Prognostic Factors and Antibiotics in *Vibrio vulnificus* Septicemia

Jien-Wei Liu, MD; Ing-Kit Lee, MD; Hung-Jen Tang, MD; Wen-Chien Ko, MD; Hsin-Chun Lee, MD; Yung-Ching Liu, MD; Po-Ren Hsueh, MD; Yin-Ching Chuang, MD

**Background:** Immunocompromised patients with *Vibrio vulnificus* septicemia are at high risk for fatality. When a hemorrhagic bullous necrotic cutaneous lesion (HBNCL) and decreased blood pressure develop, approximately 50% of *V. vulnificus* septicemic patients die within 48 hours. This study aimed to evaluate the risk factor(s) for fatality among patients with *V. vulnificus* septicemia, emphasizing the role of prescribed antimicrobial agents in general and the therapeutic efficacy of the combination of a third-generation cephalosporin and tetracycline or its analogue in particular.

**Methods:** Patients with the diagnosis of *V. vulnificus* infection admitted to 5 large medical centers in Taiwan between 1995 and 2003 were included in this retrospective study. Patients were divided into 2 groups: those with HBNCLs and those without HBNCLs. Patients were further divided into subgroups without fatalities (fatal subgroup) and those without fatalities (nonfatal subgroup).

**Results:** A total of 93 patients participated in the study. In group 1, the fatal subgroup had higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (P = .006) and a higher proportion of shock at arrival at the medical center (P = .015) than the nonfatal subgroup. In group 2, the effect of a first- or second-generation cephalosporin plus an aminoglycoside was negative (P = .01) and that of combined third-generation cephalosporin and tetracycline or its analogue was positive (P < .001); significant differences were found between the fatal and nonfatal subgroups in the APACHE II score (P < .001), number who were in shock at arrival at the medical center (P = .02), delayed surgical intervention (P = .03), and peripheral leukocytosis (P = .03). Shock at arrival at the medical center (odds ratio [OR], 19.25; 95% confidence interval [CI], 1.768-209.54; P = .02) was an independent risk factor for fatality in patients without HBNCLs. Use of a third-generation cephalosporin and tetracycline or its analogue significantly reduced fatality rates in patients with HBNCLs (OR, 0.037; 95% CI, 0.007-0.192; P < .001).

**Conclusion:** Septic shock is a determinant of fatality in patients with *V. vulnificus* septicemia without HBNCLs; our data suggest that the combination of a third-generation cephalosporin and tetracycline or its analogue may be a better choice in antimicrobial treatment of *V. vulnificus* septicemic patients with HBNCLs.

Arch Intern Med. 2006;166:2117-2123

**Author Affiliations:** Division of Infectious Diseases, Chang Gung Memorial Hospital–Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung (Drs J.-W. Liu and I.-K. Lee), Departments of Medicine (Drs Tang and Chuang) and Medical Research (Dr Chuang), Chi-Mei Medical Center, Tainan, Division of Infectious Diseases, National Cheng Kung University Hospital, Tainan (Drs Ko and H.-C. Lee), Section of Infectious Diseases, Kaohsiung Veterans General Hospital, Kaohsiung (Dr Y.-C. Liu), and Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, Taipei (Dr Hsueh), Taiwan.
than 50% of *V. vulnificus* septicemic patients with complicated hemorrhagic bullous necrotic cutaneous lesions (HBNCLs) and decreased blood pressure die, and the median interval from the time of admission to death is approximately 2 days.5,11 A characteristic HBNCL in a patient with *V. vulnificus* septicemia is illustrated in **Figure 1**.

*Most V. vulnificus* isolates are susceptible in vitro to a great variety of antibiotics.15,16 As a result, great arrays of antibiotics have been administered to treat infections caused by *V. vulnificus* based on the in vitro susceptibility testing of this pathogen.5,14 In 1983, Bowdre et al17 reported a study using a murine model of *V. vulnificus* septicemia induced by intraperitoneal inoculation of the culprit bacteria. The results of that study indicated that tetracycline was superior to cefotaxime and thereby the drug of choice for *V. vulnificus* infections. However, later observations in Taiwan suggested that a third-generation cephalosporin might be clinically superior to tetracycline in the treatment of infections due to this pathogen.5,18 Sanford et al19 proposed a combination of tetracycline and a broad-spectrum cephalosporin for the treatment of *V. vulnificus* infections; because the proposal was not based on solid evidence, whether it works in improving the unacceptably high mortality rate in patients with *V. vulnificus* sepsis is uncertain. Ensuing reports16,20 from Taiwan, in which necrotizing soft tissue was created by inoculating the bacteria in the thighs of the animals, have clearly demonstrated the in vitro synergism between cefotaxime and minocycline against *V. vulnificus* and the superiority of these combined antibiotics compared with either agent alone in the treatment of experimental murine *V. vulnificus* infection. Since the late 1990s, it has been common practice in Taiwan to prescribe a third-generation cephalosporin alone or in combination with tetracycline or its analogue for patients with *V. vulnificus* septicemia.8 However, clinical-based evidence that supports the superiority of the combination of a third-generation cephalosporin and tetracycline is not available. To elucidate the important information regarding the clinical efficacies of such combined antibiotics, retrospective analyses of patients with *V. vulnificus* septicemia diagnosed at various centers in Taiwan were performed. The objective of this study was to identify the risk factor(s) for fatality in patients with *V. vulnificus* septicemia, emphasizing the role of prescribed antimicrobial agents in general and the therapeutic efficacy of the combination of a third-generation cephalosporin and tetracycline or its analogue in particular. The information from this series may be valuable in improving treatment of severe *V. vulnificus* infections, thereby reducing the fatality rate.

**METHODS**

**PARTICIPATING HOSPITALS**

Patients with a diagnosis of *V. vulnificus* infection admitted to 5 large medical centers in Taiwan between 1995 and 2003 were included in this retrospective study. These medical centers and their capacities are as follows: Chang Gung Memorial Hospital–Kaohsiung Medical Center (2300 beds), Chi-Mei Medical Center (1325 beds), Kaohsiung Veterans General Hospital (1100 beds), National Cheng Kung University Hospital (1000 beds), and National Taiwan University Hospital (1800 beds). Patients with *V. vulnificus* infections were identified from the records of the clinical microbiology laboratories of the participating medical centers.

**CASE DEFINITION AND BACTERIAL IDENTIFICATION**

All included septicemic patients fulfilled the criteria of sepsis, as previously described.21 Staff members of these clinical microbiology laboratories in Taiwan where *V. vulnificus* infections are endemic were experienced in identifying this pathogen. Each *V. vulnificus* isolate was a halophilic gram-negative rod identified by test results positive for cytochrome oxidase, glucose fermentation, citrate use, indole production, ornithine decarboxylase, and hydroxylase of ortho-nitrophenyl galactoside. The *V. vulnificus* isolates identified by conventional methods were further verified by one of the following automated detection systems: API-20E System (bioMérieux Vitex Inc, Hazelwood, Mo), ID 32 GN System (bioMérieux Vitek Inc), and Vitek 2 ID-GNB identification card (bioMérieux Inc, Durham, NC).

**PATIENT CHARACTERISTICS AND CLASSIFICATION**

The medical records of the included patients were reviewed, and their demographic, clinical, and laboratory information was retrieved and collected for analysis. Most patients with severe *V. vulnificus* septicemia who presented with a distinctive HBNCL have an unequivocal history of recent exposure to saltwater or marine creatures or consumption of raw or undercooked seafood, which is explicitly suggestive of *V. vulnificus* infections, and patients with HBNCLs are subject to rapid clinical deterioration and high risk of fatality.11,12 Therefore, establishing the effective antibiotic regimen for a timely initiation of therapy for *V. vulnificus* sepsis cannot be overemphasized. Surgical debridement may be additionally indicated for patients with HBNCLs when necessary. Based on this rationale, the included *V. vulnificus* septicemic patients were separated into the following groups for further analyses: patients without HBNCLs (group 1) and patients with HBNCLs (group 2).

**STATISTICAL ANALYSES**

Variables in group 1 and group 2 were compared with each other using univariate analyses. To disclose the prognostic factors, including the antimicrobial modality for fatality in each group, pa-
tients in group 1 and group 2 were further divided into a subgroup with fatalities and one without (fatal and nonfatal subgroups, respectively). Within the same group, demographic, clinical, and laboratory data of patients in the fatal and nonfatal subgroups were compared with each other using univariate analyses. In univariate analyses were separately entered into a multiple logistic regression model to identify independent prognostic factor(s) in each group. A 2-tailed \( P < .05 \) was considered statistically significant. All comparisons were performed using the SPSS software package, version 11.0 (SSPS Inc, Chicago, Ill).

### RESULTS

#### PATIENT CHARACTERISTICS AND CLASSIFICATION

In total, 93 \( V \) *vulnificus* septicemic patients were included in the study. Some of these patients had additional specimens obtained from infection sites other than blood (mostly from soft tissue) that were culture positive for this culprit pathogen. The demographic, clinical, and laboratory information of the included patients is summarized in Table 1. Among the included patients, males were predominant (male-female ratio = 67:26).

#### Table 1. Demographic, Clinical, and Laboratory Characteristics of *Vibrio vulnificus* Septicemic Patients With and Without HBNCLs*

| Characteristic                                      | All Patients (N = 93) | Group 1 (Without HBNCLs) (n = 30)† | Group 2 (With HBNCLs) (n = 63)‡ | \( P \) Value | \( \frac{P}{Value} |§ |
|-----------------------------------------------------|-----------------------|------------------------------------|---------------------------------|---------------|---------------|
| Age, y                                               |                       |                                     |                                 | .08           |               |
| Mean (SD)                                           | 62.2 (13.0)           | 58.9 (14.4)                        | 63.7 (12.1)                     |               |               |
| Median (range)                                      | 64 (9-87)             | 59.0 (9-82)                        | 66.0 (34-87)                    |               |               |
| Sex                                                 |                       |                                     |                                 | .03           |               |
| Male                                                | 67 (72)               | 17 (57)                            | 50 (79)                         |               |               |
| Female                                              | 26 (28)               | 13 (43)                            | 13 (21)                         |               |               |
| APACHE II score (n = 70)                            |                       |                                     |                                 | .27           |               |
| Mean (SD)                                           | 16.4 (7.3)            | 14.9 (6.4)                         | 17.1 (7.7)                      |               |               |
| Median (range)                                      | 15 (4-37)             | 12 (7-33)                          | 16 (4-37)                       |               |               |
| Without comorbid disease                            | 6 (6)                 | 2 (7)                              | 4 (6)                           | >.99          |               |
| Underlying disease¶                                  |                       |                                     |                                 |               |               |
| Chronic hepatitis B or C virus                       | 18 (19)               | 9 (30)                             | 9 (14)                          | .09           |               |
| Cirrhosis of the liver                              | 44 (47)               | 22 (73)                            | 22 (35)                         | .001          |               |
| Hepatocellular carcinoma                            | 10 (11)               | 7 (23)                             | 3 (5)                           | .01           |               |
| Diabetes mellitus                                   | 21 (23)               | 7 (23)                             | 14 (22)                         | >.99          |               |
| Corticosteroid use                                  | 23 (25)               | 4 (13)                             | 19 (30)                         | .12           |               |
| Chronic renal insufficiency                         | 12 (13)               | 3 (10)                             | 9 (14)                          | .74           |               |
| Alcoholism                                           | 20 (22)               | 4 (13)                             | 16 (25)                         | .28           |               |
| History of exposure                                 |                       |                                     |                                 |               |               |
| Prior exposure to saltwater or marine creatures      | 34 (37)               | 0                                  | 34 (54)                         | <.001         |               |
| Recent ingestion of raw or undercooked seafood       | 5 (5)                 | 2 (7)                              | 3 (5)                           | .66           |               |
| Septic shock at arrival                             | 54 (58)               | 28 (93)                            | 26 (41)                         | <.001         |               |
| Leukocytosis (leukocyte count >12.0 \times 10^9/L)  | 32 (34)               | 8 (27)                             | 24 (38)                         | .35           |               |
| Leukopenia (leukocyte count <3.5 \times 10^9/L)     | 11 (12)               | 7 (23)                             | 4 (6)                           | .03           |               |
| Hypoalbuminemia (albumin level <3.5 g/dL), No. (%)§  | 48/52 (92)            | 16/17 (94)                         | 32/35 (91)                      | >.99          |               |
| Initial empirical antibiotic(s) therapy within 24 h  |                       |                                     |                                 |               |               |
| Third-generation cephalosporin plus tetracycline or its analogue** | 32 (34) | 2 (7) | 30 (48) | <.001 |
| Third-generation cephalosporin alone or plus other antibiotic***‡‡ | 23 (25) | 8 (27) | 15 (24) | .80 |
| First- or second-generation cephalosporin plus an aminoglycoside | 23 (25) | 17 (57) | 6 (10) | <.001 |
| Other antibiotic combinations‡‡                     | 15 (16)               | 3 (10)                             | 12 (19)                         |               |               |
| Early fatality (≤48 h after arrival)                | 22 (24)               | 3 (10)                             | 19 (30)                         | .04           |               |
| Eventual fatality (≤14 wk after arrival)            | 31 (33)               | 10 (33)                            | 21 (33)                         | >.99          |               |

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; HBNCLs, hemorrhagic bullous necrotic cutaneous lesions.

*Data are number (percentage) of patients unless otherwise indicated.
†Including primary septicemia (17 cases), cellulitis (5 cases), spontaneous bacterial peritonitis (5 cases), ischemic bowel (1 case), liver abscess (1 case), and meningitis (1 case).
‡Including an aminoglycoside and any of the following antibiotics: a penicillin, oxacillin, amoxicillin/clavulanate, ciprofloxacin, and clindamycin.
§Including any of the following antibiotics: amoxicillin, oxacillin, amoxicillin/clavulanate, ciprofloxacin, and clindamycin.
¶One patient might have more than 1 underlying disease.
#Number (percentage) of patients with hypoalbuminemia/number of patients with data available.
**Including any of the following antibiotics: cefazidine, cefotaxime, ceftriaxone, and moxalactam.
††Including any of the following antibiotics: aminoglycoside, penicillin, and clindamycin.
...and most were elderly (mean ± SD age, 62.2 ± 13.0 years) and immunocompromised (94%). Liver cirrhosis (47%), steroid use (25%), and diabetes mellitus (23%) were the 3 leading underlying conditions that rendered these patients immunocompromised. Thirty patients (32%) did not develop HBNCLs (group 1), whereas 63 (68%) did (group 2). Between groups 1 and 2, the differences in septic shock at arrival (11 [37%] vs 44 [70%; \( P = .003 \)) and leukopenia (7 [23%] vs 4 [6%; \( P = .003 \)) were statistically significant. In total, 31 patients died, accounting for an overall mortality rate of 33%. Although the same mortality rate was found in both groups, a significantly higher early (within 48 hours after arrival) mortality rate (30% vs 10%; \( P = .04 \)) was found in group 2.

**PRESCRIBED ANTIBIOTICS**

A variety of antibiotics, including penicillins, cephalosporins, tetracycline and its analogues, aminoglycosides, clindamycin, and ciprofloxacin, were prescribed to these patients. A significantly higher proportion of a combination of a third-generation cephalosporin (ceftriaxone, cefotaxime, or moxalactam) and either tetracycline or its analogue (minocycline, doxycycline, or oxytetracycline) was prescribed for patients in group 2 (48% vs 7%; \( P < .001 \)). Fatalities among *V. vulnificus* septicemic patients who received various antimicrobial treatments are shown in **Figure 2**.

**COMPARISONS BETWEEN THE FATAL AND NONFATAL SUBGROUPS**

Comparisons between the fatal and nonfatal subgroups within group 1 and group 2 are given in **Table 2**. In group 1, the fatal subgroup had significantly higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (median, 21.0 vs 11.0; \( P = .006 \)) and a higher proportion with septic shock at arrival at the medical center (70% vs 20%; \( P = .02 \)); multivariate analysis disclosed that shock at arrival at the medical center (odds ratio [OR], 19.25; 95% confidence interval [CI], 1.768-209.54; \( P = .02 \)) was an independent risk factor for mortality in patients without HBNCLs. Between the fatal and nonfatal subgroups of group 2, significant differences were found in APACHE II score (median, 20.0 vs 12.5; \( P < .001 \)), septic shock at arrival at the medical center (19 [91%] vs 25 [60%]; \( P = .02 \)), delayed (later than 24 hours after arrival) surgical intervention (10 [67%] vs 11 [31%]; \( P = .03 \)), and peripheral leukocytosis (4 [19%] vs 20 [48%]; \( P = .03 \)), as well as use of the combination of a first- or second-generation cephalosporin plus an aminoglycoside (gentamicin, tobramycin, netilmicin, or amikacin) (24% [5/21] vs 2% [1/42]; \( P = .01 \)) and use of a combination of a third-generation cephalosporin and tetracycline or its analogue (14% [3/21] vs 64% [27/42]; \( P < .001 \)); see **Figure 2**. Of note, the effect of a combination of a first- or second-generation cephalosporin and an aminoglycoside was negative. Multivariate analysis disclosed that use of a combination of third-generation cephalosporin and tetracycline or its analogue was an independent factor (OR, 0.037; 95% CI, 0.007-0.192; \( P < .001 \)) for lower mortality in patients with HBNCLs.

**COMMENT**

The predominance of male sex and old age, as well as immunoincompetence, in most *V. vulnificus* septicemic cases in this report is consistent with previously published studies. In agreement with other series, chronic liver diseases in general and cirrhosis of the liver in particular were commonly encountered underlying diseases. Animal studies disclosed that iron could accel-
erate the growth of *V. vulnificus* to reach a lethal level with enhanced cytotoxicity in iron-overload mice. One study\(^{24}\) of *V. vulnificus* in whole blood from patients with hepatoma, cirrhosis of the liver, and a varied degree of chronic hepatic inflammation caused by hepatitis B or hepatitis C virus showed that high serum ferritin levels and low phagocytosis activity of neutrophils were independent predictors of survival of this microbe in blood. Another study\(^{25}\) disclosed that when incubated with live *V. vulnificus*, a variety of toxins that trigger vigorous septic response in the host. The well-known toxins generated by *V. vulnificus* include capsular polysaccharides,\(^{32,33}\) metalloprote-
minocycline, an in vivo study is needed to determine if the combination of cefotaxime and ciprofloxacin is justifiable. The blood supply will be seriously compromised in such a histopathological milieu, and a high tissue antibiotic level can hardly be expected. Large numbers of V. vulnificus embedded in the inflammatory and devitalized soft tissue make the situation worse. The low concentrations of different administered antibiotics that separately reach the ongoing inflammatory site may act synergistically against the V. vulnificus as suggested by in vitro and murine experiments. Previously published experiments disclosed the superiority of combined cefotaxime and minocycline over either one used alone in severe soft tissue infection caused by V. vulnificus, and in these experiments the severity of sepsis was proportional to the quantity of bacteria inoculated. Animals used in the aforementioned experiments were immunocompetent. Our study is consistent with the in vitro and experimental data and suggests that this antibiotic combination remains effective in immunocompromised human hosts. Although in vitro efficiency of cefotaxime and ciprofloxacin was recently reported to be superior to that of cefotaxime and minocycline, an in vivo study is needed to determine if the combination of cefotaxime and ciprofloxacin is justified for clinical trial.

The limitations of this retrospective study are that the performance of surgical debridement depended on an internist’s decision regarding whether a consultation with a surgeon was needed and was in turn at the discretion of the consulted surgeon; as a consequence, the decision regarding debridement or the timing of debridement in the event that an operation was scheduled was not made based on standardized criteria. However, because the in vitro and in vivo experiments clearly demonstrated the superiority of the combination of a third-generation cephalosporin with tetracycline or its analogue over either one used alone in the treatment of severe V. vulnificus infections, which carry a high chance of fatality, it is, based on ethical considerations, no longer feasible to conduct a prospective randomized clinical study to determine the efficacy or superiority of the combination of a third-generation cephalosporin and tetracycline or its analogue. Therefore, the data disclosed in this study are extremely important in determining the definitive treatment of severe V. vulnificus septicemia or the empirical treatment of suspected V. vulnificus septicemia.

In conclusion, septic shock is an independent risk factor for fatality in V. vulnificus septicemic patients without HBNCs; our data suggest that combination of a third-generation cephalosporin and tetracycline or its analogue may be a better choice in antimicrobial treatment for V. vulnificus septicemic patients with HBNCs.

Accepted for Publication: July 13, 2006.

Correspondence: Yin-Ching Chuang, MD, Department of Medical Research, Chi-Mei Medical Center, 901 Chung-Hwa Rd, Yung-Kang City, Tainan, Taiwan (chuangkenneth@hotmail.com).


Financial Disclosure: None reported.

REFERENCES


of depressive disorder for patients receiving prepaid or fee-for-service care: results from the Medical Outcomes Study. JAMA. 1989;262:3298-3302.


**Correction**

In the Original Investigation by Liu et al titled “Prognostic Factors and Antibiotics in *Vibrio vulnificus* Septicemia,” published in the October 23 issue of the ARCHIVES (2006;166:2117-2123), errors appeared in both the text and Figure 2. In the Methods section of the abstract, the second and third sentences should have read as follows: “Patients were divided into 2 groups: those without HBNCLs (group 1) and those with HBNCLs (group 2). Patients were further divided into subgroups with fatalities (fatal subgroup) and those without fatalities (nonfatal subgroup).” In Figure 2B, the P value above the first 2 bars, for comparison of treatment outcomes using a third-generation cephalosporin plus tetracycline or its analogue vs other antibiotics, should have read “P<.001.” The ARCHIVES regrets the errors.