Necrotizing Fasciitis: Clinical Presentation, Microbiology, and Determinants of Mortality

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Background: Necrotizing fasciitis is a life-threatening soft-tissue infection primarily involving the superficial fascia. The present report describes the clinical presentation and microbiological characteristics of this condition as well as the determinants of mortality associated with this uncommon surgical emergency.

Methods: The medical records of eighty-nine consecutive patients who had been admitted to our institution for necrotizing fasciitis from January 1997 to August 2002 were reviewed retrospectively.

Results: The paucity of cutaneous findings early in the course of the disease makes the diagnosis difficult, and only thirteen of the eighty-nine patients had a diagnosis of necrotizing fasciitis at the time of admission. Preadmission treatment with antibiotics modified the initial clinical picture and often masked the severity of the underlying infection. Polymicrobial synergistic infection was the most common cause (forty-eight patients; 53.9%), with streptococci and enterobacteriaceae being the most common isolates. Group-A streptococcus was the most common cause of monomicrobial necrotizing fasciitis. The most common associated comorbidity was diabetes mellitus (sixty-three patients; 70.8%). Advanced age, two or more associated comorbidities, and a delay in surgery of more than twenty-four hours adversely affected the outcome. Multivariate analysis showed that only a delay in surgery of more than twenty-four hours was correlated with increased mortality ($p < 0.05$; relative risk = 9.4).

Conclusions: Early operative débridement was demonstrated to reduce mortality among patients with this condition. A high index of suspicion is important in view of the paucity of specific cutaneous findings early in the course of the disease.

Level of Evidence: Prognostic study, Level II-1 (retrospective study). See Instructions to Authors for a complete description of levels of evidence.

Necrotizing fasciitis is a rare, rapidly progressive infectious process primarily involving the fascia and the subcutaneous tissue, with thrombosis of the cutaneous microcirculation. It is a life-threatening infection that has been recognized for centuries[1]. A variety of terms have been used to describe this condition, including phagedena, phagedena gangrenosum, hospital gangrene, progressive bacterial synergistic gangrene (Meleney's gangrene[2]), Fournier's gangrene, and hemolytic streptococcal gangrene. The term necrotizing fasciitis, first coined by Wilson in 1952, is perhaps the most accurate for describing the key features of this infectious process[3].

Necrotizing fasciitis is an uncommon disease, with approximately 500 to 1500 cases reported in the United States annually[4]. The progression of the disease is often fulminant, and the prognosis hinges on accurate diagnosis and immediate institution of appropriate treatment. While differentiation from common soft-tissue infections such as cellulitis and abscesses is critically important, the paucity of cutaneous findings early in the course of the disease makes diagnosis challenging. The purpose of the present study was to analyze the clinical presentation and microbiological characteristics of this condition and to evaluate the determinants of mortality associated with this uncommon surgical emergency.

Materials and Methods

The medical records of all patients who had been treated at our institution for necrotizing fasciitis between January 1997 and August 2002 were retrospectively reviewed. Patients were identified by means of a computer-generated search through the Medical Records Department for all patients who

TABLE I Demographic, Clinical, Biochemical, and Radiographic Data on Patients with Necrotizing Fasciitis

Categorical variables*	
Gender	
Male	53 (59.6%)
Female	36 (40.4%)
Comorbidities	
Diabetes mellitus	63 (70.8%)
Peripheral vascular disease	20 (22.5%)
Chronic liver disease	3 (3.4%)
Cancer	2 (2.2%)
No comorbidities	12 (13.5%)
Location of infection	
Peripheral	71 (79.8%)
Lower limb	62 (69.7%)
Upper limb	9 (10.1%)
Central (trunk)	18 (20.2%)
Parameters on admission	
Temperature of >38.0°C	47 (52.8%)
Hypotension	16 (18.0%)
Admitting diagnosis	
Necrotizing fasciitis	13 (14.6%)
Cellulitis	52 (58.4%)
Abscess	16 (18.0%)
Other	8 (9.0%)
Amputation performed	20 (22.5%)
Gas on plain radiographs	15 (16.9%)
Multiple organ failure on admission	4 (4.5%)
Mortality	19 (21.3%)
Continuous variables†	
Age *(yr)*	56.0 (27-84)
Biochemical parameters on admission	
Total white blood-cell count (in thousands)	20.4 (2.9-43.8)
C-reactive protein *(mg/L)*	247 (44-476)
Erythrocyte sedimentation rate *(mm/hr)*	83 (5-145)
Number of wound débridements	2.7 (0-9)
Duration of hospitalization *(d)*	40.6 (1-176)

*The data are given as the number of patients, with the percentage in parentheses. †The data are given as the mean, with the range in parentheses.

had been diagnosed with necrotizing fasciitis (International Classification of Diseases, Ninth Revision). Eighty-nine consecutive records were found. The following operative findings were used for definitive diagnosis: the presence of grayish necrotic fascia, demonstration of a lack of resistance of normally adherent muscular fascia to blunt dissection, lack of bleeding of the fascia during dissection, and the presence of foul-smelling "dish-water" pus. Permanent histopathological tissue specimens were examined to confirm the diagnosis when available[5].

The variables that were examined in the present study included age; gender; location of infection; admitting diagnosis; number and type of comorbidities; portal of entry of infection; duration and type of symptoms; vital parameters; and physical, radiographic, and laboratory findings at the time of admission. The microbiological cultures of the tissue samples that had been obtained at the time of the first operative débridement were analyzed. The time from admission to operative treatment, the number of operative débridements, the need for amputation, the duration of hospitalization, and the in-hospital mortality rate were also documented. The anatomical site of infection was defined as either central (trunk, back, or groin) or peripheral (upper and lower limbs).

Statistical analyses were performed with use of SPSS statistical software (version 11.0; SPSS, Chicago, Illinois). Bivariate analysis was performed with the chi square test or Fisher's exact probability test for comparisons of proportion between two groups. The possible significant factors influencing mortality were evaluated with the logistic regression approach by means of a backward stepwise selection procedure. The effects of age, gender, and associated comorbidities were also adjusted for in the model as these variables were known to have a clinically important effect on the other variables. Then, the final model was constructed to determine which variables were independent predictors of mortality. A p value of <0.05 was considered significant.

Results

Eighty-nine patients with necrotizing fasciitis were treated at our institution during the period under review. Table I summarizes their demographic characteristics and the clinical, biochemical, and radiographic findings on admission. The group included fifty-three men and thirty-six women with a mean age of 56.0 years (range, twenty-seven to eighty-four years). Only thirteen patients (14.6%) had a diagnosis of necrotizing fasciitis or a suspicion of necrotizing fasciitis on admission. The majority of patients had a diagnosis of cellulitis (fifty-two patients; 58.4%) or abscesses (sixteen patients; 18.0%) on admission. The portal of entry of infection, which was identified in only forty-four patients (49.4%), included the sites of preexisting ulcers and bed sores (twenty-three patients, 25.8%), trauma (twelve patients, 13.5%) and postoperative infection (four patients, 4.5%). Postoperative necrotizing fasciitis developed in three patients after a contaminated operation and in one patient after a clean-contaminated operation. Other rare portals of entry included the site of a strangulated hernia (one patient), the site of a snakebite (one patient), the site of an intravenous line (one patient), the site of a burn injury (one patient), and the site of subcutaneous insulin injection (one patient).

The infection involved the extremities in seventy-one patients (79.8%) and the trunk in eighteen (20.2%). The most common site of infection was the lower limb (sixty-two patients; 69.7%). Comorbidities predisposing to necrotizing fasciitis included diabetes mellitus (sixty-three patients; 70.8%),

peripheral vascular disease in (twenty patients; 22.5%), alcoholism with chronic liver disease (three patients), and cancer with immunosuppression (two patients). Twelve patients (13.5%) had no comorbidities. The mean number of associated comorbidities was 1.5 (range, zero to four).

The majority of patients presented with the triad of exquisite pain (eighty-seven patients; 97.8%), swelling (eighty-two patients; 92.1%), and fever (seventy-one patients; 79.8%). As shown in Table II, tenderness beyond the apparent margins of infection, erythema, and warmth of the skin to palpation were the most common physical findings on admission. Other findings included skin induration, crepitus, fluctuance, formation of bullae, skin necrosis, and sensory and motor deficits. Gas in the soft tissues was demonstrated radiographically in fifteen patients (16.9%).

Cultures of tissue specimens obtained at the time of the first operative débridement were analyzed (Appendix). A single organism was identified in twenty-five patients (28.1%), multiple organisms were identified in forty-eight patients (53.9%), and no organism was identified in sixteen patients (18.0%). Streptococcal species, identified in thirty-one patients, were the most common isolates. Forty-eight (66%) of the positive cultures were polymicrobial necrotizing infections (Type-I necrotizing fasciitis)[6,7]. In these patients, streptococcal species, staphylococcal species, enterococci, and enterobacteriaceae (*Escherichia coli,* Acinetobacter species, Pseudomonas species, and Klebsiella species) were very common isolates. Bacteroides species was the most common anaerobic organism, while Clostridium species was an infrequent isolate. Eight infections (9%) involved *Streptococcus pyogenes* alone or in combination with *Staphylococcus aureus* (Type-II necrotizing fasciitis)[6,7].

TABLE II Physical Findings on Admission

Physical Finding	No. of Patients with Finding
Tenderness	87 (97.8%)
Erythema	89 (100%)
Warm skin to palpation	86 (96.6%)
Bullae formation	40 (44.9%)
Skin induration	11 (12.4%)
Skin fluctuance	10 (11.2%)
Crepitus	12 (13.5%)
Skin necrosis	12 (13.5%)
Sensory and motor deficits	8 (9.0%)
Hypotension	16 (18.0%)
Fever (temperature >38.0°)	47 (52.8%)
Tachycardia (pulse >100 beats per minute)	66 (74.2%)

Amputation was performed to control the infection in twenty patients (22.5%). Patients undergoing amputation had a higher prevalence of diabetes mellitus (90% compared with 62%; $p < 0.05$) but not of peripheral vascular disease (10.0%

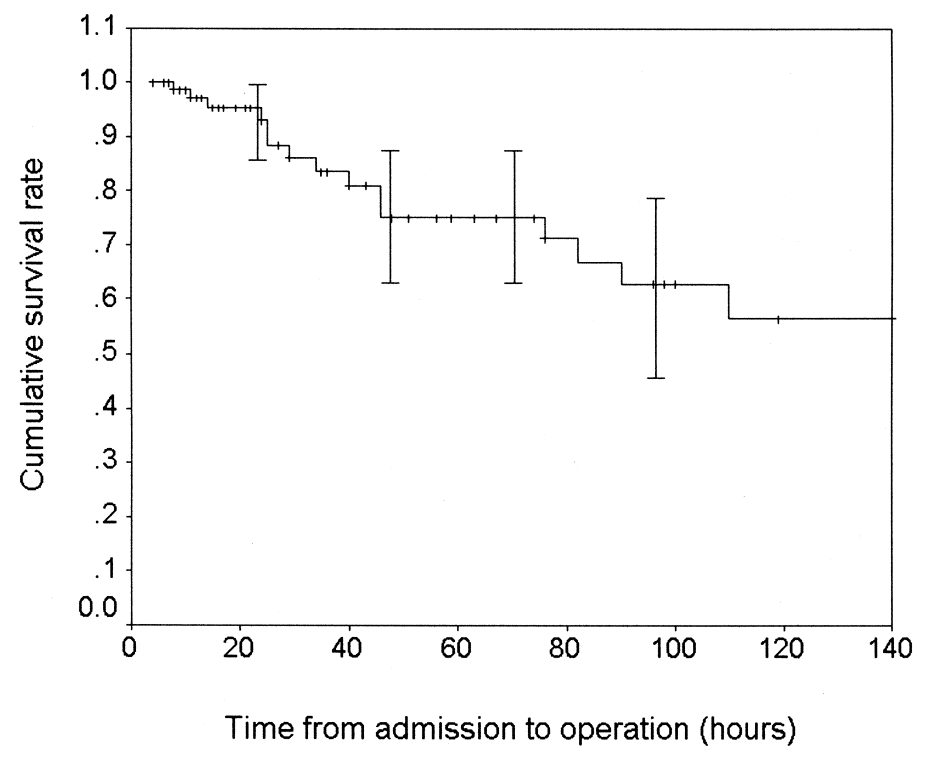

Fig. 1

Kaplan-Meier curve showing a decrease in the cumulative survival rate as the time between admission and the operation increases. The point estimates and their respective 95% confidence intervals at twenty-four, forty-eight, seventy-two, and ninety-six hours are indicated on the graph. The cumulative survival rate at twenty-four hours was 93.2% (95% confidence interval, 99.8 to 86.6). This rate declined to 75.2% (95% confidence interval, 88.4 to 62.0) at forty-eight hours.

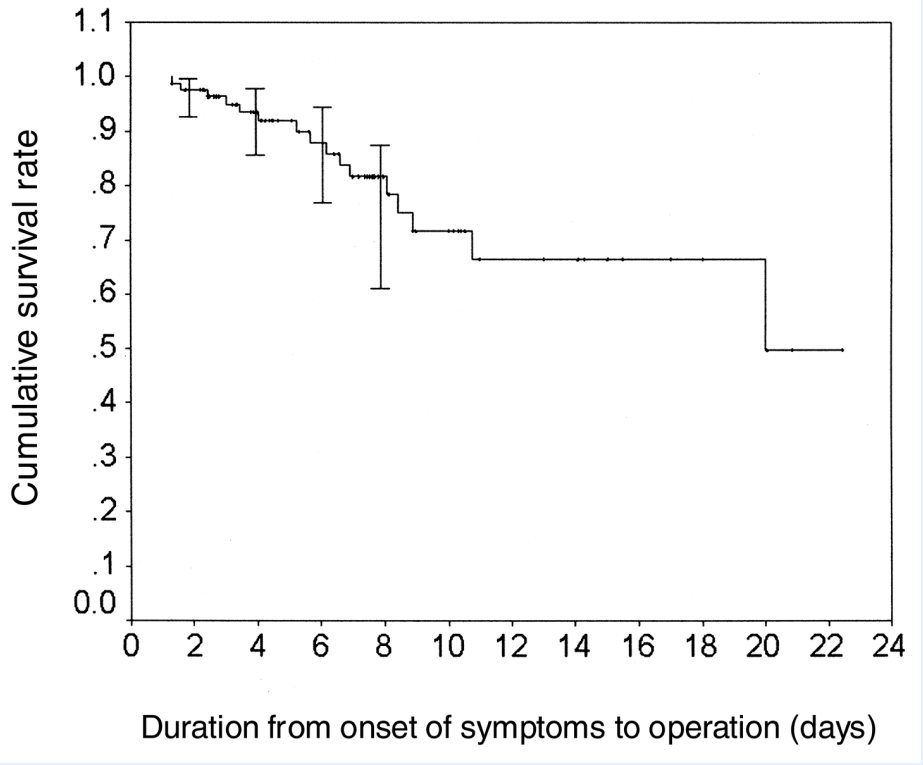

Fig. 2

Kaplan-Meier curve demonstrating a decrease in cumulative survival rate as the time between the onset of symptoms and the operation increases. The point estimates and their respective 95% confidence intervals at two, four, six, and eight days after the onset of symptoms are indicated on the graph.

compared with 24.2%; $p = 0.170$). Survivors underwent a mean of 2.7 débridements (range, zero to nine débridements) to control the infective process. While amputation was not found to reduce mortality, patients who underwent amputation had to undergo fewer operations to control the infection and to achieve wound coverage (2.59 compared with 3.45; $p < 0.05$). The mean duration of hospitalization was 40.6 days (range, one to 176 days).

Nineteen patients (21.3%) died. Twelve factors were analyzed for associations with mortality (Appendix): age, gender, diabetes, the duration of symptoms prior to admission, group-A streptococcal infection, nutritional status (with use of an albumin level of <30 g/dL as the indicator), the presence of two or more associated comorbidities, hypotension on admission, the location of necrotizing fasciitis (central or peripheral), a delay of more than twenty-four hours from admission to surgery, the number of débridements, and the need for an amputation. Bivariate analysis revealed that age, two or more associated comorbidities, and a delay of more than twenty-four hours from admission to surgery were significantly associated with increased mortality ($p < 0.05$). Multivariate logistic regression analysis showed that a delay of more than twenty-four hours from admission to surgery was the only independent predictor of mortality after adjusting for age, gender, diabetes, and hypotension on admission. Kaplan-Meier survivorship analysis revealed that the survival rate decreased with delayed surgery and prolonged symptoms (Figs. 1 and 2). Survival sharply declined with a delay in surgery of more than twenty-four hours.

Discussion

Necrotizing fasciitis is a surgical emergency. Early recognition and prompt aggressive débridement of all necrotic tissue is critical for survival and has been demonstrated to improve the rate of survival[8-16]. However, since Meleney's time, the mortality associated with this condition has remained high, with a reported cumulative mortality rate of 34% (range, 6% to 76%)[10]. The difficulty of making an early diagnosis is due to the paucity of cutaneous findings early in the course of the disease. In our own experience, only thirteen patients (14.6%) were diagnosed as having necrotizing fasciitis at the time of admission. Often, the disease masqueraded as cellulitis or abscesses. In these patients, the diagnosis was made when the infection progressed despite treatment with broad-spectrum intravenous antibiotics.

Patients usually present with the triad of exquisite pain, swelling, and fever. Tenderness, erythema, and warm skin are commonly the only signs of early necrotizing fasciitis (Table II). Pain out of proportion to the physical findings is the most consistent feature noted at the time of presentation. In our patients, an intermediate stage characterized by the formation of small bullae was noted as the condition progressed. The presence of bullae filled with serous fluid is an important diagnostic clue and should raise the suspicion of this condition. Weiss

and Laverdiere also noted the formation of bullae early in the course of this disease[17]. So-called hard signs of necrotizing fasciitis became apparent late in the evolution of the disease. Large hemorrhagic bullae, skin necrosis, fluctuance, crepitus, and sensory and motor deficits are late signs of this condition. Gas on plain radiographs was an inconsistent sign, seen only in 16.9% of our patients.

We found that a regular review of the patient's condition (performed every few hours) was very helpful in cases of suspected necrotizing fasciitis and severe soft-tissue infection. Rapid progression of the infection with migration of the margins of erythema and skin induration despite the use of intravenous antibiotics is an important clue in cases of early necrotizing fasciitis.

This condition is characterized by an angiothrombotic microbial invasion and liquefactive necrosis. Histologically, necrosis of the superficial fascia, polymorphonuclear leukocyte infiltration of the deep dermis and fascia, thrombosis and suppuration of the veins and arteries coursing through the fascia, and microorganism proliferation within the destroyed fascia are seen[5,6]. Initially, a horizontal phase predominates. As the condition progresses, ischemic necrosis of the skin ensues with gangrene of the subcutaneous fat and dermis, manifested as formation of bullae, skin necrosis, and ulceration. Surgical débridement of all necrotic tissue is of paramount importance as antibiotic delivery to the involved area is ineffective because of the thrombosis of the supplying blood vessels. Débridement must be aggressive, with removal of all necrotic fascia and fat. The overlying skin should be excised until healthy-appearing, bleeding tissue is encountered at the margins of the wound. A second look should be done within twenty-four to forty-eight hours to assess the progression of the condition and the need for further débridement. This process is repeated as frequently as is necessary until the infective process is controlled.

The use of broad-spectrum antibiotics prior to admission may modify the clinical picture at the time of presentation. Sixty-three patients (70.8%) had a history of treatment with antibiotics prior to admission to the hospital. It has been reported that many patients present with septic shock and multiple organ failure[7,18]. In our series, however, only 52.8% (forty-seven) of the patients were febrile, 18.0% (sixteen) were hypotensive, and 4.5% (four) had multiple organ failure at the time of admission. This changing clinical presentation that we observed has been reported by other authors[19-21] and is probably due to the increasing use of broad-spectrum antibiotics at the primary-care level, which reduces the bacterial load and the frequency of organ failure but has very little effect on the primary pathology. The antibiotics, however, only serve to temporarily mask the severity of the underlying infectious process[5-7,16]. Regardless of the clinical presentation, all patients need operative débridement. In fact, we found that a delay in surgical débridement had a significant ($p = 0.02$) adverse impact on survival (Figs. 1 and 2). Modulation of this clinical syndrome by means of prehospital treatment makes early recognition of this entity increasingly difficult, and a high index of suspicion is therefore important.

Necrotizing fasciitis has been divided into distinct groups on the basis of microbiological cultures[6,7]. Type-I infections are polymicrobial, synergistic infections that usually are caused by non-group-A streptococci, aerobic organisms, and anaerobic organisms. Type-II infections usually are caused by *Streptococcus pyogenes* alone or with staphylococci. A further type of infection, caused by marine vibrios (gram-negative rods), is usually associated with seawater or marine animal exposure[6,7,22]. Chronic liver disease is the reported predisposing factor for this type of infection[23]. One of our patients with cirrhosis of the liver had necrotizing fasciitis caused by *Vibrio vulnificus*. While their clinical manifestations are similar, Type-I and Type-II infections tend to affect different subgroups of patients. Type-I infections occur in immunocompromised hosts, whereas Type-II infections tend to occur in individuals with no underlying comorbidities. Seven of our eight patients who had a Type-II infection had no underlying predisposing factors such as diabetes. Polymicrobial synergistic (Type-I) infections were the most common type of infection in the present study (prevalence, 53.9%). Consistent with other published data[6,10,24], the most common organisms isolated were streptococci and enterobacteriaceae. Only 25% of our patients who had a polymicrobial infection had anaerobic organisms isolated. This low isolation rate as compared with data in previous reports[11,24-26] may have been due to a delay in processing specimens or to imprecise isolation and culture techniques.

Several interesting findings were noted in our patients who had monomicrobial necrotizing fasciitis. The most common single causative organism was still *Streptococcus pyogenes* (six patients). Compared with the series reported by McHenry et al.[10] and Elliot et al.[6], in our series we noted some organisms that are rarely reported to be causative of monomicrobial necrotizing fasciitis, namely, group-B streptococcus (five patients) and Klebsiella species (three patients). Necrotizing fasciitis caused by group-B streptococcus is rare, with fewer than ten cases reported in the literature[27-31]. The reported predisposing factors for this type of infection included obstetrical complications (in postpartum adult females and in infants) and diabetes[27-31]. A recent increase in necrotizing fasciitis due to group-B streptococcus, particularly in nonpregnant adults, has been noted by several authors. Gardam et al.[28] speculated that the increasing ability of group-B streptococcus to cause necrotizing fasciitis may represent the emergence of a new clinical syndrome in adults. All five of our patients who had a monomicrobial infection caused by group-B streptococcus were diabetic, but none were recently pregnant. Monomicrobial necrotizing fasciitis caused by Klebsiella species is unusual, with fewer than ten cases reported in the literature to date[32-34]. The association of Klebsiella species necrotizing fasciitis with liver abscesses and endogenous endophthalmitis of the eye has recently been highlighted[32-34]. Therefore, when Klebsiella species is a single isolate in a patient with necrotizing fasciitis, the liver and the eye should be screened and treated as needed.

While *Streptococcus pyogenes* is a very important causative organism, particularly in healthy individuals, there recently has been a disturbing trend toward an increased prevalence of

necrotizing soft-tissue infections caused by non-group-A streptococcal species[27,29]. These organisms, particularly in immunocompromised hosts (patients with diabetes, chronic liver disease, or cancer), are very important in necrotizing fasciitis. The initial choice of antibiotics should therefore be broad spectrum and tailored carefully according to the results of culture.

The mortality rate in our series of eighty-nine patients was 21.3%. We analyzed twelve factors that have been reported to adversely affect outcome (Appendix)[2,10,13,14,16,35,36]. The three factors that we found to affect survival adversely were advanced age, the presence of two or more associated comorbidities, and a delay from admission to operation of more than twenty-four hours. On multivariate logistic regression analysis, the only factor that was found to independently affect survival was a delay from admission to operative débridement of more than twenty-four hours ($p < 0.05$, relative risk = 9.4). The conclusion is clear: while nonmodifiable risk factors (age and comorbidities) may affect survival, the one modifiable factor that adversely affects survival is how quickly the patient undergoes operative débridement.

Early diagnosis and aggressive surgical débridement is the cornerstone principle in the treatment of necrotizing fasciitis. The use of broad-spectrum antibiotics tends to mask the severity of the underlying infection, modulates the clinical presentation, and even delays hospital admission. This factor, coupled with the paucity of cutaneous findings early in the course of the disease, makes early diagnosis difficult. When patients with severe soft-tissue infections or suspected necrotizing fasciitis are admitted to a nonsurgical unit, early involvement of an experienced surgical team is important. A high index of suspicion is important, and when intravenous antibiotics fail to adequately control the infective process within twenty-four hours after admission, emergent operative débridement should be seriously considered. While doing so may subject some patients to surgery who would otherwise have responded to nonoperative therapy, this approach may ultimately reduce the mortality associated with this dreaded condition. Adjuncts reported to aid in the early diagnosis, such as frozen-section biopsy[5,36], computed tomography[37], and magnetic resonance imaging[38-40], may be used judiciously to aid in the diagnosis but should never delay operative intervention.

Appendix

eA Tables showing the causative organisms and the twelve factors that were analyzed as predictors of mortality are available with the electronic versions of this article, on our web site at www.jbjs.org (go to the article citation and click on "Supplementary Material") and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

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