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Necrotizing Soft Tissue Infections

Risk Factors for Mortality and Strategies for Management

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Objective

The authors evaluate in a retrospective fashion the factors influencing outcome in a large group of patients presenting with necrotizing soft tissue infections, and, based on this analysis, propose a plan for optimal care of such patients.

Summary Background Data

In many smaller series of patients with necrotizing soft tissue infections, similar analyses of risk factors for mortality have been performed, producing conflicting conclusions regarding optimal care. In particular, debate exists regarding the impact of concurrent physiologic derangements, type and extent of infection, and the role of hyperbaric oxygen in treatment.

Methods

A retrospective chart review of 198 consecutive patients with documented necrotizing soft tissue infections, treated at a single institution during an 8-year period, was conducted. Using a model for logistic regression analysis, characteristics of each patient and his/her clinical course were tested for impact on outcome.

Results

The mortality rate among the 198 patients was 25.3%. The most common sites of origin of infection were the perineum (Fournier's disease; 36% of cases) and the foot (in diabetics; 15.2%). By logistic regression analysis, risk factors for death included age, female gender, extent of infection, delay in first debridement, elevated serum creatinine level, elevated blood lactate level, and degree of organ system dysfunction at admission. Diabetes mellitus did not predispose patients to death, except in conjunction with renal dysfunction or peripheral vascular disease. Myonecrosis, noted in 41.4% of the patients who underwent surgery, did not influence mortality.

Conclusions

Necrotizing soft tissue infections represent a group of highly lethal infections best treated by early and repeated extensive debridement and broad-spectrum antibiotics. Hyperbaric oxygen appears to offer the advantage of early wound closure. Certain markers predict those individuals at increased risk for multiple-organ failure and death and therefore assist in deciding allocation of intensive care resources.

Necrotizing bacterial and fungal infections of the soft tissues have been recognized and reported for centuries, yet only within the last century have detailed analyses brought to light the clinical course and pathology of this collection of diseases.[1-4] Recent reports[5-7] have emphasized the following important points:

- Distinguishing between the various categories of necrotizing soft tissue infections serves little purpose because the prognosis and treatment are the same;
- Necrotizing soft tissue infections occur predominantly in patients predisposed by immune compromise, diabetes mellitus, or vascular insufficiency; and
- Mortality from necrotizing soft tissue infections can be reduced by expeditious diagnosis and adequate early debridement.

Although, historically, the use of hyperbaric oxygen (HBO) has been controversial in the management of soft tissue infections, we have found it beneficial. Our report explores the impact of aggressive surgery, antibiotics, critical care management, and HBO therapy on the outcomes of patients with such infections.

We undertook a review of all patients with necrotizing cellulitis, fasciitis, or myonecrosis admitted to a tertiary university-affiliated referral institution during an 8-year period. The study institution is a 100-bed Level 1 trauma center, with a multipatient hyperbaric chamber capable of treating 21 patients simultaneously, serving a state with a population of 4.9 million, as well as surrounding states.

MATERIALS AND METHODS

Between March 1985 and June 1993, 198 patients with necrotizing soft tissue infections were admitted and treated. Diagnosis was confirmed by either histologic examination or a combination of clinical, microbiologic, and gross anatomic findings. All patients had complete medical records available for retrospective review.

Each patient's record was analyzed to determine preexisting illnesses, admitting symptoms (including length of time to accessing medical care), admission physical findings, laboratory and roentgenographic results, site of origin of the necrotizing infection, extent and depth of spread, and microbiology of the initial wound cultures. Also examined were the type and duration of antibiotic therapy, the frequency and type of operative procedures performed, the number of HBO treatments administered, and subsequent complications. Supporting modalities such as dialysis, blood product transfusion, and mechanical ventilation were reviewed. Each patient's premorbid medical profile, condition at admission, and subsequent treatment were analyzed to assess effect on mortality and development of complications.

Standard treatment after admission included cardiovascular stabilization and assessment of extent of infection. Broad-spectrum antibiotics were administered to cover gram-positive cocci, gram-negative enteric rods, and anaerobic flora. Patients were taken to the operating room expeditiously for aggressive debulking of infected tissue. All necrotic skin, subcutaneous tissue, fascia, and obviously nonviable muscle were removed and sent for microbiologic and histologic examination. Viable dermis and soft tissue were saved to aid later closure, even after undermining with dissection to remove all necrotic fascia. The wounds were then dressed loosely with gauze moistened with saline. Colostomies for Fournier's gangrene generally were not performed unless the anal sphincter muscle had been destroyed by infection. In later years, colostomies were created, when required, after the abdominal wall infection had localized.

After initial debridement, patients received their first HBO treatment, which then continued twice daily for 90 minutes until all wounds were closed. Those patients whose critical condition warranted further mechanical ventilation underwent bilateral myringotomy to prevent pressure-related ear injuries during subsequent HBO treatments. Debridements generally were repeated every 2 days until progression of the disease had been halted and all necrotic tissue had been removed. Amputation for necrotizing infections of the extremities was required frequently and generally was performed in two stages, leaving the tissues open after the initial debriding amputation. Closure of the wounds commenced as soon as healthy, viable tissue allowed reapproximation or skin grafting, often as soon as 2 to 4 days after initial debridement. Antibiotics were adjusted based on wound culture and sensitivities. Anaerobic coverage usually was continued despite initial lack of growth on anaerobic plates.

Critical care support was required for most of the patients and was routinely comprehensive and aggressive. Prolonged mechanical ventilation, invasive monitoring, and inotropic support frequently were necessary for cardiopulmonary failure. In recent years, continuous arteriovenous or venovenous hemofiltration with dialysis was used for acute renal failure. Coagulopathy was treated aggressively, using blood component therapy. Support was withheld or withdrawn only when the medical staff and the family agreed that further treatment appeared futile. Most patients who survived were referred for further inpatient or outpatient therapy at a rehabilitation facility.

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Table 1. MORTALITY RATES IN GROUPS DEFINED BY PRE-EXISTING CHARACTERISTICS AND MEDICAL CONDITIONS

	No. of Patients	Nonsurvivors [n (%)]	*p* Value		No. of Patients	Nonsurvivors [n (%)]	*p* Value
All patients	198	50 (25.3)		Alcohol abuse			
Age (yr)				Yes	34	12 (35.3)	
≤60	137	23 (16.8)		No	161	35 (21.7)	0.09
>60	61	27 (44.3)	<0.001	Peripheral vascular disease			
Gender				Yes	32	11 (34.4)	
Male	113	21 (18.6)		No	163	36 (22.1)	0.14
Female	84	28 (33.3)	0.02	Pulmonary disease			
Race				Yes	30	13 (43.3)	
White	99	29 (29.3)		No	165	34 (20.6)	0.007
Nonwhite	97	20 (20.6)	0.16	Intravenous drug abuse			
Diabetes mellitus				Yes	26	1 (3.8)	
Yes	110	29 (26.4)		No	169	46 (27.2)	0.009
No	85	18 (21.2)	0.40	Carcinoma			
Hypertension				Yes	23	14 (60.9)	
Yes	69	22 (31.9)		No	173	34 (19.6)	<0.001
No	127	26 (20.5)	0.08	Chronic azotemia			
Obesity				Yes	20	8 (40.0)	
Yes	62	17 (27.4)		No	175	39 (22.3)	0.10†
No	133	30 (22.6)	0.46	Hepatic disease			
Heart disease				Yes	7	3 (42.9)	
Yes	52	22 (42.3)		No	188	44 (23.4)	0.36†
No	144	26 (18.1)	<0.001	HIV infection			
Malnutrition				Yes	8	0 (0.0)	
Yes	35	14 (40.0)		No	190	50 (26.3)	0.21†
No	160	33 (20.6)	0.02	Myonecrosis			
				Yes	82	22 (26.8)	
				No	113	25 (22.1)	0.45

HIV = human immunodeficiency virus.
* Value is based on a comparison of two proportions using Pearson's chi square statistic unless otherwise noted.
† Value is based on Fisher's exact test for 2 × 2 tables.

Data Analysis

To assess possible risk factors for mortality, univariate analyses were completed initially to aid in determining the variables that should be included in a stepwise logistic regression model. Comparisons of proportions were made using Pearson's chi square statistic to identify univariate differences among defined variables with respect to mortality. Fisher's exact test for 2 × 2 tables was used in the small-sample case. For measured variables, the F statistic was used to compare means between survivors and nonsurvivors.

Clinically relevant variables were selected from the large pool of variables with univariate p values less than 0.15 for inclusion in the initial step of the logistic regression analysis. A p value of 0.15 also was chosen as the criterion by which to judge the entry and removal of variables at each step of the regression procedure. Results of the logistic regression analysis were expressed using beta-coefficient values, odds ratios (defined as exp[coefficient]), and 90% confidence limits for the odds ratios. An odds ratio of 1.24 for serum creatinine level, for example, indicates a 24% increase in the risk of death for every 1 mg/dL increase in serum creatinine. Statistical analysis was performed using SAS software (SAS Institute, Inc., Cary, NC).

RESULTS

The study group consisted of 113 males and 84 females (one patient's gender could not be determined from chart review). There were 95 black patients, 99 white patients, 1 Asian patient, and 1 Hispanic patient. All but six patients had been transferred from other hospitals (a total of 58 other institutions).

Pre-Existing Conditions

Table 1 shows the pre-existing characteristics and medical conditions present in the 198 patients with necrotizing soft tissue infections. Also shown are the number and percent of patients who died, as well as the relationship of age, race, and gender on mortality. Women were more likely to die than men, and death was associated significantly with age greater than 60 years. The average age of all patients was 51.5 years (range, 12–90 years); the average age for the 50 patients who died was 59.7 years and 48.8 years for the 148 who lived. Race was not associated with mortality.

Diabetes mellitus was the most common pre-existing medical condition, present in 56.4% of admitted patients; however, the presence of diabetes did not affect mortality, unless it occurred in conjunction with certain other diseases. Eleven patients had combined diabetes mellitus and chronic renal insufficiency, six of whom died (54.6%). Nineteen had both diabetes and peripheral vascular disease, eight of whom died (42.1%). When the conditions of diabetes, acute renal failure, and age greater than 60 years were combined, the mortality rate increased remarkably (64.7% among 17 patients, respectively).

Other premorbid medical diagnoses that influenced mortality included cardiac disease, carcinoma, malnutrition, intravenous drug abuse, and pulmonary disease (Table 1).

Findings at Admission

The average time from initiation of symptoms until hospital admission was 4.1 days. Those who survived had complained of symptoms for 4.5 days, whereas those who died had symptoms for a shorter time, 2.5 days, possibly reflecting a more fulminant infection.

Table 2 lists the prevalence of symptoms and physical signs among the 198 patients with necrotizing soft tissue infections. The nonspecific inflammatory signs of pain, swelling, and erythema occurred most commonly, whereas the most specific signs, crepitus and blistering, existed in less than 40% of patients (Table 2). Soft tissue gas detected by plain or computed tomography occurred in 108 of 148 patients (73%) whose radiographic records could be found. Either crepitus, blistering, or radiographic evidence of soft tissue gas was evident in 145 of 170 evaluated patients (sensitivity for diagnosis of necrotizing infection, 85.3%). Thus, these three signs serve as a helpful screening profile because they are present in more than four fifths of patients with documented necrotizing soft tissue infections and rarely occur otherwise; however, almost 20% of patients with such infections do *not* possess *any* of these three signs, making it imperative that the treating clinician pursue other means of achieving diagnostic certainty when a high level of clinical suspicion exists.

Table 3 delineates mean values for the defined parameters listed among three sets of patients: those who survived, those who did not survive, and all 198 patients. At admission, nonsurvivors had a statistically significant lower systolic blood pressure and Glasgow Coma Scale score; 18 of 29 patients (62.1%) who were mentally obtunded at admission died of their disease. Ninety of 182 evaluated patients (49.5%) were afebrile on admission. Survivors had less extensive infections, as shown by a lower mean percentage of body surface area involved with the disease process (6.9% *vs.* 13.0%).

Certain admission laboratory values were distinctly different between survivors and nonsurvivors, specifically with reference to those values reflecting pulmonary, renal, hepatic, hematologic, and coagulation function. An admission serum creatinine level exceeding 2 mg/dL was associated with double the risk of mortality—up to 49%. Base deficit and arterial blood lactate values also were greater in nonsurvivors. The mortality rate for the 30 patients with arterial blood lactate levels exceeding twice the normal values was 63.3%. Because it has been speculated that hypocholesterolemia reflects the release of tumor necrosis factor and subsequent development of sepsis,[8,9] the risk of multiple-organ system dysfunction was assessed relative to our patients' serum cholesterol level: those with cholesterol levels lower than 100 mg/dL held a 32.8% risk of multiorgan failure; those with levels higher than 110 mg/dL had only a 12.5% risk of the same.

Admission laboratory parameters found *not* to reflect survivability included leukocyte count, serum glucose

Table 2. PREVALENCE OF PHYSICAL FINDINGS

Symptom or Sign	N	n	%
Swelling	192	144	75.0
Pain	192	140	72.9
Erythema	190	126	66.3
Foul discharge	190	89	46.8
Induration	190	86	45.3
Crepitus	189	69	36.5
Fever	190	60	31.6
Skin slough or necrosis	190	59	31.1
Blistering	190	45	23.7
Skin discoloration	190	35	18.4
Mental obtundation	190	34	17.9
Hypotension	190	21	11.1
Numbness	198	2	1.0
Weakness or paraplegia	198	2	0.5
Soft tissue air	148	108	73.0
Plain x-ray only		85	57.4
Computed tomogram only		18	12.2
Both		5	3.4
Crepitus, blisters, or soft tissue air	170	145	85.3

Table 3. MEAN ADMISSION VITAL SIGNS AND LABORATORY VALUES

Parameter	All Patients			Survivors			Nonsurvivors			p Value*
	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	
Systolic blood pressure (mmHg)	194	128	2.2	146	131	2.2	48	119	5.7	0.02
Pulse rate (bpm)	191	111	4.6	144	111	6.0	47	109	3.0	0.87
Temperature (C)	182	37.9	0.1	138	38.1	0.1	44	37.3	0.2	<0.001
Glasgow Coma Scale score	183	13.8	0.2	137	14.4	0.1	46	12.1	0.5	<0.001
No. of organs failed on admission	193	1.4	0.1	146	1.0	0.1	47	2.9	0.3	<0.001
Hemoglobin (g/dL)	195	11.5	0.2	147	11.7	0.2	48	10.8	0.4	0.03
Leukocyte count (1000/mm³)	198	18.1	0.7	148	18.0	0.7	50	18.4	1.7	0.83
Platelet count (1000/mm³)	191	300	12.1	145	325	14.2	46	222	18.6	<0.001
Glucose, serum (mg/dL)	194	259	12.2	146	255	14.6	48	270	21.1	0.60
Urea nitrogen, serum (mg/dL)	193	34.4	2.2	145	27.7	2.1	48	54.4	5.1	<0.001
Creatinine, serum (mg/dL)	193	2.1	0.2	145	1.8	0.2	48	3.1	0.4	<0.001
Bilirubin, total serum (mg/dL)	168	1.5	0.2	126	1.2	0.1	42	2.6	0.5	<0.001
Calcium, serum (mg/dL)	182	8.1	0.1	136	8.2	0.1	46	7.8	0.2	0.01
Albumin, serum (g/dL)	152	2.2	0.1	113	2.3	0.1	39	2.2	0.1	0.55
Lactate, blood (% above normal)†	153	81.1	20.6	109	22.4	13.2	44	226.5	58.6	<0.001
Cholesterol, serum (mg/dL)	104	101	4.2	77	106	5.1	27	87	6.8	0.06
Prothrombin time (sec)	179	13.7	0.3	135	13.2	0.2	44	15.1	0.7	0.001
Partial thromboplastin time (sec)	180	34.4	1.5	135	31.9	1.3	45	41.6	4.4	0.005
PaO_2/FiO_2 ratio	168	356	8.7	123	373	9.8	45	312	17.2	0.002
Base deficit (mEq/L)	159	2.9	0.4	115	2.4	0.4	44	4.4	0.7	0.02
Body surface area (%)‡	196	8.4	0.4	148	6.9	0.4	48	13.0	1.1	<0.001

SEM = standard error of the mean.
* Value is based on a comparison of mean survivors and mean nonsurvivors using the F statistic.
† Three assays for arterial blood lactate were utilized during the course of the study, all with different normal values; therefore, values are expressed in terms of percent above the top normal value.
‡ Body surface area involved with necrotizing infectious process, expressed as percent of total body surface area.

levels, and albumin levels. Leukocyte counts exceeding 11,000/mm³ existed in 155 patients; elevated serum glucose levels existed in 159 patients.

Pathology and Microbiology

Table 4 lists the sites of origin among the 197 patients in whom this information could be elicited. The most common sites of necrotizing soft tissue infections were the perineal region (Fournier's gangrene, 36% of cases), foot ulcerations and infections (generally among diabetics, 15.2% of patients), and traumatic wounds (14.7% of patients). Other common sources included dermal abscesses (especially of the inguinal and medial thigh regions), recent surgical wounds, and infections resulting from intravenous injection or "skin popping" of illicit drugs. Necrotizing soft tissue infections arising from certain locations were more likely to result in death than others. In particular, infections arising from perineal sources predisposed patients to death; Fournier's gangrene carried an overall mortality of 36.6%. Other significantly lethal sites of origin included burn wounds, perforated intra-abdominal viscera (usually colon), and dermal infections associated with the Group A beta-hemolytic streptococcal toxic shock syndrome (Strep TSS).

A necrotizing infection associated with Strep TSS was defined as one occurring in an individual with evidence of shock on admission (*e.g.*, profound hypotension or lactic acidosis) and growth of only Group A beta-hemolytic *Streptococcus pyogenes* from the wound. Five patients in our study group had this condition, and two of them died. Mortality was related to failure to provide expeditious debridement (80% of patients had a delay in diagnosis and first surgery), paucity of pathognomonic physical signs (only 20% of patients demonstrated either crepitus or radiographic air in the soft tissues), and large number of organs failed on admission (mean, 5.2). Both patients who died had failure of seven organ systems on admission. Because of the uncharacteristic physical findings in patients with Strep TSS, early recognition and treatment may be difficult. All five of our patients with Strep TSS demonstrated profound skin discoloration (ranging from violaceous to black with frank sloughing) and formation of epidermal bullae.

Pure clostridial myonecrosis occurred in four individuals but resulted in 100% mortality, despite aggressive

Table 4. SOURCE OF INFECTION AND RELATIVE MORTALITY

Source	No. of Patients	Nonsurvivors [n (%)]
Fournier's gangrene	71	26 (36.6)
Anal abscess	21	8 (38.1)
Bartholin abscess	11	3 (27.3)
Urinary system	8	4 (50.0)
Foot ulcer/infection	30	3 (10.0)
Traumatic wounds	29	8 (27.6)
Upper extremities	11	1 (9.1)
Lower extremities	11	3 (27.3)
Scrotal trauma	4	2 (50.0)
Burns	3	2 (66.7)
Skin abscess	27	5 (18.5)
Surgical wound infection	18	5 (27.8)
Intravenous drug abuse	15	1 (6.7)
Streptococcal toxic shock	5	2 (40.0)
Decubitus ulcer	4	2 (50.0)
Dental abscess	3	0 (0.0)
Perforated viscus	4	3 (75.0)
Munchausen's syndrome	2	0 (0.0)
Strangulated hernia	2	1 (50.0)
Unknown	7	3 (42.9)

hyperbaric oxygen treatment. In three of these patients, the sole infecting organism was *Clostridium perfringens*; in the other, *Clostridium septicum* (associated with an occult colonic adenocarcinoma). In all, 82 evaluated patients (41.4%) were noted to have involvement of the muscle, either grossly or histologically. Of those with documented myonecrosis, the mortality rate was 26.8%, not significantly different from the rate among patients with only fascial infection.

Table 5 indicates the microbial agents responsible for the necrotizing infections (information was available in 182 patients). Gram stain analysis revealed leukocytes in the smear in 80 patients and bacteria in 126 patients. A mean of 4.4 microbes grew from original wound cultures from the 182 patients; 4.5 microorganisms grew in survivors, whereas 4.0 grew in nonsurvivors ($p = 0.28$). Only one organism from wound culture grew in 28 of the 182 evaluated patients (in 15, the single organism was a streptococcus; 5 of these 15 presented with Strep TSS). In 38 patients, two organisms grew; in 26, three organisms grew; and in 90, four or more organisms grew from initial culture.

Twelve of the 182 patients had only anaerobic growth on culture; 85 patients grew out only aerobes, 9 had fungal growth, and 85 patients had both aerobic and anaerobic organisms grow on initial wound culture. The most common bacteria, in order of appearance, were aerobic streptococci, *Bacteroides* spp., staphylococci, and enterococci. Facultative anaerobic gram-negative rods also grew out on culture commonly, with the predominant organisms being *Escherichia coli* and *Proteus* spp. Nineteen patients who had growth of *Streptococcus* on initial wound culture grew out more than one streptococcal species. Thirty-one patients grew more than one species of *Bacteroides*; 24 patients demonstrated growth of more than one species of gram-negative Enterobacteriaciae. Twenty-nine isolates of various clostridial species were discovered, most of them part of a polymicrobial infection. As aforementioned, four patients harbored pure clostridial myonecrosis.

Treatment

Surgical treatment consisted of early debridements and delayed reconstructive procedures (Table 6). Wound closure was begun as soon as the infection was controlled, and often, partial wound closure was accomplished at the same operation as debridement of a different segment of the wound. Wound closure often was started early—2 to 4 days after initial debridement. A total of 152 of the 198 patients successfully achieved wound closure during initial hospitalization, an average of 26.4 days after initial debridement. Eight patients were discharged from the hospital with open wounds, left to close by secondary intention. The remainder of the patients (38 in all) died before wound closure could be accomplished. As shown in Table 6, there was little difference between survivors and nonsurvivors with respect to number of debridements performed, either total or within the first 5 days of surgical treatment. However, survivors had a shorter time to wait between admission

Table 5. MICROBIOLOGIC ORGANISMS RECOVERED FROM ORIGINAL WOUNDS

Organism	N	n	%
Aerobic			
Streptococci	182	83	45.6
Enterococci	182	61	33.5
Staphylococci	182	64	35.2
Escherichia coli	182	57	31.3
Proteus species	182	38	20.9
Other gram-negative rods*	182	76	41.8
Anaerobic			
Peptostreptococci	131	45	34.4
Bacteroides species	128	70	54.7
Clostridium perfringens	129	12	9.3
Other clostridial species	128	17	13.3
Other anaerobic species	128	27	21.1
Fungal species	171	9	5.3

* Including (in order of prevalence) *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas* spp., *Acinetobacter* spp., *Eikenella corrodens*, *Citrobacter freundii*

Table 6. TREATMENT MODALITIES

Modality	All Patients N	Mean	SEM	Survivors N	Mean	SEM	Nonsurvivors N	Mean	SEM	p Value*
Debridements										
Total	197	3.8	0.2	148	3.9	0.2	49	3.8	0.4	0.84
No. (first 5 days)	197	2.1	0.1	148	2.1	0.1	49	2.0	0.2	0.35
Reconstructions										
Total	197	1.6	0.1	148	1.9	0.1	49	0.7	0.2	<0.001
STSG	197	0.6	0.1	148	0.8	0.1	49	0.2	0.1	<0.001
Operative intervals (days)										
Admission to first debridement	192	1.7	0.3	146	1.2	0.2	46	3.1	1.0	0.005
First to last debridement	191	14.4	1.3	145	14.7	1.5	46	13.7	2.2	0.74
First debridement to first closure	153	12.5	0.9	137	12.6	0.9	16	12.3	3.2	0.93
First to last closure	147	13.7	1.7	134	12.6	1.6	13	25.8	7.5	0.02
First debridement to final closure†	152	26.4	1.9	139	25.5	2.0	13	36.1	6.6	0.12
HBO										
Total treatments	198	31.7	1.6	148	36.0	1.7	50	19.0	2.9	<0.001
Total days	194	24.9	1.5	147	27.7	1.7	47	15.9	2.7	<0.001
Mechanical ventilation (days)	196	14.8	2.8	146	10.4	3.3	50	27.6	4.7	0.006
Nutrition (first day)	186	3.1	0.3	140	2.6	0.2	46	4.8	0.9	<0.001
Dialysis (days)	197	2.5	0.7	147	1.1	0.5	50	6.6	2.1	<0.001
Packed erythrocytes (units given)	169	17.5	1.7	125	10.5	1.1	44	37.3	4.2	<0.001
Antibiotics (days given)	179	12.8	0.4	135	13.1	0.5	44	11.9	1.0	0.22

SEM = standard error of the mean; STSG = split-thickness skin graft; HBO = hyperbaric oxygen.
* Value is based on a comparison of mean survivors and mean nonsurvivors using the F statistic.
† For those patients whose wounds ultimately achieved 100% closure.

and first debridement (3.1 *vs.* 1.2 days), reflecting a delay in treatment among the nonsurvivors. Not surprisingly, survivors were able to have more reconstructive procedures performed and had a shorter mean time from first debridement to total wound closure. Five patients had colostomies before developing their necrotizing soft tissue infection, and 30 others (15.2%) received colostomies as part of their surgical therapy, at an average of 12.6 days after admission, generally because fecal soilage was interfering with wound healing. Although most of the stomas were constructed in patients with Fournier's gangrene, only 26 of 71 patients with Fournier's gangrene (36.6%) received colostomies. Fifty-five patients (27.8%) received amputations as part of surgical debridement to gain control of the infectious process, varying from transmetatarsal amputation to hip disarticulation and forequarter amputation.

Also reflected in Table 6 are the statistics related to HBO therapy. With only one exception, surgical debridement was carried out *before* HBO treatment was initiated. The 90-minute HBO sessions initially were conducted two or three times daily for five sessions at 2.4 atmospheres absolute (ATM abs; 138.1 kPa), then twice daily at 2 ATM abs (101.3 kPa) for 2 weeks. As the infection came under control, HBO therapy was cut back to once daily at 2 ATM abs until total wound closure had been accomplished. Hyperbaric oxygen was withheld whenever the surgeon in charge of the patient's care deemed the patient too unstable for transport to the hyperbaric chamber. Mechanical ventilation and continuous arteriovenous or venovenous hemofiltration with dialysis did not constitute contraindications to HBO, and patients treated with these modalities generally continued HBO unabated. Nonsurvivors received fewer HBO treatments than survivors, without exception, because of hemodynamic instability for transport (Table 6).

Nonsurvivors spent longer periods of time on dialysis and mechanical ventilation and received significantly more packed erythrocyte transfusions. The average patient with necrotizing soft tissue infection spent 14.8 days on mechanical ventilation and received 17.5 units of transfused blood. Almost all patients who could not tolerate a regular (or diabetic) diet on the first or second postoperative day were given parenteral or enteral hyperalimentation (depending on adequacy of bowel function), beginning a mean of 3.1 days after admission.

The patients received a mean of 12.8 days of intravenous antibiotic therapy (no significant difference between survivors and nonsurvivors). Coverage was universally broad spectrum, covering gram-positive cocci, facultative anaerobic gram-negative rods, and anaerobic organisms. The most common combinations of antibi-

Table 7. TWENTY MOST FREQUENT COMPLICATIONS

Complication	N	n	%
Acute renal failure	196	62	31.6
ARDS/other respiratory failure	196	57	29.1
Delay in diagnosis	196	57	29.1
Delay in first debridement	195	54	27.7
Bacteremia	196	53	27.0
Other infection (*e.g.*, pneumonia, UTI)	195	53	27.2
Wound infection	194	43	22.2
Multiorgan system dysfunction	195	41	21.0
Inadequate debridement	195	24	12.3
Clostridium difficile colitis	196	18	9.2
Seizure	198	9	4.5
Decubitus breakdown/ulcer	198	8	4.0
Osteomyelitis	198	8	4.0
Iatrogenic source of necrotizing infection	198	7	3.5
Cerebrovascular accident/TIA	198	7	3.5
Cardiopulmonary resuscitation	198	5	2.5
STSG slough	198	5	2.5
Antibiotic reaction	198	4	2.0
Heart failure	198	4	2.0
Fecal wound soilage	198	4	2,0

ARDS = adult respiratory distress syndrome; UTI = urinary tract infection; TIA = transient ischemic attack; STSG = split-thickness skin graft.

otics were 1) ampicillin or penicillin plus gentamicin and clindamycin; 2) imipenem/cilastatin or ampicillin/sulbactam or ticarcillin/clavulanic acid; and 3) vancomycin or a penicillin plus a cephalosporin and metronidazole or clindamycin. On review, 16 patients (8.1%) were considered to have received inadequate antibiotics, more than three quarters of whom lacked coverage for enterococci, a pathogen appearing in 61 wound cultures.

Complications

Thirty-six patients (18.2%) recovered from necrotizing infection without complications. Review of the medical records of 198 patients led to tabulation of more than 70 complications in the other 162 patients. The 20 most frequent complications are listed in Table 7.

The following observations can be made from this review:

- Acute renal failure, defined as an increase in serum creatinine levels to more than twice the level of baseline and at least greater than 2 mg/dL, occurred in 62 patients (31.6% incidence) and was associated with a mortality rate of 50.8%.
- Adult respiratory distress syndrome, defined as radiographic evidence of diffuse pulmonary edema, found not to be cardiogenic, associated with an arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio less than 150 and decreased pulmonary compliance, occurred in 57 patients (29.1%) and was associated with a mortality rate of 59.3%.
- Multiorgan system dysfunction, defined as objective evidence of acutely diminished function in two or more organ systems requiring intervention, occurred in 41 patients (21%) and incurred a mortality rate of 77.5%.
- Diagnosis or initial surgery was delayed in more than one fourth of the patients; delay of either was associated with a mortality rate of 30%, compared with 23% among those without such delays ($p = 0.075$). Inadequate surgery (insufficient debridement or inadequate frequency of debridements), occurring in 24 patients, was more notably associated with a fatal outcome (50% mortality rate, $p < 0.005$).
- Infectious complications were common. Wound infections occurred in 43 patients but did not affect mortality, although five patients required reoperations because of sloughed skin grafts. Bacteremias were associated with increased mortality (47.2%, $p = 0.002$). Acalculous cholecystitis developed in two patients.
- Complications from HBO therapy were uncommon and minor, including hemotympanum (1 patient), seizures (4 patients), hypoglycemia (1 patient), and claustrophobia (2 patients).
- Complications found to be somewhat surprisingly uncommon included pulmonary embolism (2 patients), pneumothorax (3 patients), myocardial infarction (2 patients), wound dehiscence (3 patients), complications from continuous arteriovenous or venovenous hemofiltration with dialysis (1 patient), and bleeding from gastric stress ulceration (3 patients).
- Seven cases of necrotizing soft tissue infections occurred as a result of iatrogenic mismanagement of traumatic or surgical wounds. One patient was transferred from an outlying institution in grossly unstable condition and died soon after arrival at our institution's admitting area. Four other patients, because of the massive extent of their infections combined with shock and multiorgan failure, were allowed to die without therapeutic intervention other than relief from pain.

Logistic Regression Analysis

Because of the large number of potentially interdependent parameters examined in this retrospective analysis, it was believed that a more suitable test for significance would reside in a multivariate analysis, using a model of logistic regression analysis. From the large pool of univariately significant variables ($p < 0.15$), a smaller and more manageable group of 12 clinically relevant vari-

Table 8. LOGISTIC REGRESSION ANALYSIS: RESULTS OF SIGNIFICANT VARIABLES

Variable	Coefficient	Odds Ratio	90% CI Lower	90% CI Upper
Age (> 60 yr)	1.65	5.19	1.97	13.65
Gender (female)	1.08	2.94	1.17	7.39
Creatinine (mg/dL)	0.21	1.24	1.01	1.51
Lactate, blood (% above normal)	0.37	1.45	1.11	1.89
Days: admission to first debridement	0.24	1.27	1.10	1.48
Body surface area (%)	0.12	1.12	1.04	1.21
No. of organs failed on admission	0.37	1.44	1.06	1.96

CI = confidence interval.

ables were selected for inclusion in the first step of the stepwise regression model. The selected parameters were age, gender, Glasgow Coma Scale score, systolic blood pressure, platelet count, serum creatinine level, activated partial thromboplastin time, PaO_2/FiO_2 ratio, days from admission to first debridement, body surface area involved with infection, number of organ systems failed on admission, and blood lactate level. In this model, 125 observations could be assessed and 36 events (deaths) occurred.

The variables found on logistic regression analysis to significantly increase the risk of death are shown in Table 8, with each variable's odds ratio and corresponding 90% confidence interval. For this sample of patients, death occurred more than five times as often among the elderly (age > 60 years) compared with younger patients (odds ratio = 5.19). Females were almost three times as likely as males to die (odds ratio = 2.94). Other variables having a direct increased effect on mortality include serum creatinine level, blood lactate level, delay in first debridement, extent of infection, and degree of organ system dysfunction at admission.

These findings support the significant impact of admission lactic acidosis and multiple organ dysfunction on survival. Using criteria previously published by the Society for Critical Care Medicine for defining organ dysfunction,[10] nonsurvivors had a substantially greater number of organ systems in failure on admission than survivors (2.9 *vs.* 1). Figure 1 illustrates the relationship between organ failure and mortality rate.

The significance of extent of infection and delay in initial surgery on survival is born out in the logistic regression analysis, giving cogent support to the importance of early surgical intervention to halt the spread of the infectious process and prevent systemic complications.

DISCUSSION

The treatment of infections such as Fournier's disease or gas gangrene may induce dread and trepidation among surgeons. This reaction results from the belief that necrotizing soft tissue infections require hours of arduous and unrewarding surgery, followed by a prolonged downward course in the intensive care unit and a slow, unavoidable death. However, this and other recent reports point out that this is not necessarily the case. To the contrary, if the diagnosis is made early and treatment instituted promptly, prognosis is good.

To our observation and to that of others,[5,6,11,12] differentiating between such entities as streptococcal necrotizing cellulitis, Fournier's gangrene, Meleney's synergistic gangrene, necrotizing fasciitis, clostridial cellulitis, and others serves no purpose other than to confuse the issue. The diagnostic and treatment regimens are the same for all. Based on the widely varying levels of soft tissue affected by the infection and the variety of microflora, only two types of necrotizing soft tissue infections need to be delineated: pure clostridial myonecrosis (because of the homogeneity of its invasion of muscle and its vastly higher mortality rate) and other necrotizing soft tissue infections (NSTI).

The patients with NSTI included in this study, as well as those described in other reports,[6,13–15] had a great number of premorbid medical problems, especially diabetes mellitus and peripheral vascular disease. However, diabetes in this study did not significantly affect mortality, as it often seemed to do in other reports[6,11,12,16–18]; a few other reports failed to find a tie between diabetes and death from NSTI.[7,19,20] Many other studies confirm the effect of advanced age on mortality from these infections,[6,7,11,12,16–19] as does the present one.

Although little can be done to influence the time between the patient's development of symptoms due to NSTI and receipt of medical attention, measures can be taken to hasten diagnosis and early operative debride-

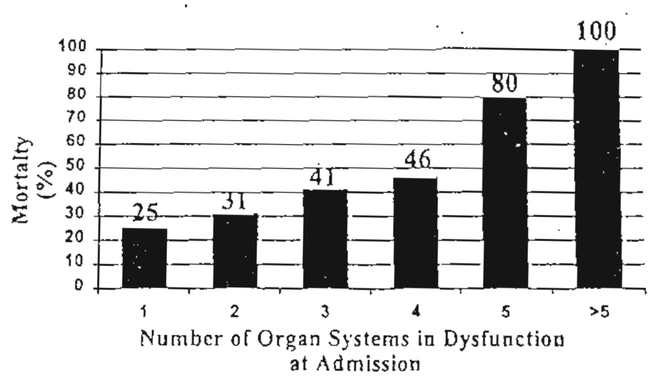

Figure 1. Mortality rate vs. organ failure evident on admission in 198 patients with soft tissue infections.

ment. Delay in the time between admission and first debridement significantly affects ultimate outcome.[5,6,11,13,17,18,21] Also, limited incision and drainage is inadequate, as is a one-time debridement. Complete and repeated debridement of all necrotic tissue must be performed every 24 to 48 hours (based on the aggressiveness of the infection) until the infection is halted. The importance of adequate debridement on decreasing mortality has been borne out in this and previous studies.[5,11,13,18] The surgical literature has been divided regarding the impact of extent of infection on survival; in this study, patients with less extensive infection, expressed in terms of body surface area involved (much as for burns), had a definite survival advantage, whereas such an association was not borne out in the study of 57 patients with Fournier's gangrene by Clayton et al.[7] In contradistinction, depth of infection (*i.e.*, myonecrosis) had no effect on mortality. In many other published reports, no instances of myonecrosis were even reported; in others, it was rare.[16,17] In only two other reports[22,23] did muscle involvement by the necrotizing process by nonclostridial agents approach the frequency of that in this study—*i.e.*, 41.4%.

Symptoms and signs expressed by the patients correlate well with those reported elsewhere[6,11,18,19,21]: pain, edema, erythema. Crepitus and radiographic evidence of soft tissue air, although very suggestive of an anaerobic necrotizing process,[11] do not occur frequently enough to afford sufficient negative predictive value in their absence.[7,11,15,16,18,19,24] However, the combination of crepitus, blistering, and soft tissue air seen on radiography can serve as a useful screening triad. One or more are present in 85% of patients and make further diagnostic maneuvers, short of operation, moot.

Evaluation of admission vital signs and laboratory values revealed that no single "vital sign" (blood pressure, pulse rate, temperature, Glasgow Coma Scale score) independently predicted survival. Serum creatinine level, blood lactate level, and organ failure were significant in predicting mortality. No other study reports increased mortality as related to number of organ systems in dysfunction on admission. However, two describe decreased survival among patients with acute renal failure.[7,20] When combined with other factors, such as age, premorbid health, and extent of infection, the number of organ systems in dysfunction at admission as reflected in Figure 1, proved accurate as a predictor of mortality in this group of NSTI patients.

In regard to sites where the NSTI occurred, truncal and perineal locations incurred greatest mortality.[6,16,17] Microbiologic growth on wound culture did not influence survival, other than the occurrence of pure clostridia associated with myonecrosis. In this study, the four patients with "gas gangrene" died, despite aggressive debridement, massive antibiotics, and expeditious HBO treatment. Other than elevated blood lactate levels, no other risk factors for mortality appeared obvious in these four patients. The bacteria infecting the other patients with NSTI, averaging more than four organisms per person, were of such diverse variety that broad-spectrum antibiotic coverage was warranted. Other studies have corroborated such polymicrobial characteristics of NSTI wounds.[6,16,19,25] The most common organisms not covered by initial therapy were enterococci.

Regarding treatment strategies, colostomy was not routinely performed, even when the infection involved the perianal area. Most patients did not experience wound problems from fecal soilage and eventually regained continence after reconstruction. Because truncal and perineal NSTI can ascend the anterior abdominal wall, withholding colostomy until the infection has been halted, rather than performing it at initial presentation, may be prudent. Other authors concur with this strategy of delayed colostomy.[7,16,19,22] Orchiectomy almost is never required when the scrotum is involved with necrotizing infection. Because the blood supply is different, the testes can be protected effectively in subcutaneous pouches in the thighs.[16,26] As opposed to other reports in the literature,[19,24,27] we found that amputation was required frequently for necrotizing infections of the extremities, due in most cases either to failure to control progression of the infection by other means or to lack of viability of the remaining tissues after debridement.

The value of HBO in treatment of NSTI has been debated in the literature, with some studies finding survival benefit from its use[13,24,26,28] and others finding no benefit.[6,20] Although evidence for decreased mortality seems convincing when HBO is used for clostridial myonecrosis,[20,24] no survival benefit has been well demonstrated by a prospective, randomized, controlled trial for HBO used for nonclostridial necrotizing soft tissue infections. The current study, retrospective and uncontrolled, shows no survival benefit from HBO compared with historical controls; the death rate of 25% appears similar to that in many other recent reports, ranging from 9% to 47%.[5–7,14,15,19,21,22,28] However, HBO may hasten wound closure. In the present study, HBO-treated patients achieved wound closure an average of 28 days after first debridement. In contrast, Asfar et al.[14] note a mean time to wound closure of 48 days in similarly infected patients *not* given HBO.

CONCLUSIONS

Necrotizing soft tissue infections represent a diverse collection of potentially lethal, rapidly progressive bacterial diseases. They share a histologic pattern of invasion of the subepithelial soft tissues by microorganisms, resulting in perivascular lymphocytic infiltrate, vascular hrombosis, tissue edema, and necrosis.[23] Additionally, they have a common strategy for treatment: resuscitation from shock, expeditious and repeated debridement of all necrotic tissue, wide-spectrum intravenous antibiotic coverage, and early hyperalimentation. In the present study, HBO was used to enhance oxygen delivery to compromised, ischemic tissue at the margins of the infection and to enhance polymorphonuclear cell phagocytosis of invading microbes. Hyperbaric oxygen also may halt alpha-toxin production by clostridial organisms and act as a direct bacteriocidal agent against anaerobic organisms.[16,24,26] Although it did not improve survival, HBO did hasten ultimate wound closure.

From the present study, the following conclusions also can be drawn:

1. Advanced age, female gender, and possibly certain premorbid medical conditions increase the risk of dying from NSTI.
2. Lactic acidosis and multiple-organ dysfunction predispose patients with NSTI to death. The number of organ systems in failure at admission correlates with outcome.
3. Crepitus, blistering, and radiographic evidence of soft tissue air serve as useful findings when screening for NSTI.
4. Extent and site of infection influence mortality from NSTI. Myonecrosis is common with such infections, but does not influence outcome.
5. Survival from necrotizing infections was enhanced by early debridement and adequate, repeated debridement.
6. Colostomy is not required universally for perineal NSTI, unless fecal soiling impedes wound healing.
7. Complications resulting from NSTI are common, and some, such as acute renal failure and adult respiratory distress syndrome, increase the risk of death.
8. Except for those patients with overwhelming risk factors for dying at the time of admission (*e.g.*, more than 4 organ systems in failure combined with profound metabolic acidosis), aggressive resuscitation, surgical debridement, and intensive care result in survival for three fourths of the patients presenting with necrotizing soft tissue infections.

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