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Microbiology and factors affecting mortality in necrotizing fasciitis

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Necrotizing fasciitis is a life-threatening soft-tissue infection primarily involving the superficial fascia. This study investigated the microbiologic characteristics and determinants of mortality of this disease. The medical records of 87 consecutive patients with a diagnosis of necrotizing fasciitis from 1999 to 2004 were retrospectively reviewed. A single pathogen was identified as the infectious agent in 59 patients (67.8%), multiple pathogens were identified in 17 patients (19.6%), and no organism was identified in 11 patients (12.6%). *Klebsiella pneumoniae*, identified in 17 patients, was the most commonly isolated species. The most common comorbidity was diabetes mellitus (41 patients; 53.2%). Multivariate logistic regression analysis showed that more than 1 comorbidity, thrombocytopenia, anemia, more than 24 h delay from onset of symptoms to surgery and age greater than 60 were independently associated with mortality. This study found that *K. pneumoniae* was the most common cause of necrotizing fasciitis. Early operative debridement was independently associated with lower mortality.

Key words: Debridement, *Klebsiella pneumoniae*, necrotizing fasciitis

Necrotizing fasciitis is a life-threatening soft tissue infection primarily involving the superficial fascia [1-9]. It is perhaps the most aggressive form of soft tissue infection [2-7]. Meleney reported the first major series of patients with necrotizing fasciitis in 1924, which was a group of 20 cases observed in China [1]. His study disclosed beta-hemolytic streptococci infection in all of the patients, and he named the disease "acute streptococcal gangrene".

The term necrotizing fasciitis was first used by Wilson in 1952 [2]. The consensus was that necrotizing fasciitis was an infection involving the superficial fascia and the subcutaneous tissue with very minor superficial epidermal or mucosal focus as a portal of bacterial entry. The progression of the disease is fulminant [2-4]. The prognosis hinges on accurate diagnosis and immediate institution of appropriate treatment [4-7]. We had observed that a high portion of cases of necrotizing fasciitis in our institute were caused by *Enterobacteriaceae* but that epidemiologic data were lacking. This study analyzed the microbiologic spectrum of this condition at our hospital. The factors affecting mortality associated with necrotizing fasciitis were also evaluated.

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Materials and Methods

A computer-generated search in the database of the Medical Records Department was used to identify patients with operative findings suggesting necrotizing fasciitis or computed tomography (CT) revealing asymmetric fascia thickening [3] who were treated between 1999 and 2004.

Diagnosis of necrotizing fasciitis was made based on the following characteristics at operative exploration: 1) the presence of grayish necrotic fascia; and 2) easy separation of the superficial fascia from the underlying tissues during surgery. Permanent histopathologic tissue examination was used to confirm the diagnosis [4].

Data collected from records of each patient included age, gender, location of infection, number and type of comorbid illnesses, portal of entry of infection, symptoms at admission (including the time to access medical care), vital signs, and physical, radiographic, and laboratory findings at the time of admission. The results of microbiologic cultures of tissue samples

obtained at the first operative debridement were analyzed. Data on delay from initial presentation of symptoms to operative treatment, initial antibiotics used, number of operative debridements, performance of amputation, duration of hospitalization, and the in-hospital mortality rate were also recorded. The anatomic site of infection was classified as either central (trunk, back, or groin) or peripheral (upper and lower limbs).

Statistical analyses were performed using Statistical Package for the Social Sciences software. Comparisons of proportions were made using Pearson's chi-squared test to identify univariate differences among defined variables with respect to mortality. Student's *t* test was used for the analysis of continuous variables. The significance of factors with a possible influence on mortality was evaluated using a logistic regression approach by means of a backward stepwise selection procedure. A *p* value of 0.2 was chosen as the criterion to judge the entry and removal of variables at each step of the regression procedure. Then, the final model was constructed to determine the factors independently associated with mortality.

Results

The medical charts of 113 patients identified as having a diagnosis of necrotizing fasciitis at our institute during the study period were obtained for review. Twenty six of these patients were excluded because their histopathologic tissue examinations did not favor the diagnosis. The remaining 87 patients were included in this study. Table 1 summarizes the demographic characteristics and the clinical, biochemical and radiographic findings in these patients at admission. The major presenting symptoms included swelling (69 patients, 89.6%), pain (68 patients, 88.3%), erythema (49 patients, 63.6%), local heat (22 patients, 36.3%), and bullae (22, 26.0%). Other findings included skin induration, crepitus, fluctuance, and skin necrosis as well as sensory and motor deficits.

The portal of entry of infection was identified in 50 patients. The source of necrotizing fasciitis could not be found in 39 patients. Trauma was the most common portal of entry, which was found in 39 patients (44.8%). Nine patients had necrotizing fasciitis spread from a local infection. These infections included peritonsillar abscess (3 patients), angioedema of the lip (1 patient), empyema thoracis (1 patient), diverticulitis (1 patient), site of pre-existing bed sore (1 patient), and *Klebsiella pneumoniae* metastatic infection (2 patients).

Table 1. Demographic, clinical, biologic, and radiographic data of patients with necrotizing fasciitis

Variable	n or mean (range [%])
Gender	
Male	65 (74.7)
Female	22 (25.3)
Age (years)	53.4 (1-86)
Comorbidity	
Diabetes mellitus	44 (50.6)
Liver cirrhosis	25 (28.7)
Alcoholism	18 (20.7)
Immunosuppressant agent	6 (6.9)
Chronic renal insufficiency	2 (2.6)
Cancer	2 (2.3)
Human immunodeficiency virus	1 (1.3)
Aplastic anemia	1 (1.3)
No comorbidities	16 (18.3)
Location	
Head and neck	5 (5.7)
Trunk	10 (11.5)
Inguinal area	9 (10.3)
Upper limb	6 (6.9)
Lower limb	57 (65.5)
Findings on admission	
Temperature >38°C	21 (24.1)
Hypotension	28 (32.2)
Amputation performed	9 (10.3)
Gas on radiograph	4 (4.6)
Mortality	30 (34.5)
Total WBC count (k/mL)	13.5 (0.7-50.6)
C-reactive protein (mg/dL)	15.0 (0.9-60.8)
Number of debridements	3.0 (0-23)
Duration of hospitalization (days)	33.7 (1-163)

Abbreviation: WBC = white blood cell

Cultures of tissue specimens obtained during the first operative debridement were analyzed. A single pathogen was isolated in 59 patients (67.8%), more than 1 pathogen was identified in 17 patients (19.6%), and no organism was identified in 11 patients (12.6%). *K. pneumoniae*, identified in 17 patients, was the most common pathogen isolated.

The bacteriology of monomicrobial necrotizing fasciitis is summarized in Table 2. Among the 59 patients with monomicrobial necrotizing infections, Gram-positive bacteria were isolated in 25 patients. *Staphylococcus aureus* was the most common Gram-positive isolate, found in 13 patients. Gram-negative bacteria were isolated in 34 patients. Nineteen of these isolates were members of *Enterobacteriaceae*. *K. pneumoniae* was the most common Gram-negative pathogen isolated. *Aeromonas* spp. were isolated in 7 patients, all of whom died. *Vibrio vulnificus* was

Table 2. Bacteriology of monomicrobial necrotizing fasciitis

	No.
Gram-positive	
Staphylococcus aureus	13
Group A *Streptococcus*	8
Group B *Streptococcus*	2
Group F *Streptococcus*	1
Viridans group streptococci	1
Gram-negative	
Klebsiella pneumoniae	13
Escherichia coli	2
Enterobacter cloacae	1
Citrobacter	1
Proteus spp.	2
Aeromonas	7
Vibrio vulnificus	3
Acinetobacter baumannii	2
Pseudomonas aeruginosa	3
Mixed infection	17

isolated in 3 patients, 2 of whom died. Three patients had *Pseudomonas aeruginosa* necrotizing fasciitis and all of them survived.

Mixed infection was documented in 17 patients. *Enterobacteriaceae* were the most common bacteria isolated in polymicrobial necrotizing fasciitis, as in monomicrobial infections. Among the *Enterobacteriaceae* isolates, *Escherichia coli* and *K. pneumoniae* were the most common species, followed by *Enterobacter cloacae*, *Morganella morganii* and *Proteus vulgaris*. *P. aeruginosa* was isolated in 3 patients, and *Acinetobacter* spp. in 2 patients. Among anaerobic organisms isolated, *Bacteroides fragilis* was the most common. *Prevotella* spp. were isolated in 2 patients, *Veillonella* in 1 patient, *Propionibacterium propionicum* in 1 patient, and *Eikenella corrodens* in 1 patient.

Amputation was performed to control the infection in 9 patients (11.7%). Patients underwent a mean of 3.0 debridements (range, 0 to 15 debridements) to control the infective process. The average duration of hospitalization was 33.7 days (range, 1 to 163 days).

Thirty patients (32.5%) died. Table 3 shows the relationship of pre-existing characteristics and medical condition to mortality. Death was significantly associated with age greater than 60 years. Mortality was not significantly influenced by other physical findings during hospitalization such as pain, swelling, erythema or local heat.

Although diabetes mellitus was the most common pre-existing medical condition, it was not significantly associated with mortality unless it occurred with other disease. Mortality was significantly increased in patients with 2 or more comorbidities, such as diabetes mellitus combined with liver cirrhosis.

Table 4 compares the laboratory data between survivors and non-survivors. Conditions significantly associated with mortality included thrombocytopenia, abnormal liver function, and low serum albumin level. Patients who received emergent debridements at least 24 h before the onset of symptoms had a lower mortality rate than those who had delayed operations (26.0% versus 45.9%, p=0.069). Although mortality was lower when the isolated organisms were sensitive to initial antibiotics treatment, this difference was not significant (31.9% versus 37.5%, p=0.654).

Because of the large number of potentially inter-dependent parameters examined in this retrospective study, logistic regression analysis was performed to assess the independent effect of variables on mortality. Variables that were significant in the univariate analysis (p<0.2) were selected for inclusion in the first step of the stepwise regression model. These parameters included age, shock, fever, cirrhosis, 2 or more underlying conditions, use of immunosuppressant, low hemoglobin, decreased platelet count, acute renal failure, decreased serum albumin level, delay of more than 24 h from symptom onset to surgery, number of times of debridement and bacteremia. The multivariate logistic regression analysis revealed that risk of death was independently associated with more than 1 underlying condition, thrombocytopenia, anemia, delay of more than 24 h from symptom onset to surgery, and age greater than 60 years.

Discussion

Giuliano et al were the first to divide bacteriologic culture results in necrotizing fasciitis into 2 distinct groups in a study of 16 cases reported in 1977 [5]. From their point of view, aerobic organisms other than Group A *Streptococcus* alone could not cause necrotizing fasciitis. Subsequent studies revealed that mixtures of aerobes and anaerobes could act synergistically, thus affecting the virulence of necrotizing fasciitis [5-10].

It was also demonstrated that solitary aerobic organisms other than Group A *Streptococcus* could cause necrotizing fasciitis. Howard et al reported 18 patients with necrotizing fasciitis caused by *Vibrio* spp. in 1985 [11]. These infections usually occur in apparently insignificant wounds exposed to sea water or fish [10-14]. The mortality rate in their study was 33.3%.

Table 3. Mortality in groups defined by pre-existing characteristics and medical conditions

	Survivors	Non-survivors	Mortality rate (%)	*p*
Initial presentation				
Age (years)				
<60	36	14	28.0	
≥60	21	16	43.2	0.173
Gender				
Female	15	6	28.6	
Male	42	24	36.4	0.802
Shock				
No	42	17	28.8	
Yes	15	13	46.4	0.147
Disturbed consciousness				
No	51	24	32.0	
Yes	6	6	50.0	0.326
Fever				
No	40	26	39.4	
Yes	17	4	19.0	0.116
Bullae				
No	44	19	30.2	
Yes	13	11	45.8	0.210
Trauma				
No	25	16	39.0	
Yes	32	14	30.4	0.499
Pain				
No	6	4	40.0	
Yes	51	26	33.8	0.732
Swelling				
No	4	5	55.6	
Yes	53	25	32.1	0.265
Local heat				
No	38	18	32.1	
Yes	19	12	38.7	0.639
Erythema				
No	18	13	41.9	
Yes	39	17	30.4	0.348
Peripheral				
No	15	8	34.8	
Yes	42	22	34.4	0.972
Cormorbidity				
Diabetes mellitus				
No	31	12	27.9	
Yes	26	18	40.9	0.261
Cirrhosis				
No	44	18	29.0	
Yes	13	12	48.0	0.134
Alcoholism				
No	44	25	36.2	
Yes	13	5	27.8	0.589
Immunosuppressant				
No	55	26	32.1	
Yes	2	4	66.7	0.176
≥2 comorbidities				
No	39	9	18.8	
Yes	18	21	53.8	0.001

Table 4. Relationship of laboratory data with mortality

Variable (mean ± SD)	Survivors	Non-survivors	*p*
Hemoglobin (mg/dL)	11.2 ± 2.6	10.3 ± 2.7	0.177
WBC count (/mL)	13,442 ± 8790	13,745 ± 9730	0.883
Platelet (k/mL)	248 ± 162	129 ± 123	0.01
Bilirubin (mg/dL)	3.1 ± 2.7	5.8 ± 5.4	0.68
AST (U/L)	110 ± 277	88 ± 58	0.72
ALT (U/L)	64 ± 171	46 ± 24	0.637
BUN (mg/dL)	24 ± 17	48 ± 41	<0.001
Creatinine (mg/dL)	1.3 ± 0.7	2.9 ± 2.9	<0.001
Albumin (mg/dL)	2.1 ± 0.9	1.6 ± 0.5	0.05
CRP (mg/dL)	14 ± 14.9	15.9 ± 13.1	0.72

Abbreviations: SD = standard deviation; WBC = white blood cell; AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein

In this series, *Vibrio* spp. were isolated in 3 patients. Two of these patients had cirrhosis and died despite debridements and adequate antibiotic therapy.

Another highly virulent bacterium which can cause necrotizing fasciitis is *Aeromonas* spp. This organism was the etiologic agent in 7 patients in our study and all of them died. *Aeromonas hydrophila* has been described as the cause of the necrotizing fasciitis in patients with immunosuppression, burns or trauma in an aquatic setting [15]. Patients with liver cirrhosis or malignancy had a higher mortality rate within 7 days after admission [16]. Among the 7 patients with necrotizing fasciitis caused by *Aeromonas* spp. in this series, 4 had cirrhosis, 3 had diabetes mellitus, and only 1 patient had no underlying disease. The prevalence of these underlying conditions is consistent with previous studies [15-18].

Highly virulent bacteria such as many of the facultative bacteria and *P. aeruginosa*, just like the group A streptococci, can cause necrotizing fasciitis alone, especially in high-risk patients [19].

Enterobacteriaceae were the most common group of bacterial organisms isolated in this series. A single *Enterobacteriaceae* was isolated in 19 patients. Most patients with necrotizing fasciitis caused by solitary *Enterobacteriaceae* had underlying disease including diabetes mellitus in 13, cirrhosis in 4, both diabetes and cirrhosis in 3, while only 5 patients had no underlying disease. *K. pneumoniae*, found in 17 patients, was the most common pathogen isolated in this series, unlike a previous series in which beta-hemolytic *Streptococcus* was the most common single pathogen isolated [12]. The association of *K. pneumoniae* necrotizing fasciitis with liver abscess and endogenous endophthalmitis of the eye has recently been highlighted [20-22]. Two of the patients with *K. pneumoniae* necrotizing fasciitis in this series had metastatic infection. Necrotizing fasciitis was not the initial presentation in these 2 patients, both of whom had *K. pneumoniae* bacteremia and diabetes mellitus. One of the patients also had acute pyelonephritis and the other had liver abscess. Necrotizing fasciitis developed later in the course of hospitalization. These cases emphasize the need for including necrotizing fasciitis in the differential diagnosis of patients with *K. pneumoniae* infection who present with limb swelling.

Necrotizing fasciitis was caused by Group B *Streptococcus* in 2 patients in this series, both of whom had diabetes mellitus. The reported predisposing factors to this etiology include obstetric complications in postpartum adult females and in infants as well as diabetes [23-27].

The somewhat high rate of monomicrobial isolation in this study might have been due to the use of relatively unsophisticated techniques for collection, transfer or culture of anaerobic specimens. The empirical use of antibiotics with activity against anaerobes antibiotics, however, had no impact on mortality rate. This may imply that anaerobes were easily eliminated by aggressive debridements. Anti-anaerobic antibiotics were used for more than 6 h before obtaining culture in only 12 of the 87 patients in this series. The impact of empirical antibiotics on the results of culture was thus likely to be limited.

Multivariate logistic regression analysis revealed that more than 1 comorbidity, thrombocytopenia, anemia, delay of more than 24 h from symptom onset to surgery, and age greater than 60 years independently affected survival. These findings are similar to the study of Wong et al, who reported that advanced age, 2 or more associated comorbidities, and a delay in surgery of more than 24 h adversely affected outcome [14]. The retrospective nature of this study, however, makes

these findings inconclusive. Age and underlying disease reflect the immune status of patients. The presence of chronic, debilitating disease may contribute to the uncontrollable nature of both local and systemic infection. Early debridement offers the only opportunity to correct these problems.

The paucity of cutaneous findings early in the course of necrotizing fasciitis made early diagnosis difficult in this series. The use of broad-spectrum empirical antibiotics to cover staphylococci, streptococci, and *Enterobacteriaceae* from the beginning appears indicated based on the bacteriologic findings. The need for a high index of suspicion of necrotizing fasciitis, and prompt early debridement in identified cases cannot be overemphasized.

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