nuclear protein, which may form immunostimulatory complexes with IL-1β. They are present in a greater amount at the site of infection, and their level correlates to the severity of infections8.

Type B infections are problematic due to the mentioned way of spread. By the time NSTI can be verified on the body surface (skin on the upper and lower extremities, front abdominal wall, chest wall etc.), advanced infection is already present. We can learn about extremely rare form of NSTI mainly from case reports or small case series (Table 1).

### RISK FACTORS

Of all the patients with NSTI, 82% have one of the risk factors: diabetes mellitus (DM), obesity, alcoholism, smoking, immunodeficiency, malnutrition and low socio-economic status. DM is present in around 57% of the cases, while immunodeficiency of some degree is identified in 17%23. Martinschek et al5 reported that, out of the total number of patients, 52.7% had some of the predisposing factors: in 32.6% there was myocardial insufficiency, 27.3% had DM, 25.4% suffered from hypertension, and atherosclerosis was discovered in 23.6%. A systematic review of Angoules et al22, analyzed 12 studies with 451 patients where DM was the predominant risk factor in 31%, smoking in 27%, alcoholism in 17%, cirrhosis in 8%, HIV infection in 6%, various stages of malignancy in 3%, corticosteroids and chronic kidney insufficiency in 3% of cases. Other rare risk factors presented in the same study were: angina pectoris in 2% of the cases, chronic liver insufficiency in 2%, and chronic obstructive lung disease in 1.3%, peripheral vascular disease in 1.3% and esophageal varices in 1.1%. In Basoglus study in 2007, even 64.4% of patients with Fournier gangrene had some of the predisposing factors, most commonly DM - 24.4%24. Evidently, risk factors are present in about half of all the cases suffering from NSTI,

### TABLE 2
DATA FROM THE LITERATURE ABOUT THE TYPE OF BACTERIAL INFECTION IN NSTI

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients (n)</th>
<th>Multi bacterial infection</th>
<th>Mono bacterial infection</th>
<th>Predominant type of microorganisms</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinschek et al5</td>
<td>55</td>
<td>65.5%</td>
<td>34.5%</td>
<td>Clostridium perfrigens (67.3%)</td>
<td>16.4%</td>
</tr>
<tr>
<td>Angoules et al23</td>
<td>355</td>
<td>-</td>
<td>-</td>
<td>Staphylococcus aureus (18.9%)</td>
<td>21.9%</td>
</tr>
<tr>
<td>Anaya &amp;Dellinger2</td>
<td>73</td>
<td>66.6%</td>
<td>33.3%</td>
<td>Streptococcus (19.1%)</td>
<td>-</td>
</tr>
<tr>
<td>Elliott et al26</td>
<td>182</td>
<td>56.6%</td>
<td>43.4%</td>
<td>Streptococcus (45.6%)</td>
<td>19.1%</td>
</tr>
<tr>
<td>Nai-Chen Cheng et al27</td>
<td>134</td>
<td>24.7%</td>
<td>65.7%</td>
<td>Streptococcus pyogenes (12%)</td>
<td>19%</td>
</tr>
<tr>
<td>Rajan S28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Staphylococcus aureus (44.6%)</td>
<td>23.5%</td>
</tr>
<tr>
<td>Kao et al29</td>
<td>296</td>
<td>46%</td>
<td>54%</td>
<td>MRSA (35%)</td>
<td>17%</td>
</tr>
</tbody>
</table>

### TABLE 3
DATA FROM THE LITERATURE (Medline/PubMed's article) ABOUT THE MORTALITY AND TREATMENT OF NSTI

<table>
<thead>
<tr>
<th>Authors</th>
<th>No of pts</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norton et al42</td>
<td>1726</td>
<td>16%</td>
</tr>
<tr>
<td>Angoules AG et al23</td>
<td>451</td>
<td>22%</td>
</tr>
<tr>
<td>Yilmazlar T et all32</td>
<td>67</td>
<td>49%</td>
</tr>
<tr>
<td>Basoglu M et al24</td>
<td>45</td>
<td>8.8%</td>
</tr>
<tr>
<td>Chinchilla RM et al33</td>
<td>20</td>
<td>10%</td>
</tr>
<tr>
<td>Lee et al43</td>
<td>46</td>
<td>15.2%</td>
</tr>
<tr>
<td>Chernyshev et al44</td>
<td>86</td>
<td>51.5%</td>
</tr>
<tr>
<td>Martinschek et al5</td>
<td>55</td>
<td>16.4%</td>
</tr>
<tr>
<td>Kalaivani et al45</td>
<td>60</td>
<td>25%</td>
</tr>
</tbody>
</table>
and the most frequent among them is DM, very important when considering therapy options.  

**MICROBIOLOGY**

The two most important factors in microbiology of NSTI are the type and number of bacterial species. Regarding the type, they can be:

Type 1 - Infection caused by the mixed aerobic and anaerobic bacterial flora

Type 2 - Infection caused by anaerobic flora

Type 3 - Infection caused by bacteria Vibrio vulnificus.  

Regarding the number of different species, they can be:


2. Monobacterial infections (Staphylococcus, Streptococcus, Clostridia, Candida albicans, Candida glabrata)


Multibacterial aerobic and anaerobic NSTI are most common, present in 27.7%-65.5% (average 51.9%), while monobacterial infections range between 33.3%-65.7 % (average of 46.2%) of cases (Table 2).

**CLINICAL PRESENTATION**

NSTIs are characterized by local and systemic signs of inflammation, depending on the infection stage and the way of spread. Local signs of skin inflammation, redness, swelling and impaired function, appear in 66%-100%, severe pain in 31%-73%, crepitation in 36.5%-73.6%, swelling in 49%, induration in 31%-45% and locally increased temperature in 18%-66.3% of the affected individuals. In type A infection, local signs represent early disease, while in type B, it is just a “tip of the iceberg” with the already developed intra-abdominal infection and commonly high morbidity and mortality. Cheung et al. described 3 stages of the local development of NSTI, according to the severity of the disease. The first stage is characterized by the occurrence of increased sensitivity, redness, swelling and locally increased temperature, in the second, bullae are formed, and the third, advanced stage, is characterized by tissue necrosis, hyposensitivity/total insensitivity, crepitation and present hemorrhagic bullae.

Systemic effects of NSTI are manifested by sepsis, i.e., septic shock in 43.6%, hemodynamic instability in 27.3%, fever in 15% and disorientation in 3%. Redness, swelling, disturbed function, severe pain and crepitation are indicators of possible NSTI, which, in almost half of the total number of patients, has a chance to progress into sepsis. For this reason, we have to be extra careful in patients with the mentioned symptoms.

In relation to the origin of NSTI, Martinsche et al present the data on 55 patients where the infection was initially localized on lower extremities in 63.2%, on the anterior abdominal wall in 30.9% and on the perineum in 14.5%. Yilmazlar et al published the retrospective study including 67 patients. In 50.7%, the infection was localized in the anorectal and urogenital region, in 30%, on the skin of the extremities, and in 19.4%, on other locations (conditions after trauma, post-operative wounds etc.). In the same study, 64% of the patients had a disseminated form of NSTI, while only 36% had a localized form. Analyzing this study, we can see that a high percentage of disseminated infections originated from the perianal and perineal region, which was explained by the late diagnosis. Most probably, due to the inconvenient location of the initial infection, the patients hesitated to see a physician.

The NSTI spread in the anogenital region is considered to be 2-3 cm per hour, in the direction of the anterior abdominal wall, i.e., ischiorectal fossa, gluteal region and thigh, explained by the fascial anatomy of the perineal region.
region and pelvic floor. Superficial fascia of the perineum continues as tunica dartos of the scrotum, i.e. penis and, at the same time, it is fixed to the pubic bone, fascia (late) laterally and to the urogenital diaphragm posteriorly, presenting a natural barrier for the infection spreading towards the ischiorectal fossa, gluteal and thigh regions, and it merges with Scarpa’s fascia of the anterior abdominal wall.

Buck’s fascia, is often an origin of infection spreading towards Colles fascia and tunica dartos, often caused by injuries. The infection with necrosis of the male genital region is mostly localized at the level of the skin and subcutaneous tissue, due to excellent vascularization, and the existence of resistant tunica vaginalis,. In the cases of disrupted Colles fascia, the infection spreads towards the ischiorectal fossa, gluteal region and thigh

Laboratory tests can be an important diagnostic tool. Wall et al39 showed that a leukocyte count of over 15,400 cells/mm3, i.e. serum sodium below 135 mmol/l, indicates the existence of NSTI with the precision of 26%, but that the nominal values of the above stated parameters exclude the existence of infection in 99% of the cases. Wong et al published a study in 2004, where they present a set of the laboratory analyses significant in the discrimination between NSTI and non-NSTI 39.

In relation to the number of recorded points, it is possible to determine the existence of necrotizing infection 2.

Pathohistological analysis is one of the possible ways of establishing a correct diagnosis. Some authors recommend frozen section biopsy in order to timely discover the exact type of infection. Others argue that there is no great practical significance of pathohistology because macroscopic appearance (gray necrotic tissue, absence of bleeding, blood vessel thrombosis, so-called, pus like “water after dish washing”, absence of muscle contraction during dissection) is enough 2,40,41.

**TREATMENT**

The treatment of NSTI includes drainage, wide incisions of the affected region, debridement, tissue decompression and the use of broad-spectrum antibiotics.

Historically, the exclusive use of antibiotics leads to 100% mortality, indicating the necessity for surgical intervention, which decreases the level of mortality from 88 to 51.2% 23 (Table 3).
Comparing the mortality risk with HBOT, the study found a statistically significant lower mortality (P < 0.001) compared to those treated without HBOT. However, in 2012, Schmale et al. reported the advantage of HBOT use in the treatment of NSTI, due to the proven bacteriostatic and bactericidal effect and faster wound healing owing to increased oxygen tissue concentration. The need for a controlled prospective randomized multicenter study is evident, in order to ascertain the real importance of HBOT in the treatment of NSTI.

SCORING SYSTEMS, AND PREDICTION THE OUTCOME FOR PATIENTS WITH NSTI

Considering the fact that NSTI is a life-threatening condition, some authors have used different scoring systems with numerous clinical parameters, to predict the outcome. The most frequently mentioned in literature are so-called Fourmier’s gangrene severity index score (FGSIS), Acute Physiology, Age, and Chronic Health Evaluation or APACHE II scoring system and the system of NSTI dissemination (Table 5).

For FGSIS, the cutoff value is 9, and the cases of Fourmier’s gangrene with a score of over 9, have a mortality risk of 75%, while the probability of survival is 78% with a score below 9. The cutoff value of the APACHE II is 13; below 13, the predicted mortality is 20%; over 14, 86%, while in the most severe forms of infection, with a score of 20, the mortality is 100%. As mentioned, NSTI involves two forms of infection, the localized and the disseminated one. The extent of NSTI was determined using the Lund and Browder burn area chart. NSTIs are defined as local if the disease remains confined to one region, with the predicted mortality of 21%. NSTIs with spreads to other region are defined as disseminated ones, with the mortality risk of 65%.

CONCLUSION

NSTI is a life-threatening condition, characterized by widespread necrosis of the skin, subcutaneous, fascial and muscle tissue. One of the most common localizations of the infection is the perianal and perineal region. It is mainly caused by mixed bacterial flora, aerobic and anaerobic, predominated by E coli, S. aureus, Clostridium, β-hemolytic streptococcus, and Bactereoides, though the possibility of monomicrobial infection is not excluded. Early diagnosis is mandatory for successful treatment. In the cases of perianal and perineal localization, a possible perforation of intra-abdominal organs must be kept in mind. Diagnosis can sometimes be made by clinical examination, but imaging (CT scan is the “gold standard” method) is necessary, to determine the extent of the disease and treatment response. The treatment itself is based on the principle of “source control” using triple therapy: wide incisions with debridement and tissue de compression, wide spectrum antibiotics and intensive resuscitation. In some cases the use of HBOT may be beneficial, but further randomized controlled studies are needed to prove its value. Scoring systems are recommended and useful for a universal determination of the disease stage and prognosis.
SUMMARY

NEKROTIZIRAJUĆA INFEKCIJA MEKIH TKIVA PERIANALNE I PERINEALNE REGIJE: FAKORI RIZIKA, DJIAGNOZA I TRETMAN

Nekrotizirajuća infekcija mekih tkiva predstavlja po život opasno stanje, koje se karakteriše širokim zah-vatanjem kože, potkožnog masnog tkiva fascije i mišića. 82% pacijenata poseduje neki od faktora rizika, kao što su dijabetes mellitus, gojaznost, alkoholizam, pušenje, imunodeficijentna stanja, malnutricija ili loš socioekono-mski status. Nekrotizirajuća infekcija mekih tkiva se u početku dijagnostikuje kliničkim pregledom. Korišćenje imaging tehnike, naročito kompjuterizovane tomografije, predstavlja zlatni standrad; CT pregled pokazuje prisustvo tečnih kolekcija, abscesa, degeneraciju masnog tkiva i subkutani emfizem. Tretman nekrotizirajuće infekcije mekih tkiva uključuje hirurški debridman, drenažu, široke incizije zahvaćene regije, tkivna dekompresija i primena antibiotika širokog spektra. Upkos postojanju modernih metoda tretmana, ili tzv. principa “kontrola izvora infekcija”, mortalitet je i dalje do 51%. Nekro-tizirajuća infekcija mekih tkiva je vrlo opasna infekcija na koju moramo da mislimo i tretirati je što je pre moguće.

Ključne reči: Nekrotizirajuća infekcija mekih tkiva; Nekrotizirajuća infekcija; Fournier’ova gangrena; perianalna regija; perinealna regija

REFERENCES


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