World J Surg (2010) 34:1669–1675
DOI 10.1007/s00268-010-0455-y

World Journal of Surgery

Predictors of Mortality in Skin and Soft-tissue Infections Caused by *Vibrio vulnificus*

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Published online: 12 February 2010

Abstract
Background *Vibrio vulnificus* infection can progress rapidly in skin or soft tissue, and it is potentially life-threatening. The purpose of the present study was to explore the predictors of mortality in patients with *V. vulnificus* infections of skin or soft tissue.
Methods The medical records of 119 consecutive patients aged ≥18 years, hospitalized for *V. vulnificus* infections of skin or soft tissue between January 2000 and December 2007 were reviewed. Co-morbidities, clinical manifestations, laboratory studies, treatments, and outcomes were analyzed. Multiple logistic regression with the exact method was performed.
Results The mean age of the patients was 63.7 ± 12.0 years. Twenty-four patients died, yielding an overall case fatality rate of 20%. Of the 24 deaths, 20 (83%) occurred within 72 h after hospital admission. Of 119 patients, 45 patients had primary septicemia, and 74 patients had wound infection. Multivariate analysis revealed that the following factors were associated with mortality: hemorrhagic bullous skin lesions/necrotizing fasciitis ($p = 0.003$), primary septicemia ($p = 0.042$), a greater organ dysfunction and/or infection score ($p = 0.005$), absence of leukocytosis ($p = 0.0001$), and hypoalbuminemia ($p = 0.003$). Treatment with surgical intervention plus antibiotics ($p = 0.038$) and surgical intervention within 24 h after admission ($p = 0.017$) were protective factors.
Conclusions This study demonstrates that the presence of hemorrhagic bullous skin lesions/necrotizing fasciitis, primary septicemia, a greater severity-of-illness, absence of leukocytosis, and hypoalbuminemia were the significant risk factors for mortality in these patients. Moreover, patients treated with surgery plus antibiotics, especially those receiving a prompt surgical evaluation within 24 h after hospital admission, may have a better prognosis.

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Introduction

Vibrio vulnificus is a lactose-fermenting, halophilic, gram-negative, opportunistic human pathogen that is often found in warm coastal seawaters and raw seafood. Since the first report of *V. vulnificus* infection in humans was presented by Hollis et al. in 1976 [1], many case reports and reviews

have been published. *V. vulnificus* infections cause three distinct clinical manifestations: gastroenteritis, primary septicemia, and primary wound infections. Primary septicemia and wound infections, unlike self-limited gastroenteritis, are potentially life-threatening, with reported case fatality rates of 10–54% in the past two decades [2–9]. *V. vulnificus* infection that manifests initially as primary septicemia or wound infection may progress rapidly to a skin/soft-tissue infection (SSTI), and these infections can have a fulminant course resulting in death within 48–72 h after hospital admission, most notably in patients with hemorrhagic or necrotic cutaneous bullae, necrotizing fasciitis, or coexisting septic shock [2–12]. These SSTIs may require early surgical intervention, in addition to antibiotics and supportive therapy, to eradicate the infection and to avoid adverse outcomes [4, 12–15]. Thus, it is important to recognize the prognostic factors of *V. vulnificus* SSTI for selection of appropriate therapeutic approaches and disposition. Patients with underlying chronic disorders, such as cirrhosis, diabetes mellitus, and immunocompromise, have been noted to be predisposed to *V. vulnificus* infection [3, 5–11]. However, the prognostic factors for *V. vulnificus* SSTIs are by far less comprehensively reported than the predisposing factors. To identify risk factors for mortality, we conducted an 8-year retrospective study to collect detailed clinical information including clinical manifestations and laboratory findings, microbiological studies, treatment, and outcomes of *V. vulnificus* patients with SSTI.

Materials and methods

Study subjects

From January 2000 to December 2007, consecutive patients aged $\geq$ 18 years who were diagnosed with *V. vulnificus* infection and were admitted to the Chi Mei Medical Center, were enrolled through a systematic search of patient records. The medical record for each identified patient was reviewed, and *V. vulnificus* SSTI was diagnosed if the following conditions were met: (1) skin/soft-tissue lesions, including infected wounds, cellulitis with/without bullous, necrotic, or gangrenous change necrotizing fasciitis, or myositis prior to admission or during hospitalization, and (2) *V. vulnificus* isolated from blood, wound, and/or stool cultures. In total, 119 patients met these criteria and were included for further analysis.

Data collection

Demographic data, clinical presentations and course, treatment, and outcomes were reviewed and analyzed. Among *V. vulnificus* patients with SSTI, those with sepsis without another obvious source of infection were regarded as having primary septicemia, whereas those with a history of exposure of a wound to seawater/marine creatures or a recent injury from handling seafood were considered to have primary wound infections [2–6, 10, 16]. The severity of illness on admission was evaluated with the first-day Organ Dysfunction and/or Infection (ODIN) score (score range: 0–7, higher scores indicating more severe illness) [17]. Each *V. vulnificus* isolate was a halophilic gram-negative rod positive for cytochrome oxidase, glucose fermentation, citrate use, indole production, ornithine decarboxylase, and hydroxylase of orthonitrophenyl galactoside [18]. The *V. vulnificus* isolates identified by conventional methods were further verified by the API-20E system (bioMérieux Vitek Inc., Hazelwood, MO). Antimicrobial susceptibility testing was performed with the Kirby-Bauer, broth dilution, and E-test methods. The initial empirical broad-spectrum antibiotics were administered parenterally after the blood, wound, or stool specimens had been obtained. Case fatality was defined as death during hospitalization.

Statistical analysis

Comparisons between groups for continuous variables were made using either the Student's *t*-test or the Mann–Whitney *U*-test, as appropriate. Categorical variables were compared between groups, with either the chi-square test or Fisher's exact test, as appropriate. The relationships between (1) demographics, clinical features, laboratory results, and therapeutic variables and (2) mortality were analyzed. Variables significant by univariate analysis were subjected to the regression model with the exact method to identify significant independent risk factors for mortality [19]. Odds ratios (OR) and 95% confidence intervals (CI) were estimated in the exact logistic regression model. The statistical analyses above were performed with SAS software, version 8.2 (SAS Institute Inc., Cary, NC). A two-tailed p value <0.05 was considered statistically significant.

Results

Demographics, clinical characteristics, co-morbidities, and laboratory findings

The mean age of the 119 Taiwanese patients with *V. vulnificus* infection was 63.7 $\pm$ 12.0 years (range: 32–89 years); 55% of these patients were men. Twenty-four patients died, yielding an overall case fatality rate of 20%. The mean interval between the onset of symptoms prior to admission and the time of suspicion or diagnosis of

V. vulnificus after arrival was 1.5 ± 0.8 days. Among 45 patients with primary septicemia, 34 had a recent history of consuming raw/undercooked seafood, and the remaining 11 patients did not have the relevant information recorded. Seventy-four patients, including 68 fishers/related fishery workers and 6 working at other occupations, had primary wound infections. There were 47 patients with septic shock at admission. *V. vulnificus* was isolated from 80% of wound cultures (95/119 patients) and from 56% of blood cultures (57/119 patients). None of the stool cultures was positive for *V. vulnificus*.

Patients who died during hospitalization had a significantly high percentage of underlying liver disorders, primary septicemia, hemorrhagic bullous skin lesions or necrotizing fasciitis, hypotension (blood pressure <90/60 mmHg) on admission, serum aspartate aminotransferase level >40 IU/l, blood urea nitrogen >22 mg/dl, serum creatinine level >1.3 mg/dl, and hypoalbuminemia (serum albumin level <3.5 mg/dl), as well as a greater ODIN score, than the patients who survived. Those who died during hospitalization also had a significantly lower frequency of leukocytosis than those who survived (Table 1).

Therapeutic modalities and outcomes

The treatment and outcomes of these patients are summarized in Table 2. A total of 51 patients (16 who died and 35 who survived) initially received third-generation cephalosporins either with or without minocycline or quinolones. A significantly higher proportion of patients who died had been treated with antibiotics alone ($p < 0.0001$) and had been treated initially with third-generation cephalosporins or quinolones ($p = 0.015$) as compared with those who survived. All patients subsequently received antibiotic therapy as directed by the results of the antibiotic susceptibility profiles. Patients who survived were significantly more likely to have had surgical intervention within 24 h of admission than were those who died ($p = 0.013$). In 97 patients who underwent surgery, 85 had a fasciotomy, based on a high index of suspicion of necrotizing fasciitis with/without compartment syndrome, determined by the signs and symptoms on admission or during hospitalization, and 12 out of the 85 subsequently needed an amputation (Table 3). Of the 24 deaths, 20 (83%) occurred within 72 h after arrival at the hospital.

Multivariate analysis of clinical factors in relation to mortality

When the significant variables obtained from univariate analysis were subjected to multivariate analysis, seven of them attained statistical significance: hemorrhagic bullous skin lesions/necrotizing fasciitis, origin of infection, ODIN score, white blood cell count, hypoalbuminemia, treatment method, and the time to surgical treatment after arrival <24 h (Table 4).

Discussion

The demographic characteristics and clinical features in our series are similar to those reported for *V. vulnificus* infection elsewhere [2–13]. Based on the multivariate analysis, we learned that the occurrence of hemorrhagic bullous lesions or necrotizing fasciitis, absence of leukocytosis, and the presence of primary septicemia, the greater ODIN score, and hypoalbuminemia on admission were the significant risk factors for mortality. Additionally, the timing of surgical intervention can influence patient outcome.

As reported in the literature [2–10, 12, 13], the prognosis of primary septicemia in the patients reported here was worse than that of wound infection among *V. vulnificus*-infected patients. It is noteworthy that the case fatality rate for *V. vulnificus*-infected patients with primary septicemia in our study group was relatively lower than the rates of 46–79% reported elsewhere [2–10, 20]. It is possible that better access to medical care in this locality and a high index of suspicion of *V. vulnificus* infection contributed to this relatively low case fatality. This speculation may be supported by the fact that the mean duration of symptoms prior to suspicion/diagnosis of *V. vulnificus* infection was 1.5 days, and there was no difference in duration of symptoms prior to suspicion/diagnosis of *V. vulnificus* infection between the survival and nonsurvival groups. Additionally, most of these patients had a recent history of consumption of raw/undercooked seafood, an injury from fishing or handling seafood, or coexisting wounds that had been exposed to seawater, findings that may alert clinicians to the possibility of *V. vulnificus* infection. Underlying hepatic disorder, which was more prevalent in the nonsurvivors, has been shown to be associated with *V. vulnificus* primary septicemia and is considered to be a predisposing factor [3, 5–11]. This may explain why underlying hepatic disorder was significant in univariate analysis but not in multivariate analysis.

Few studies of *V. vulnificus* infection have identified serum albumin levels as a marker of poor prognosis. In this work, hypoalbuminemia and a greater ODIN score were significant indicators of mortality, which is reflective of the clinical severity of infection. Our data revealed that *V. vulnificus*-infected patients without leukocytosis had a higher case fatality rate than those with leukocytosis. A host with a severe infectious condition may be too ill to mount an effective immune response, perhaps because of anergy or suppression of host immunity [21, 22].

Table 1 Demographic data, underlying diseases, presenting signs/symptoms, and laboratory findings in 119 patients with *Vibrio vulnificus* infection of skin or soft tissue

Variable	All patients ($n = 119$)	Survivors ($n = 95$)	Nonsurvivors ($n = 24$)	p Value
Gender, male, no. (%)	65 (55)	55 (58)	10 (42)	0.154
Age, years[a]	63.7 ± 12.0	63.2 ± 11.4	65.8 ± 14.2	0.338
Interval between symptoms before admission and suspicion/diagnosis of *V. vulnificus,* days[a]	1.5 ± 0.8	1.4 ± 0.9	1.9 ± 0.7	0.101
Co-existing medical conditions, no. (%)[b]				
Diabetes mellitus	36 (30)	32 (32)	4 (17)	0.105
Hepatic disorders[c]	31 (26)	19 (20)	12 (50)	0.003
Chronic renal insufficiency	12 (10)	8 (8)	4 (17)	0.258
Immunosuppressive agents used	19 (16)	16 (16)	4 (17)	1.000
Malignancy	11 (9)	7 (7)	4 (17)	0.229
Aplastic anemia	4 (3)	4 (4)	0	0.582
Substance abuse	1 (1)	1 (1)	0	1.000
HIV infection	1 (1)	1 (2)	0	1.000
Without co-morbid disease	41 (35)	35 (37)	6 (25)	0.275
Origin of infection				0.001
Primary septicemia	45 (38)	29 (30)	16 (67)	
Wound infection	74 (62)	66 (70)	8 (33)	
Signs and symptoms on admission, no. (%)[b]				
Skin or soft-tissue lesions				0.002
Cutaneous cellulitis or necrotic cutaneous lesions with hemorrhagic bullae or necrotizing fasciitis[a]	55 (46)	37 (39)	(75)	
Cutaneous cellulitis without bullae[b]	64 (54)	58 (61)	6 (25)	
Fever/chills	47 (40)	39 (41)	8 (33)	0.489
Blood pressure <90/60 mmHg	47 (40)	31 (33)	16 (67)	0.002
Abdominal pain	4 (3)	2 (2)	2 (8)	0.181
Nausea/emesis	2 (2)	2 (2)	0	1.000
ODIN score on admission[a]	1.6 ± 0.8	1.4 ± 0.6	2.5 ± 0.9	<0.0001
Laboratory findings on admission, no. (%)				
WBC count $>10^4$ cells/mm^3	80 (67)	76 (80)	4 (17)	<0.0001
Hemoglobin level <14 g/dl in males, or <12 g/dl in females	48 (40)	38 (40)	10 (42)	1.000
AST level >40 IU/l	67 (56)	49 (52)	18 (75)	0.039
BUN >22 mg/dl	80 (67)	59 (62)	21 (88)	0.020
Serum creatinine level >1.3 mg/dl	66 (56)	44 (46)	22 (92)	<0.0001
Serum albumin level <3.5 mg/dl	37 (31)	25 (26)	12 (50)	0.025

AST aspartate aminotransferase, *BUN* blood urea nitrogen, *HIV* human immunodeficiency virus, *ODIN* organ dysfunctions and/or infection, *WBC* white blood cell

[a] The values are given as mean ± standard deviation

[b] When patients fit into multiple categories, they were counted in each category

[c] Hepatic disorders including chronic hepatitis B, chronic hepatitis C, alcoholic hepatitis, liver cirrhosis, and hepatocellular carcinoma

Additionally, some investigators have found that *V. vulnificus*-infected patients with septicemia or severe illness had low phagocytic activity of neutrophils and low levels of proinflammatory cytokines, including interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor α, compared with those without septicemia or severe illness [23–25]. The interaction between the host inflammatory reaction and severity of illness or underlying conditions in *V. vulnificus*-infected patients remains to be elucidated.

In the present study, the majority of patients who died did so within 72 h after admission. *V. vulnificus* produces a variety of toxins such as capsular polysaccharide, lipopolysaccharide, cytolysin, iron, and metalloprotease [23, 25–28], which may cause rapid deterioration of the host

Table 2 Treatment and outcomes in 119 patients with *Vibrio vulnificus* infections of skin or soft tissue

Variable	All patients ($n = 119$)	Survivors ($n = 95$)	Nonsurvivors ($n = 24$)	p Value
Treatment method, n (%)				<0.0001
Surgical intervention[a] plus antibiotics	97 (82)	85[b] (90)	12[c] (50)	
Antibiotics alone	22 (18)	10 (10)	12 (50)	
Initial antibiotic treatment, n (%)				0.067
Penicillin group	34 (29)	32 (33)	2 (8)	
First- or second-generation cephalosporin with or without an aminoglycoside	24 (20)	18 (19)	6 (25)	
Third-generation cephalosporin with or without minocycline (or analog)	43 (36)	31 (33)	12 (50)	
Quinolone group	18 (15)	14 (15)	4 (17)	
Subsequent antibiotic treatment, n (%)[d]				0.154
Penicillin group	7 (6)	7 (7)	0	
Second-generation cephalosporin with minocycline (or analog)	9 (8)	7 (7)	2 (8)	
Third-generation cephalosporin with minocycline (or analog)	92 (77)	70 (74)	22 (92)	
Quinolone group	11 (9)	11 (12)	0	
Time to surgical treatment after admission <24 h, n (%)	84 (71)	72 (76)	12 (50)	0.013
Subsequent ICU admission, n (%)	53 (45)	33 (35)	20 (83)	0.002
Subsequent amputation needed, n (%)	12 (10)	10 (11)	2 (8)	1.000
Hospital stay, days[e]	18.5 ± 17.0	21.7 ± 16.9	2.8 ± 3.1	<0.0001

ICU intensive care unit

[a] Surgical intervention: incision and drainage, debridement, and/or fasciotomy, as well as amputation if necessary

[b] Surgical modalities in the survival group including (1) incision and drainage + debridement ($n = 12$), (2) debridement + fasciotomy ($n = 58$), (3) fasciotomy ($n = 5$), (4) incision and drainage + debridement + fasciotomy + amupation ($n = 2$), and (5) debridement + fasciotomy + amupation ($n = 8$)

[c] Surgical modalities in the fatal group including (1) debridement + fasciotomy ($n = 4$), (2) fasciotomy ($n = 6$), and (3) fasciotomy + amupation ($n = 2$)

[d] The subsequent antibiotics administrated were modified according to the results of the microbiological studies and antimicrobial susceptibility tests

[e] The values were given as mean ± standard deviation

Table 3 Outcomes of fasciotomy for *Vibrio vulnificus*-infected patients with necrotizing fasciitis and those with complicating compartment syndrome during hospitalization

Variable	Group A[a] ($n = 22$)	Group B[b] ($n = 63$)	p Value
Time to fasciotomy after admission, h[c]	8.7 ± 9.1	11.2 ± 13.2	0.236
Time to fasciotomy after admission in fatal group, h[c]	10.8 ± 11.9[d]	15.0 ± 10.4[d]	0.214
Time to fasciotomy after admission in survival group, h[c]	7.5 ± 7.4[e]	10.9 ± 13.5[e]	0.275
p Value	0.764	0.208	
Subsequent amputation needed, n (%)	6[f] (27)	6[g] (10)	0.070
Death, n (%)	8 (36)	4 (6)	0.002

[a] Group A: 22 patients had necrotizing fasciitis confirmed by histopathologic examination with complicating compartment syndrome

[b] Group B: 63 patients had necrotizing fasciitis confirmed by histopathologic examination without compartment syndrome

[c] The values are given as mean ± standard deviation

[d] Eight deaths in group A and four deaths in group B

[e] Fourteen survivors in group A and 59 survivors in group B

[f] Of the six patients, two patients eventually died

[g] All six patients survived

Table 4 Prognostic factors in relation to mortality by multivariate analysis in 119 patients with *Vibrio vulnificus* infections of skin or soft tissue

Variable	OR (95% CI)	*p* Value
Hemorrhagic bullous skin lesions or necrotizing fasciitis (present vs. absent)	10.1 (2.3–45.3)	0.003
Origin of infection (primary septicemia versus wound infections)	4.6 (1.1–20.4)	0.042
ODIN score on admission	3.2 (1.4–7.3)	0.005
WBC count ($>10^4$ cells/mm^3 versus $\leq 10^4$ cells/mm^3)	0.05 (0.01–0.2)	0.0001
Serum albumin (<3.5 mg/dl versus ≥3.5 mg/dl)	14.7 (2.6–83.9)	0.003
Treatment method (surgical intervention plus antibiotics versus antibiotics alone)	0.2 (0.03–0.9)	0.038
Time to surgical treatment after admission <24 h (yes versus no)	0.1 (0.02–0.7)	0.017

CI confidence interval, *OR* odds ratio

condition, may result in skin lesions, or may cause early death. The clinical course of *V. vulnificus* SSTI has been described as having three stages, including inflammatory (the initial) stage, bullous (the second) stage, and gangrenous (the third) stage [14, 20]. From our results, as well as those reported in previous reports [2, 3, 7], *V. vulnificus* infection with hemorrhagic bullous cutaneous lesions or necrotizing fasciitis (progressing to ≥stage 2) is regarded as a significant predictor of mortality. The ability to distinguish *V. vulnificus* infection from common cellulitic lesions early in the course of the infection is a challenge to clinicians, and is crucial to the patient outcome. Because it usually takes 1–3 days for the culture results to become available, the likelihood of *Vibrio* infection is mainly assessed by clinical manifestations and history of the illness, as well as the presence of gram-negative bacilli on a gram-stained smear on admission [17, 29].

V. vulnificus has been reported to be susceptible to several antibiotics, which include erythromycin, tetracycline, cephalosporins, minocycline, extended spectrum penicillins, and quinolones [30–34]. Recently, several groups of investigators [3, 7, 33, 35] disclosed that some combinations of antibiotics were superior to a single agent in killing *V. vulnificus*, and suggested that a combination of cefotaxime plus minocycline or tetracycline, or ceftazidime plus doxycycline should be the treatment of choice for *V. vulnificus* infection. In the present study, the nonsurvivors had a higher proportion of individuals receiving antibiotics alone than did survivors; the majority of the nonsurvivors died early in the course of hospitalization despite having ICU admission and/or receiving an advanced generation antibiotic on admission. Antibiotic treatment alone may be insufficient to cure severe *V. vulnificus* SSTIs. Howard and other investigators [12, 14, 15] have claimed that early surgical intervention, including incision and drainage, debridement, fasciotomy, and even limb amputation (if necessary), play an essential role in eradicating *V. vulnificus* SSTIs. Some infections progressed rapidly to an adverse outcome, even death, before clinicians could initiate surgical interventions. How early surgical intervention could benefit *V. vulnificus* patients with SSTI is less well investigated. We demonstrated that patients receiving treatment with surgery plus antibiotics as well as receiving prompt surgical intervention within 24 h after admission have a more favorable prognosis.

Our study is limited by its retrospective nature, and by the small sample size; however, the fact that *V. vulnificus* SSTI is a sporadic infection makes it difficult to collect a large sample during a finite study period. Our study included 119 *V. vulnificus* patients with SSTI, which makes it one of the largest of its kind [8, 9, 12–15]. Furthermore, we applied the exact method instead of the asymptotic method for logistic regression, and inference from the exact method may be more valid in such a situation [19]. Finally, we must draw the readers' attention to the wide CIs for many of the variables, and point out that such intervals do not rule out important differences between groups.

In conclusion, we have demonstrated by this study that *V. vulnificus*-infected patients with hemorrhagic bullous cutaneous lesions/necrotizing fasciitis, primary septicemia, a greater ODIN score and hypoalbuminemia, and those without leukocytosis have a significant risk of mortality. The severity of the host condition and the origin of the infection also may play an important role in the prognosis of *V. vulnificus* SSTI. Moreover, treatment with surgical intervention plus antibiotics, and the initiation of surgery within 24 h after admission are of great benefit to *V. vulnificus* patients with SSTI.

Acknowledgments We gratefully acknowledge the help of Professor H.-S. Lee, School of Public Health, Chung Shan Medical University, in medical statistics.

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