The Microbiology of Necrotizing Soft Tissue Infections

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OBJECTIVE: A large number of necrotizing soft tissue infections (NSTI) treated at a single institution over an 8-year period were analyzed with respect to microbial pathogens recovered, treatment administered, and outcome. Based on this analysis, optimal empiric antibiotic coverage is proposed.

METHODS: A retrospective chart review of all patients with documented NSTI was conducted. Microbiologic variables were tested for impact on outcome using Fisher's exact test and multivariate analysis by logistic regression.

RESULTS: Review of the charts of 198 patients with documented NSTI revealed 182 patients with sufficient microbiologic information for analysis. These 182 patients grew an average of 4.4 microbes from original wound cultures, although a single pathogen was responsible in 28 patients. Eighty-five patients had combined aerobic and anaerobic growth, the most common organisms being, in order, *Bacteroides* species, aerobic streptococci, staphylococci, enterococci, *Escherichia coli*, and other gram-negative rods. Clostridial growth was common but did not affect mortality unless associated with pure clostridial myonecrosis. Mortality was affected by the presence of bacteremia, delayed or inadequate surgery, and degree of organ system dysfunction on admission.

CONCLUSIONS: NSTI are frequently polymicrobial and initial antibiotic coverage with a broad-spectrum regimen is warranted. The initial regimen should include agents effective against aerobic gram-positive cocci, gram-negative rods, and a variety of anaerobes. The most common organisms not covered by initial therapy were enterococci. All wounds should be cultured at initial debridement, as changes in antibiotic coverage are frequent once isolates are recovered. *Am J Surg.* 2000;179:361–366. © 2000 by Excerpta Medica, Inc.

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Necrotizing soft tissue infections (NSTI) encompass a wide clinical spectrum of diseases, ranging from invasive streptococcal cellulitis to Fournier's gangrene and clostridial myonecrosis. Although discrete differences between these syndromes exist, many clinical similarities among them allow a common discussion. The foremost similarities include the angiothrombotic microbial invasion resulting in necrosis and rapid progression, the necessity of early, adequate surgical debridement in controlling the infection, and the propensity for multiple organ dysfunction and death in patients receiving inadequate treatment.

A prior review at the authors' institution elicited 198 patients admitted and treated for confirmed NSTI over an 8-year period.[1] Multivariate regression analysis of these patients revealed a number of independent factors that influenced mortality: age greater than 60 years, female sex, elevated admission serum creatinine, elevated admission blood lactate, delay in initial surgical debridement, body surface area involved with infection, and number of organ systems in failure on admission. In addition, it was found that most patients had preexisting medical conditions that predisposed them to necrotizing infections, that hyperbaric oxygen therapy (HBO) appeared to shorten the time to wound closure after debridement, that complications of the disease and its treatment were common (82% patients), and that most infections were polymicrobial.

This study attempts to analyze, in more detail, the microbiologic aspects of these necrotizing infections. It is felt that such an analysis might better afford the practicing physician an understanding of "the enemy:" likely bacterial and fungal agents responsible for the infections. Such an understanding might empower the physician to provide optimal surgical and medical care, prevent complications, and direct most appropriate antimicrobial therapy.

MATERIALS AND METHODS

The data reported herein are from a single institution, a 100-bed level I trauma center serving a state and surrounding region with population exceeding 5 million people and possessing a multipatient hyperbaric chamber capable of treating 21 patients simultaneously. Between March 1985 and June 1993, 198 patients with NSTI 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.

For this analysis, each patient's record was queried for

information to include age, gender, preexisting illnesses, site of origin of the necrotizing infection, and extent of spread. Of particular interest were the bacterial and fungal agents recovered from the wound by culture, the antibiotic medications used, and subsequent complications that developed. All wound cultures were obtained at time of initial surgical debridement, transferred to standard aerobic and anaerobic swab/transport tube and plated within 1 hour in the University of Maryland Medical Center laboratory on appropriate 6% sheep blood agar plates. These included standard anaerobic medium and broth to test for anaerobic growth, and casein-soy, chocolate, and MacConkey agar mediums for aerobic growth. Plates were incubated at 36°C under aerobic and anaerobic conditions.

Potential factors affecting mortality were tested using univariate analysis. Pearson's chi-square statistic was utilized for comparisons of proportions, Fisher's exact test for two-by-two tables of small-sample size, and the F statistic for comparison of means of measured variables between survivors and nonsurvivors. Owing to the large number of potentially significant variables identified through univariate analysis, further analysis using a model for multivariate logistic regression was employed. A P value of 0.15 or less was chosen as the criterion for initial variable entry, and $P = 0.05$ as criterion for determining significance. Thirteen clinically relevant variables were selected for stepwise regression analysis. These variables included the infectious factors most potentially affecting mortality, in addition to other demographic, diagnostic, and therapeutic variables. Statistical analysis was performed using SAS software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Among the 198 patients studied, mortality was 25.3%, the average age was 51.5 years, male patients accounted for 57.3% of the total, and 56.4% of patients were diabetic. The mean extent of infection was 8.4% (±0.4%) of body surface area, and the most common sites of infection were perineal sources (Fournier's gangrene, 36% of cases), podiatric sources (15.2%), and traumatic wounds (14.7%). **Tables I** and **II** list the preexisting medical conditions and sites of origins among the study patients.

On 182 charts, growth on initial wound culture was sufficient for microbiologic analysis. **Table III** lists the microbiologic agents responsible for the NSTI, as recovered through initial wound culture. Of note, a mean of 4.4 pathogens grew from original wound cultures, 4.5 microorganisms in survivors versus 4.0 microorganisms in nonsurvivors ($P = 0.28$).

In 28 of the 182 patients, only one organism was recovered from wound culture. In 15 of these 28 patients, the sole pathogen was a streptococcus isolate. Five of these patients presented with the clinical picture of group A beta-hemolytic streptococcal toxic shock syndrome, typified by isolation of the appropriate organism from the necrotic wound and the additional evidence of shock on admission (profound hypotension and/or lactic acidosis). The mortality for this condition, 40% of patients (2 of 5), was higher than the mean mortality rate for all patients. This appeared to be due to two factors: delay in recognizing and surgically debriding the infection (elicited in 80% of this group versus 27.7% of the whole study group), and number of organ systems in failure at time of admission (5.2 organ systems versus 1.5 in the whole study group). Our prior study pointed out the strong effect that admission organ failure had upon subsequent mortality (see **Figure**).[1] Delay in recognition and treatment of this lethal disease may be due in part to the insignificant appearance of the external wound present and the paucity of characteristic physical findings such as crepitus.

In 4 of these 28 patients with a single microbial pathogen, a clostridial organism resulted in classic clostridial myonecrosis (gas gangrene). Mortality in this small group was 100%, despite aggressive surgical debridement, antibiotics, and HBO. In 3, the offending organism was *Clostridium perfringens*, and in the fourth, *C septicum* (associated with an occult colonic adenocarcinoma). As an aside, 78 other patients harbored muscle tissue bacterial invasion, grossly or histologically, concomitant with necrotizing fasciitis of polymicrobial etiology (total 41.4% patients). The mortality rate was 26.8% among all patients with evidence of myonecrosis, not significantly different from the chance of mortality among patients with only fascial or pannicular infection.

Despite the higher mortality associated with streptococcal toxic shock syndrome and with clostridial myonecrosis, patients with only one organism isolated on initial culture had no greater chance of dying than those with multiple organisms recovered on culture (mortality 34.5% versus 22.4%, $P = 0.17$).

The remaining 154 patients harbored polymicrobial NSTI. In 38 patients, two microorganisms were isolated; in 26, three microorganisms; in 90, four or more microorganisms grew out on initial wound culture. Analysis of the data presented in Table III reveals several interesting trends:

1. Streptococcal species were the most common aerobic organisms recovered, with a total of 106 isolates.
2. Staphylococcal species, particularly *Staphylococcus epidermidis*, were common pathogens, often in combination with beta-hemolytic streptococci.
3. Enterococcal species were extremely common pathogens.
4. A wide variety of enterobacteriaceae were recovered from wound culture, most commonly *E coli*, *Proteus mirabilis*, and *Klebsiella pneumonia*. *Pseudomonas aeruginosa* was not uncommon.
5. *Bacteroides* species were the most common isolates recovered.
6. Anaerobic gram-positive cocci and various clostridial species were common anaerobic species recovered. Clostridial species were common participants in polymicrobial infections, not necessarily causative of myonecrosis.
7. Fungal species were occasional pathogens in necrotizing infections and should be sought in culture.
8. Notable absences from the list of pathogens include *Streptococcus pneumonia*, *Haemophilus influenza*, and isolates of *Salmonella*, *Shigella*, *Campylobacter*, and *Vibrio* species.

Information on antibiotic therapy was available in 193 patients. Patients received a mean of 12.8 days of antibiotics (± 0.4 days), survivors 13.1 days and nonsurvivors 11.9 days ($P = 0.22$). Antibiotic therapy was typically

TABLE I

Mortality Rates in Groups Defined by Preexisting Characteristics and Medical Conditions

		Patients	Number of Deaths	Percent	Nonsurvivors *P* Value*
All Patients		198	50	25.3	
Age (years)	≤60	137	23	16.8	
	>60	61	27	44.3	<0.001
Gender	Male	113	21	18.6	
	Female	84	28	33.3	0.02
Race	White	99	29	29.3	
	Nonwhite	97	20	20.6	0.16
Diabetes mellitus	Yes	110	29	26.4	
	No	85	18	21.2	0.40
Hypertension	Yes	69	22	31.9	
	No	127	26	20.5	0.08
Obesity	Yes	62	17	27.4	
	No	133	30	22.6	0.46
Heart disease	Yes	52	22	42.3	
	No	144	26	18.1	<0.001
Malnutrition	Yes	35	14	40.0	
	No	160	33	20.6	0.02
Alcohol abuse	Yes	34	12	35.3	
	No	161	35	21.7	0.09
Peripheral vascular disease	Yes	32	11	34.4	
	No	163	36	22.1	0.14
Pulmonary disease	Yes	30	13	43.3	
	No	165	34	20.6	0.007
IV drug abuse	Yes	26	1	3.8	
	No	169	46	27.2	0.009
Carcinoma	Yes	23	14	60.9	
	No	173	34	19.6	<0.001
Chronic azotemia	Yes	20	8	40.0	
	No	175	39	22.3	0.10†
Hepatic disease	Yes	7	3	42.9	
	No	188	44	23.4	0.36†
HIV infection	Yes	8	0	0.0	
	No	190	50	26.3	
Myonecrosis	Yes	82	22	26.8	
	No	113	25	22.1	0.45
Bacteremia	Yes	53	25	47.2	
	No	143	24	16.8	0.002

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

broad spectrum, with a number of common usage patterns emerging:

1. Penicillin or ampicillin plus anaerobic coverage (clindamycin or metronidazole) and an aminoglycoside: 91 patients; by far the most common antibiotic regimen utilized.
2. Vancomycin plus anaerobic coverage and gram-negative coverage (an aminoglycoside or aztreonam or third-generation cephalosporin): 27 patients; used primarily in penicillin-allergic patients.
3. Ampicillin/sulbactam with/without additional gram-negative coverage: 20 patients.
4. Imipenem with/without additional coverage: 16 patients.
5. Antipseudomonal penicillin plus anaerobic and gram-negative coverage: 7 patients.
6. Nafcillin plus anaerobic and gram-negative coverage: 8 patients.
7. Anaerobic agent plus gram-negative coverage without additional gram-positive coverage: 5 patients.
8. Other antibiotic combination: 5 patients
9. Changes in antibiotic regimens were common, based on clinical response and growth on wound culture. Of the 193 patients, 115 (59.6%) had antibiotic regimens altered for treatment of NSTI.

Comparing antibiotic usage patterns to pathogens recovered on culture, it appears that most patients had adequate antimicrobial coverage; however, 16 patients (8.1%) were considered to have received inadequate antibiotic coverage for the pathogens involved. Most of these (13 of 16) lacked adequate coverage for *Enterococcus*, a common pathogen (60 patients). Although no single antibiotic regimen was

TABLE II
Source of Infection and Relative Mortality

Source	Number 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
Perforated viscus	4	3	75.0
Munchausen syndrome	2	0	0.0
Strangulated hernia	2	1	50.0
Unknown	7	3	42.9

TABLE III
Microbiology

Aerobic	
Gram-positive cocci	
Staphylococcus aureus	27
MRSA	3
Coagulase-negative *Staphylococcus*	40 (incl *S epidermidis, S hemolyticus*)
Streptococcus	
Beta-hemolytic	70
Group A	40
Group B	17 (incl *S agalactiae*, 1)
Group D	6 (non-*Enterococcus*)
Group F	5
Group G	2
Alpha-hemolytic/ *S viridans*	31
Gamma (non)-hemolytic	5
Enterococcus	60 (incl *E faecium*, 1)
Gram-positive rods	
Corynebacterium	7
Bacillus cereus	4
Lactobacillus	2
Gram-negative rods	
Escherichia coli	58
Proteus mirabilis	36
Klebsiella	28
Enterobacter	10
Serratia marcescens	6
Citrobacter	5
Pseudomonas	17
Eikenella corrodens	4
Acinetobacter anitratus	8
Other gram-negative rods	21
Anaerobic	
Bacteroides/Prevotella spp	116
Fragilis	18
Melanogenicus	2
Fusobacterium	7
Propionibacterium	3
Clostridium	
Perfringens	20
Septicum	5
Sporogenes	2
Other	10
Peptococcus/Peptostreptococcus	49
Veillonela	3
Other anaerobes	19
Fungal	
Candida spp	7
Torulopsis glabrata	1
Cryptococcus	1

clearly superior in preventing mortality and complications, those patients receiving ampicillin/sulbactam or nafcillin regimens tended toward a lower mortality rate (0% to 10%) than other regimens (mortality 21% to 46%). The sample sizes among these subgroups are too small, and the frequency of antibiotic changes too great to draw significance from this mortality trend, however.

Bacteremia occurred in 53 patients (27.2%) and was associated with increased mortality when present (47.2%, $P = 0.002$). Wound infections occurred in 43 patients (22.2%) but did not affect mortality. *Clostridium difficile* colitis occurred in 18 patients (9.2%), 11 of whom had received combinations of penicillin and clindamycin. The rate of bacteremia, wound infection, superinfection with C *difficile* colitis, and other complicating infections was not different between the different antibiotic regimens, nor was there a significant difference in the incidence of these complications with respect to the pathogens recovered on culture.

Multivariate stepwise logistic regression was conducted utilizing significant variables identified by univariate analysis, including ones identified during the authors' prior NSTI analysis.[1] The 13 variables for multivariate regression analysis included age, sex, Glasgow Coma Scale score; admission values of systolic blood pressure, platelet count, serum creatinine level, blood lactate level, activated partial thromboplastin time, and PaO2/FiO2 ratio; days from admission to first debridement, body surface area involved with infection, number of organ systems failed on admission, and presence of bacteremia at admission. Variables found by logistic regression to independently predict mortality are shown in **Table IV**. Of note, the presence of bacteremia (by blood culture) on admission was the only microbiologic variable found to affect mortality. Adjusting for other covariates, patients with bacteremia were 5.2 times at risk for death as those without bacteremia. As opposed to the authors' former study,[1] extent of infection (as reflected by percent of body surface area affected by NSTI), sex, and serum creatinine on admission did not emerge by logistic regression as independents predictor of mortality; however, the presence of bacteremia was highly associated with female sex and a higher percentage of body surface area involved with NSTI.

COMMENTS

This retrospective analysis of 198 cases of NSTI establishes that such infections are capable of harboring a wide

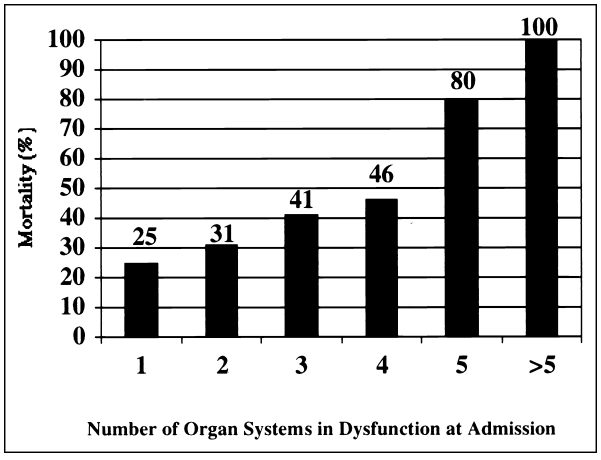

Figure. Mortality rate versus organ failure evident on admission in 198 patients with necrotizing soft tissue infections. Reprinted with permission from: Elliott DC et al.[1]

TABLE IV
Logistic Regression Analysis Results: Covariates Found to Be Risk Factors for Mortality from Necrotizing Soft-Tissue Infections

Variable	*P* Value	Odds Ratio	90% Confidence Interval	
			Lower	Upper
Age (>60 years)	0.0005	8.1	3.2	22.9
Lactate (% above normal)	0.0019	1.6	1.3	2.1
Days ADM to first DEBR	0.0119	1.2	1.1	1.4
Number of organs failed on ADM	0.0006	1.8	1.4	2.5
Bacteremia	0.0035	5.2	2.1	13.7

ADM = admission; DEBR = debridement.

variety of microbial pathogens. Most infections are polymicrobial (average 4.4 microbes per case), but single-pathogen infections are not uncommon. Beta-hemolytic streptococci are the most frequent solitary pathogens (15 of 28 cases). The most common bacterial species overall include *Bacteroides/Prevotella* (116 isolates), streptococci (106 isolates), and gram-negative enterobacteriaceae (*E coli*, *K pneumonia*, *Proteus mirabilis*, 121 isolates). Enterococci and staphylococcal species were also commonly recovered (60 and 67 isolates, respectively). A close consideration of Table III reveals that, indeed, very few major bacterial species are not represented. Some notable absences include *S pneumonia*, *H influenza*, and *Vibrio*, *Campylobacter*, *Salmonella*, and *Shigella* species.

Other smaller published series, when viewed collectively, demonstrate similar patterns of microbiologic growth with NSTI. Predominant bacterial species recovered on culture mirrored our institution's experience in 11 cases of neonatal omphalitis-associated NSTI,[2] 55 cases of NSTI in India,[3] 8 cases of NSTI in children,[4] 14 cases of NSTI at the Mayo Clinic,[5] 16 cases of NSTI reported from San Francisco General Hospital,[6] 29 cases of Fournier's gangrene from the same institution,[7] 57 cases of Fournier's gangrene from Chicago,[8] 20 cases of Fournier's gangrene in Madrid, Spain,[9] 65 cases of NSTI from Cleveland,[10] 29 cases of NSTI from Seattle,[11] and 151 cases of NSTI from other institutions.[12–15]

A number of case reports and small published series document that many microorganisms not found in our series, as well as other unusual organisms in our series not usually associated with necrotizing infections, may yet be responsible for NSTI. *Streptococcus pneumoniae* has been a pathogen implicated in NSTI,[16] as have *Aeromonas* species in patients with hepatic insufficiency,[17,18] and *Edwardsiella*[19] and *Haemophilus* species.[20,21] *Serratia* and *Pseudomonas* species, found commonly in our series, have appeared in many others as well.[6,10–12,14,15,22,23] *Vibrio* species (including *V cholerae*, *V vulnificus*, *V parahemolyticus*, and *V alginolyticus*) have been implicated in many cases of NSTI, especially in cirrhotic patients,[13,24–28] but did not appear as pathogens in our series. Fungal species, including *Candida*, *Aspergillus*, *Cryptococcus*, *Rhizopus*, and *Apophysomyces*,[5,10,29-32] have been cultured from NSTI, as has *Mycobacterium tuberculosis*.[33] All these data serve to point out that initial antibiotic treatment should be broad spectrum, that culture of the wound at initial debridement is imperative, and that the clinician should be prepared to treat any combination of microbiologic pathogens, since just about every microbiologic pathogen has occurred at one time or other in NSTI.

That being stated, common pathogens occur commonly, and initial antibiotic therapy shown to be effective include agents effective against streptococci, enterococci, staphylococci, bacteroides, clostridia, and community-acquired enterobacteriaceae. Our series demonstrates that many regimens possess nearly equivalent efficacy. Examples of effective regimens include (1) the combination of ampicillin, gentamycin, and clindamycin; (2) ampicillin/sulbactam; and (3) the combination of vancomycin, ceftriaxone, and metronidazole. The most common antibiotic prescribing error in our series was inadequate coverage of the pathogen enterococcus, which optimally requires ampicillin or vancomycin plus an aminoglycoside.

Much has been written regarding the increasing virulence of group A streptococcus, the "flesh-eating bacterium." Numerous excellent scholarly molecular studies point to the elucidation of distinctive proteins produced by the organisms, scarlatina pyrogenic exotoxins (SPE) types A, B and C, and streptococcal superantigen (SSA), especially in the M-1 and M-3 subtypes of *S pyogenes*, that may be responsible for its special invasive characteristics, its proclivity to cause shock, and its rising incidence.[34–37] Regardless, NSTI caused by the flesh-eating bacterium are difficult to distinguish clinically from those caused by other, polymicrobial sources, and the clinician should approach all NSTI with a similar algorithm of care:[1]

1. Resuscitate the patient in shock.[38]
2. Begin broad-spectrum antibiotic coverage as described above.
3. Take the patient to the operating room for expeditious, comprehensive debridement of all dead tissue. Doubt as to the diagnosis can be settled using frozen-section histologic analysis.[39] Obtain gram stain and cultures from the wound.

4. Further debridements should be repeated every 24 to 48 hours until the infection is controlled.
5. Antibiotic therapy should be adjusted to adequately cover organisms obtained on initial culture.
6. HBO can be considered in the hemodynamically stable patient, if available.[1]

CONCLUSIONS

Necrotizing soft tissue infections are frequently polymicrobial and initial antibiotic coverage with a broad-spectrum regimen is warranted. The initial regimen should include agents effective against aerobic gram-positive cocci, gram-negative rods, and a variety of anaerobes. The most common organisms not covered by initial therapy were enterococci. All wounds should be cultured at initial debridement, as changes in antibiotic coverage are frequent once isolates are recovered.

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