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The predictors of mortality in patients with anogenital necrotizing fasciitis (Fournier's gangrene)

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(5):650–655

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Προγνωστικοί παράγοντες θνησιμότητας σε ασθενείς με νεκρωτική περιτονίτιδα (γάγγραινα Fournier)

Περίληψη στο τέλος του άρθρου

OBJECTIVE **To evaluate the predictors of mortality in the Fournier's gangrene form of necrotizing fasciitis (NF).** METHOD **The medical records of patients with anogenital NF who were treated in a tertiary care hospital between January 2010 and December 2018 were reviewed, retrospectively.** RESULTS **This study included 86 patients, 76 males and 10 females. Perianal abscess (30.2%) was the leading precipitating event causing NF. The scrotum and perineum were the most commonly affected sites, 73.2% and 40.7%, respectively. NF extended beyond the urogenital and or anorectal triangle in 30.2% of cases. *Escherichia coli (E. coli)* was the most common microorganism isolated in tissue cultures (55.3%), and *Klebsiella pneumoniae* the second most common (15.3%). Admission to the intensive care unit (ICU) was required for 50 patients (58.1%), and the mortality rate was 23.3%. Older age (>60 years), smoking, and extension of the infection beyond the urogenital and or anorectal triangle were all significantly associated with mortality.** CONCLUSIONS **Age >60 years, smoking, and extension of the infection beyond urogenital and or anorectal triangle were significantly related with mortality in anogenital NF. Prompt diagnosis and timely intervention are essential to prevent spread of the infection.**

Key words

Fournier's gangrene
Mortality
Necrotizing fasciitis
Necrotizing soft tissue infections

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Necrotizing soft tissue infection (NSTI) is an infection of deep soft tissues that result in necrosis of epidermis, dermis, subcutaneous tissue, fascia, and muscle.[1] It is characterized by fulminant tissue destruction and systemic signs of toxicity, and carries a high risk of mortality. Necrotizing fasciitis (NF) is a form of NSTI that results in progressive destruction of the fascia and overlying tissue. It is of low prevalence (0.4–1/100,000), but the mortality rate can reach up to 80%, with a reported range of from 5.66% to 80%.[2,3] The mortality depends primarily on the extent of the infection and the timing of the introduction of medical care.[1,4] NF has a progressive and rapidly advancing clinical course and delay in treatment of more than 6 to 12 hours and inadequate surgical debridement contribute to morbidity (including amputation, organ failure) and mortality.[5,6] A major diagnostic challenge leading to misdiagnosis of NF is the normal appearance of the overlying skin because the actual infection is located deeper in soft tissues. Older age, peripheral vascular insufficiency, and diabetes mellitus (DM) are other significant risk factors for mortality.[5] Fournier's gangrene is a form of NF of the perineal, perianal and genital region, originating from genitourinary, colorectal or dermal diseases.[7]

The purpose of the present study was to evaluate the predictors of mortality in anogenital NF.

MATERIAL AND METHOD

The data of patients with NF who treated at General Surgery and Urology Departments in a tertiary care hospital in Malatya between January 2010 and December 2018 were reviewed retrospectively. The inclusion criteria were: (a) Age >18 years, (b) patients with NF operated on in the General Surgery and Urology Departments. The exclusion criteria were: (a) Age <18 years, (b) the patients treated in clinics other than the General Surgery and/or Urology Departments, and (c) absence of sufficient data.

The diagnosis of NF was based on surgical findings, when the gray-black, foul-smelling gangrenous tissue with dishwater-gray

exudate was revealed, and confirmed by the histopathological report, if available. Mortality was defined as death from any cause during hospitalization.

The data recorded for the study included demographic information, comorbidities (cardiovascular diseases, DM, malignant and or autoimmune diseases, transplantation, chronic renal failure, respiratory diseases, central nervous system diseases, immunosuppressive therapy), the etiology and origin of the disease, laboratory findings (hematocrit, hemoglobin, platelet and white blood cell counts, blood levels of glucose, sodium, creatinine, albumin, lactate dehydrogenase, international normalized ratio, C-reactive protein), the results of tissue cultures, therapeutic interventions (antibiotic usage, abscess drainage, orchiectomy, debridement, creation of de-functioning stoma, application of graft or flap, application of vacuum-assisted closure system), and the length of hospitalization. The American Society of Anesthesiologists (ASA) physical status classification and the mortality were recorded.

The study was conducted according to the principles set forth by the Helsinki Declaration of 1975. Approval from the Human Ethics Committee of the Institution was obtained.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS), version 17.0 for Windows. The demographic characteristics of the patients were analyzed using descriptive analysis, and expressed as n (%) and mean with standard deviation (mean±SD). A logistic model was set up to describe the relationship between mortality and variables associated with mortality.

The selection of variables for the logistic model was determined by the Chi-square independence test ($p<0.05$ was regarded as significant). Significant variables were included in multivariate binary logistic regression analysis. A bivariate correlation test was used to determine whether there was a relationship between independent variables to be analyzed before multivariate binary logistic regression analysis. In multivariate binary logistic regression analysis, backward stepwise method (likelihood ratio) was used. The level of significance used at the entry of the variables was 0.05, the level of significance used for removal was 0.1. The level of significance used in testing the model in general was 0.05.

RESULTS

This study included 86 patients, 76 males and 10 females, with a mean age of 58.3±16.6 years, range 20–88 years. Of the 86, 69 (80.2%) had at least one additional disease; cardiovascular diseases were the most common (36%), followed by DM (34.9%), and 28 (32.6%) of the patients were smokers (tab. 1). According to assessment of physical status, 3 (3.5%) were classified as ASA I, 48 (55.8%) ASA II, 32 (37.2%) ASA III, and 3 (3.5%) were ASA IV. The diagnosis of NF was confirmed by histopathology in 31.4% of cases.

Table 1. The predisposing comorbid factors of patients with necrotizing fasciitis.

Comorbid factors	Living patients (n=66) n (%)	Deceased patients (n=20) n (%)	Total (n=86) n (%)
Cardiovascular diseases	24 (36.3)	7 (35.0)	31 (36.0)
Diabetes mellitus	23 (34.8)	7 (35.0)	30 (34.9)
Malignancy	13 (19.6)	7 (35.0)	20 (23.3)
Immunosuppressive therapy	10 (15.1)	5 (25.0)	15 (17.4)
Transplantation	–	5 (25.0)	5 (5.8)
Solid organ (liver) disease	–	4 (20.0)	
Bone marrow disease	–	1 (5.0)	
Autoimmune disease	5 (7.57)	–	5 (5.8)
Central nervous system disease	7 (10.6)	5 (25.0)	12 (14.0)
Respiratory system disease	5 (7.57)	–	5 (5.8)
Chronic renal failure	3 (4.54)	2 (10.0)	5 (5.8)
Smoking	10 (15.1)	18 (90.0)	28 (32.6)

Perianal abscess (30.2%) was the leading precipitating event causing NF, followed by genital tract infections (25.6%), and urinary tract infections (15.1%), together accounting for 40.7% of the cases. The scrotum and perineum were the most commonly affected sites, 73.2% and 40.7%, respectively. The perianal region was involved in 31.4%, the inguinal region in 22.1%, and the penis/urethra in 11.6% of cases. The NF extended beyond the urogenital and or anorectal triangle in 30.2% of cases, of which the abdominal wall accounted for 18.6%, the thoracic wall 2.3%, lower extremity 8.1%, gluteal region 4.7%, and the sacrum 3.5%.

At least one of three culture types was obtained in 93% of patients: blood culture in 50%, urine culture in 60.5%, and tissue culture in 79.1%, and was positive in 76.7% of cases. The cultures were mono-microbial in origin (67.6%), and *Escherichia coli (E. coli)* was the most common microorganism isolated in tissue cultures (55.3%), and *Klebsiella pneumoniae* the second most common (15.3%). The significant number of antibiotic resistant and or opportunistic microorganisms were isolated (tab. 2). Table 3 shows the laboratory data of the study patients.

Misinterpretation of NF led to surgical delay in 41.8% of the patients. Surgical debridement involved total excision of all necrotic tissue at the first operation, and was repeated in 53.4% of cases, with a mean debridement number of 2.38±1.98, range 1–11. Fifteen patients (17.4%) underwent abscess drainage prior to excision. De-functioning stoma was performed in 27.9% of cases, 66.6% of which took place during the first operation. Orchiectomy was needed

in only 8 cases. The vacuum-assisted closure system was applied for 7 patients and the Bogota bag technique was used for closure of open abdominal wounds in two patients. In 28 patients the wound defects were repaired with skin grafts and or flaps: split-thickness skin graft (STSG) in 14 patients, fasciocutaneous flap in 8 patients, free muscle flap in 3 patients, both STSG and fasciocutaneous flap in 2 patients, both STSG and free muscle flap in one patient.

Table 2. The microorganisms isolated in tissue culture from patients with necrotizing fasciitis.

Microorganisms	Living patients (n=66) n (%)	Deceased patients (n=20) n (%)	Total (n=86) n (%)
ESBL (+) *E. coli*	15 (22.7)	5 (25.0)	20 (23.2)
E. coli	11 (16.6)	2 (25.0)	13 (15.0)
Carbapenemase (+) *E. coli*	2 (3.03)	1 (5.0)	3 (3.48)
Klebsiella pneumoniae	6 (9.09)	4 (20.0)	10 (11.6)
Enterococci	5 (7.57)	2 (10.0)	7 (8.13)
Gram (+) cocci	4 (6.06)	3 (15.0)	7 (8.13)
Gram (–) bacilli	3 (4.54)	3 (15.0)	6 (6.9)
Acinetobacter	3 (4.54)	3 (15.0)	6 (6.9)
Candida	2 (3.03)	4 (20.0)	6 (6.9)
Staphylococcus aureus	2 (3.03)	–	2 (2.32)
Coagulase (–) *staphylococci*	2 (3.03)	1 (5.0)	3 (3.48)
MRSA (+) *staphylococci*	1 (1.5)	–	1 (1.16)
Penicillin resistant *staphylococci*	1 (1.5)	–	1 (1.16)
Pseudomonas	3 (4.54)	2 (10.0)	5 (5.81)
Streptococcus	2 (3.03)	2 (10.0)	4 (4.65)
Gram (+) diplococci	–	1 (5.0)	1 (1.16)
Proteus	–	1 (5.0)	1 (1.16)

Table 3. The laboratory findings in patients with necrotizing fasciitis.

Laboratory findings	Living patients Mean±SD	Deceased patients Mean±SD	Total Mean±SD
C-reactive protein	35.63±58.1	49.63±103.5	38.89±70.84
White blood cells	15.07±6.93	15.38±11.6	15.14±8.09
Hematocrit	35.52±6.28	30.65±7.45	34.43±6.83
Hemoglobin	11.3±2.16	9.77±2.04	10.9±2.22
Platelets	282.2±148.8	195.15±172.2	262.7±157.6
Glucose	163.69±97.6	201.4±157.4	172.4±114.3
Sodium	134.5±4.18	137.7±6.53	135.27±4.97
Creatinine	1.13±0.62	1.52±0.74	1.21±0.66
Albumin	2.29±0.66	2.05±0.63	2.23±0.66
Lactate dehydrogenase	288.03±116.6	283±99.2	286.8±112.2
International normalized ratio	1.32±0.49	1.7±1.12	1.42±0.72

SD: Standard deviation

In 43.02% of patients, a broad-spectrum antibiotic regimen was started on the day of surgery, and switched to another antibiotic based on the culture results and clinical response. In 45.34% of cases, antibiotic therapy was initiated several days before surgery, as it was required for the treatment of prior diseases and or the leading causes of NF. Mean length of antibiotic therapy was 25.5±20.3 days, range 1–120 days.

The mean duration of hospitalization was 27.94±21.8 days, range 1–120 days, of which 8.33±18.1 days, range 0–120 days were in the intensive care unit (ICU); 50 (58.1%) patients required admission to the ICU. The mortality rate was 23.3%. The factors associated with mortality are shown in table 4. Comorbidities not shown to be associated with mortality in this series were cardiovascular diseases, DM, respiratory diseases, malignancy, autoimmune disease, chronic renal failure and immunosuppressive therapy. On both univariate and multivariate analysis, older age (>60 years), smoking, and extension of the necrotizing infection beyond the urogenital and or anorectal triangle were all shown to be significantly related with mortality.

DISCUSSION

Prompt diagnosis and immediate surgical intervention are the keys to a successful outcome in NF. Despite advances in management, the mortality in this condition has not been reduced below 20%.[8] In the current series, in concordance with other studies,[1,2,8] the mortality rate was 23.3%. Misinterpretation of NF resulted in surgical delay in 36 (41.8%) patients, which was responsible for increased mortality, although not to a statistically significant degree. A major diagnostic challenge leading to misdiagnosis of NF is the normal appearance of the overlying skin, because the actual infection is located deeper in the soft tissues. NSTIs originating in the urogenital and or anorectal triangle (Fournier's gangrene) can spread along the fascial planes to the lower extremities, abdomen, flank and even the chest.[8] We found that extension of the necrotizing infection beyond the urogenital and or anorectal triangle was independently associated with mortality in NF, as had been reported in an earlier study.[10]

Advanced age was an independent predictor of mortality in our series, as concluded by several other studies.[11–13] Similarly to previous studies, DM and cardiovascular dis-

Table 4. Factors associated with mortality in patients with necrotizing fasciitis on univariate and multivariate analysis (n=86).

Characteristics	Univariate analysis			Multivariate analysis		
	Living patients (n=66) n (%)	Deceased patients (n=20) n (%)		OR	95% CI	p
Age (years)						
≤60	40 (85.1)	7 (14.9)	0.044	4.36	0.88–21.6	0.071
>60	26 (66.7)	13 (33.3)				
Gender						
Male	57 (75.0)	19 (25.0)	0.291			
Female	9 (90.0)	1 (10.0)				
Additional diseases						
No	15 (88.2)	2 (11.8)	0.211			
Yes	51 (73.9)	18 (26.1)				
Smoking						
No	56 (96.6)	2 (3.4)	0.000	53.74	8.89–324.6	0.000
Yes	10 (35.7)	18 (64.3)				
ASA score						
I–II	42 (82.4)	9 (17.6)	0.137			
III–IV	24 (68.6)	11 (31.4)				
Disease extension						
Within urogenital and or anorectal triangle	53 (88.3)	7 (11.7)	0.000	5.93	1.21–28.9	0.028
Beyond urogenital and or anorectal triangle	13 (50.0)	13 (50.0)				
Previous abscess drainage						
No	55 (75.3)	18 (24.7)	0.466			
Yes	11 (84.6)	2 (15.4)				
De-functioning stoma						
No	50 (80.6)	12 (19.4)	0.169			
Yes	16 (66.7)	8 (33.3)				
Orchiectomy						
No	58 (74.4)	20 (25.6)	0.102			
Yes	8 (100)	0 (0)				
Debridement number						
One	30 (75.0)	10 (25.0)	0.721			
More than one	36 (78.3)	10 (21.7)				
Previous antibiotic therapy						
No	31 (83.8)	6 (16.2)	0.179			
Yes	35 (71.4)	14 (28.6)				
Surgical delay due to mis-interpretation of NF						
No	42 (84.0)	8 (16.0)	0.061			
Yes	24 (66.7)	12 (33.3)				

OR: Odds ratio, 95% CI: 95% confidence interval, NF: Necrotizing fasciitis

eases were the predominant comorbid factors, but none of them were associated with increased mortality.[11,14] Although DM increases the risk of NF, it may not have a significant impact on the prognosis.

Several studies have identified smoking as a risk factor for NF, but findings related to its effect on mortality are conflicting. In contrast to previous studies, we found that smoking had a significant association with mortality in our series.[10,15] Its effect may be multifactorial, including alteration in blood flow to the tissues and suppression of immune system function.[16]

In contrast to the prevailing body of knowledge, NF presented in our series as a mono-microbial infection (67.6%), and *E. coli* was the microorganism most commonly isolated in tissue cultures. Previous antibiotic treatment may have prevented the isolation of other microorganisms. In 45.34% of the cases antibiotic therapy was initiated several days before surgery, as it had been required for the treatment of prior diseases and or the leading causes of NF. The isolation of a significant number of antibiotic resistant and or opportunistic microorganisms was also evidence that antibiotic therapy had been used for a long time before the culture.

The incidence of de-functioning stoma (27.9%) was higher than that reported in previous studies (13–15%).[17,18] Some authors have suggested that a higher number of debridements may be related with higher mortality because patients with severe disease would require more debridements for eradication of the infected tissue.[18] One study reported that the number of debridements was not related with worse prognosis, and the authors concluded that patients with mild disease, in contrast with non-survivors, will have more time to undergo multiple surgical procedures.[19] We found that neither the presence of de-functioning stoma, nor the number of debridements had any effect on mortality.

The limitations of this study were its retrospective design, with a small number of cases, and the inclusion only of the patients who were treated in the General Surgery and or Urology Departments, but no other departments.

Despite recent advances in the diagnosis and treatment of NF, the mortality continues to be high. Older age (>60 years), smoking and extension of the infection beyond the urogenital and or anorectal triangle are significantly related to mortality in NF. Prompt diagnosis and timely intervention are essential to limiting the spread of the infection.

The impact and implications of our study are summarized in the following areas: (a) Our findings lead to the recommendation of strategies aimed at improving the education of health care practitioners about NSTIs, especially in older immunocompromised/immobilized patients, and those with DM; (b) our findings endorse initiatives for intervention within the health system designed to help smokers to stop smoking, and (c) our findings indicate the need for future studies on neovascularization and oxygenation of compromised tissues.

ΠΕΡΙΛΗΨΗ

Προγνωστικοί παράγοντες θνησιμότητας σε ασθενείς με νεκρωτική περιτονιίτιδα (γάγγραινα Fournier)

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ΣΚΟΠΟΣ Αξιολόγηση των προγνωστικών παραγόντων της θνησιμότητας στη νεκρωτική περιτονιίτιδα (γάγγραινα Fournier). **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Αξιολογήθηκαν αναδρομικά τα ιατρικά αρχεία ασθενών με νεκρωτική περιτονιίτιδα, που αντιμετωπίστηκαν σε νοσοκομείο τριτοβάθμιας φροντίδας μεταξύ Ιανουαρίου 2010 και Δεκεμβρίου 2018. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Η μελέτη περιλάμβανε 86 ασθενείς (76 άνδρες και 10 γυναίκες). Η κύρια αιτία (30,2%) ήταν το περιορθικό απόστημα. Οι κύριες προσβληθείσες περιοχές ήταν το όσχεο και το περίνεο σε ποσοστό 73,2% και 40,7%, αντίστοιχα. Η νεκρωτική περιτονιίτιδα εκτεινόταν στην ουρογεννητική ή και στην παραορθική περιοχή στο 30,2% των περιπτώσεων. Πιο συχνά απομονώθηκε στις καλλιέργειες των ιστών *E. coli* (55,3%) και *Klebsiella pneumoniae* (15,3%). Πενήντα ασθενείς (58,1%) χρειάστηκε να νοσηλευτούν σε μονάδα εντατικής θεραπείας. Το ποσοστό θνησιμότητας ήταν 23,3%. Στις αναλύσεις, με την αυξημένη θνησιμότητα συνδέονταν σημαντικά η μεγαλύτερη ηλικία, το κάπνισμα και η επέκταση της λοίμωξης πέρα από την ουρογεννητική ή και την περιπρωκτική περιοχή. **ΣΥΜΠΕΡΑΣΜΑΤΑ**

Η μεγαλύτερη ηλικία, το κάπνισμα και η επέκταση της λοίμωξης πέρα από την ουρογεννητική ή και την περιπρωκτική περιοχή σχετίζονται με αυξημένη θνησιμότητα στη νεκρωτική περιτονίτιδα. Είναι αναγκαία η έγκαιρη διάγνωση και θεραπεία για την πρόληψη της εξάπλωσης της λοίμωξης.

Λέξεις ευρετηρίου: Γάγγραινα Fournier, Θνησιμότητα, Νεκροποιητικές λοιμώξεις μαλακών μορίων, Νεκρωτική περιτονίτιδα

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