Asian Biomedicine Vol. 6 No. 3 June 2012; 495 - 502 DOI: 10.5372/1905-7415.0603.082

Clinical report

Vibrio vulnificus septicemia in Thailand: A 12-year case series and report of two fatal massive rhabdomyolysis cases

Pattarachai Kiratisin[a], Amonrut Leelaporn[a], Tumtip Sangruchi[b]
[a]Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, [b]Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

Background: *Vibrio vulnificus* infection is prevalent among tropical coastal regions and septicemia due to this bacterium is often rapidly fatal. Our review of *V. vulnificus* cases in Thailand included microbiological and clinical analyses which have rarely been documented. They included a rare complication of rhabdomyolysis which has never been reported in this country.
Objective: We reported a case series of *V. vulnificus* septicemia at a university hospital in Thailand during a 12-year period including two fatal cases with rhabdomylysis due to *V. vulnificus* infection.
Methods: Our case series of patients with *V. vulnificus* septicemia was retrospectively reviewed to determine clinical presentations, risk factors, microbiologic data, hospital courses, treatment, and outcomes.
Results: Twenty-nine patients, predominantly male, were identified. Most patients had underlying cirrhosis or related chronic liver diseases and 20 cases (69%) died rapidly. Cellulitis and necrotizing fasciitis were common presenting symptoms. Consumption of undercooked shellfish may be a local risk factor. Inadequate surgical intervention may be related to a high mortality rate. Two fatal cases with autopsy-proven acute massive rhabdomyolysis were described, which emphasized urgent appropriate management.
Conclusion: This 29-case series identified that *V. vulnificus* septicemia had a high mortality rate. Chronic liver diseases are known underlying factors. Acute massive rhabdomyolysis is very rare as a fatal complication of *V. vulnificus* infection.

Keywords: Cellulitis, cirrhosis, necrotizing fasciitis, rhabdomyolysis, septicemia, *Vibrio vulnificus*

Since the first documented case of *Vibrio vulnificus* in the late 1970s [1], septicemia due to this halophilic bacterium has been increasingly recognized in the warm-climate coastal regions, and could rapidly lead to septic shock with high mortality [2, 3]. Patients with immune-compromised status, particularly who had chronic liver diseases, are common victims and consumption of undercooked or raw seafood is often identified as an important risk factor [4]. Vibrios are also the most common cause of death associated with seafood consumption and infections due to non-foodborne *Vibrio* in the United States [5]. Thailand is among the major tropical coastal areas where a large population resides in marine surroundings. Consumption of undercooked seafood is a common habit in this country. However, the prevalence of *V. vulnificus* septicemia is not truly known and cases have never been thoroughly reviewed. Here, we report a case series with clinical and microbiological analysis of *V. vulnificus* septicemia in Thailand over a 12-year period. We also present two fatal cases with the rare autopsy-proven manifestation of acute massive rhabdomyolysis related to *V. vulnificus* septicemia.

Correspondence to: Pattarachai Kiratisin, MD PhD, Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. E-mail: sipkr@mahidol.ac.th

Materials and methods

Cases were patients who sought treatment at Siriraj Hospital, a 2,400-bed tertiary-care university hospital in Bangkok (Thailand), during 1997-2008. Records of positive blood cultures were reviewed to identify cases. Medical records of patients who had

microbiologically proven *V. vulnificus* septicemia were retrospectively analyzed including demographics, presenting symptoms, underlying diseases, hospital courses, potential risk factors, antimicrobial treatment and outcomes. Isolates of *V. vulnificus* were identified by standard biochemical methods. Antimicrobial susceptibility testing was performed by disk diffusion method according to the recommendation by the Clinical and Laboratory Standards Institute (CLSI) [6]. Fresh muscle samples from amputated limbs and autopsies were frozen in precooled isopentane at liquid nitrogen temperature. The frozen muscle tissues were serial sectioned, followed by staining with Gram's method, hematoxylin and eosin, and a battery of other dye reagents according to standard histopathological methods. Gross and microscopic pathological findings of tissue biopsies and autopsies were recorded. The Chi-square test was used where appropriate to compare the discrete variables that were considered as statistically significant if $p < 0.05$. This study complied with retrospective research ethics and was approved by the Siriraj Institutional Review Board (certificate of approval number Si 053/2009).

Results

During the study period, 29 patients had culture-proven *V. vulnificus* septicemia. The presenting symptoms, underlying illnesses, potential risk factors, antimicrobial management and hospital course of patients are summarized in **Table 1**. Male patients were predominant (75.9%). The median age of patients was 49 years old. Twenty cases (69%) were fatal with no statistical difference between males and females (63.6% versus 85.7%, $p = 0.29$). Chronic liver diseases, particularly cirrhosis, were the most common underlying condition (79.3%). Other underlying conditions included alcoholism (48.3%), chronic hepatitis B virus infection (20.7%) and chronic hepatitis C virus infection (10.3%). A majority of patients (62%) had anemia with average hemoglobin of 10.5 g/dL. Nineteen patients (65.5%) presented to the hospital with a rapid onset of skin and soft tissue inflammation (e.g. necrotizing fasciitis or cellulitis). Seven patients (24.1%) had only general symptoms such as fever and muscle ache and three patients (10.3%) primarily had diarrhea. Seven patients were already in a shock status upon arrival and six of them did not survive. Although another 22 patients were not clinically in shock, 14 of them eventually died. The mortality rates between patients who were initially in shock or not could not be distinguished ($p = 0.29$). Patients who developed cellulitis or necrotizing fasciitis at admission had a mortality rate of 70%, which was not significantly different from a mortality rate among patients who presented to the hospital with other symptoms (66.7%, $p = 0.86$). A history of undercooked seafood consumption was identified in six patients; five had undercooked shellfish and another ate raw shrimp. Two patients were exposed to flooding areas. Most fatal cases died within 24 hours after hospital admission. The organism was *in vitro* susceptible to several antimicrobial agents including ampicillin (94%), cefotaxime (94%), ceftriaxone (100%), chloramphenicol (94%), ciprofloxacin (100%), tetracycline (100%) and trimethoprim-sulfamethoxazole (100%). Extended-spectrum cephalosporins were commonly used for empiric therapy. Among patients who had soft tissue infection, very few received timely surgical debridement. Those patients who survived were mostly switched on antimicrobial therapy with fluoroquinolone or amoxicillin-clavulanate once a causative agent was identified and had no further complications.

Two patients were rapidly fatal and had autopsy-proven massive rhabdomyolysis. Patient 1, a 45-year old Thai male, presented with a history of abruptly progressive swelling and pain at both legs for 10 hours prior to arrival. He also developed chills and dyspnea. He had underlying chronic alcoholism, alcoholic cirrhosis and diabetes mellitus. Upon arrival, he had hypotension, tachycardia, moderate icterus and marked hepatomegaly. Examination of both legs revealed warmness, cyanosis, tenderness with non-pitting edema, no right dorsalis pedis and left popliteal pulses and delayed capillary refill. He denied a recent history of travel, consumption of undercooked seafood, or exposure to aquatic environments. Abnormal laboratory findings included blood urea nitrogen 28 mg/dL, creatinine 5 mg/dL, creatine kinase 18,160 U/L and elevated liver enzymes (AST 387 U/L, ALT 86 U/L, ALP 143 U/L, LDH 1605 U/L). He also had thrombocytopenia (platelets 20,000/mm^3) and a prolonged coagulogram (PT 19.3 seconds, aPTT 62.3 seconds). He was started on ceftriaxone and clindamycin for cellulitis, and later had emergency bilateral knee disarticulation. Both amputated limbs were markedly swollen with purplish red skin. After surgery, he developed profound shock with acute renal failure. Multiple hemorrhagic blebs at various sites (ranging 1-20 cm) were present at neck, arms, trunk

Table 1. Data summary of patients with *V. vulnificus* septicemia.

No.	Sex	Age	Presenting symptoms (days PTA)	Underlying conditions	Identifiable risk (days PTA)	Initial treatment	Specific treatment (days of treatment)	LOS	Outcome
1	M	15	Necrotizing fasciitis at both legs with shock (3)	Beta-thalassemia/HbE post splenectomy	-	Cefotaxime and clindamycin	-	<1	Death
2	M	16	High fever and severe diarrhea (1)	Germinoma of cerebellum	-	Imipenem	-	<1	Death
3	F	25	Ulcer at left leg (3)	Beta-thalassemia/HbE post splenectomy	Exposed to herbal medicine at ulcer site (7)	Ceftriaxone with debridement	Ceftriaxone and cloxacillin (7)	8	Survive
4	M	32	Necrotizing fasciitis with bleb at left leg (3)	Cirrhosis, alcoholism	Exposed to flooding (4)	Ceftriaxone and clindamycin with debridement	Ceftriaxone and ciprofloxacin (14)	44	Survive
5	M	39	Necrotizing fasciitis at both legs with shock (2)	Alcoholic hepatitis, DM	Consumption of undercooked seafood (2)	Ceftriaxone and ciprofloxacin	-	4	Death
6	M	41	Severe diarrhea (1)	Cirrhosis, alcoholism	-	Ceftriaxone	-	<1	Death
7	M	42	Cellulitis at left leg with shock (1)	Alcoholism	-	-	-	<1	Death
8	M	45	Cellulitis at both legs with shock (2)	Cirrhosis, alcoholism, DM	-	Ceftriaxone and clindamycin with both knee disarticulation	-	<1	Death
9	F	54	High fever (1)	Cirrhosis, DM, chronic HBV infection, alcoholism	-	Cefotaxime	-	<1	Death
10	M	47	High fever (1)	Cirrhosis, alcoholism, HCC	-	Ceftriaxone	Ciprofloxacin (14)	9	Survive
11	M	47	Severe pain at both legs with shock (2)	Cirrhosis	-	-	-	2	Death
12	M	48	Necrotizing fasciitis at right foot (3)	Cirrhosis, alcoholism	Consumption of undercooked seafood (3)	Cefotaxime	Ceftazidime and clindamycin (14)	18	Survive
13	F	54	High fever (1)	Cirrhosis, alcoholism	-	Ceftriaxone and metronidazole	-	<1	Death
14	M	48	Necrotizing fasciitis at right leg with shock (1)	Cirrhosis, chronic HBV and HCV infection, alcoholism, HCC	-	Ceftriaxone with debridement	Piperacillin/tazobactam (7)	31	Survive
15	M	48	Cellulitis at both legs (3)	Cirrhosis	Exposed to flooding (3)	Cefotaxime	-	<1	Death
16	F	64	Necrotizing fasciitis at both legs (2)	Cirrhosis, DM, HCC	-	Ceftriaxone and clindamycin	-	<1	Death

Table 1. Data summary of patients with *V. vulnificus* septicemia (continued).

No.	Sex	Age	Presenting symptoms (days PTA)	Underlying conditions	Identifiable risk (days PTA)	Initial treatment	Specific treatment (days of treatment)	LOS	Outcome
17	M	48	High fever and severe diarrhea (3)	Cirrhosis, alcoholism, DM	Consumption of undercooked seafood (3)	Ceftriaxone and piperacillin/tazobactam	-	<1	Death
18	M	50	High fever (1)	Cirrhosis, DM, chronic HCV infection	Consumption of undercooked seafood (1)	Meropenem	Ciprofloxacin (14)	11	Survive
19	M	51	High fever (1)	Cirrhosis, DM, chronic HBV infection, alcoholism	-	Ceftriaxone	Amoxicillin/clavulanate (14)	6	Survive
20	M	51	Cellulitis at both legs (1)	Alcoholic hepatitis	-	Cefepime and ciprofloxacin	-	<1	Death
21	M	51	Necrotizing fasciitis at left leg (1)	Cirrhosis, chronic HCV infection, HCC	-	Ceftazidime and clindamycin with debridement	-	<1	Death
22	M	53	Cellulitis with bleb at left leg (1)	Cirrhosis, chronic HBV infection	Consumption of undercooked seafood (2)	Cefotaxime and clindamycin	Amoxicillin/clavulanate (14)	22	Survive
23	F	56	Cellulitis at both legs with shock (1)	Cirrhosis, alcoholism	-	Ceftriaxone, meropenem and clindamycin	-	<1	Death
24	M	55	Cellulitis at left leg (1)	Cirrhosis, chronic HBV infection	-	Cefotaxime and amikacin	Ofloxacin (14)	18	Survive
25	F	74	Cellulitis at both legs (1)	Cirrhosis, chronic HBV infection	-	-	-	<1	Death
26	F	76	Necrotizing fasciitis at left hand (2)	Cirrhosis, DM	-	Imipenem and vancomycin with debridement	-	5	Death
27	M	59	High fever (1)	Cirrhosis, chronic HCV infection, alcoholism	-	Ceftriaxone and ciprofloxacin	-	<1	Death
28	M	60	Cellulitis with bleb at right leg (3)	Cirrhosis	-	Cefotaxime	-	<1	Death
29	M	72	Cellulitis with bleb at right leg (2)	Cirrhosis, alcoholism	Consumption of undercooked seafood (3)	Ceftazidime	-	<1	Death

Abbreviation: M = male, F = female, PTA = prior to admission, LOS = length of hospital stay, DM = diabetes mellitus, HCC = hepatocellular carcinoma, HBV = hepatitis B virus, HCV = hepatitis C virus

and both thighs as shown in **Figure 1**. He clinically deteriorated and died 16 hours after admission. Pre-mortem blood and bleb fluid cultures grew *V. vulnificus*. Autopsy showed diffuse petechiae. The liver had diffusely regenerating nodules with mixed macronodular and micronodular cirrhosis. Histopathological examination demonstrated microthrombi and multifocal hemorrhage of several organs. Muscle samples from thighs and arms were markedly edematous and had extensive monophasic muscle necrosis (**Figure 2**). Several perimysial vessels were occluded by microthrombi with polymorphonuclear cell infiltration. The cultures of muscle tissues and arteries from both legs also grew *V. vulnificus*.

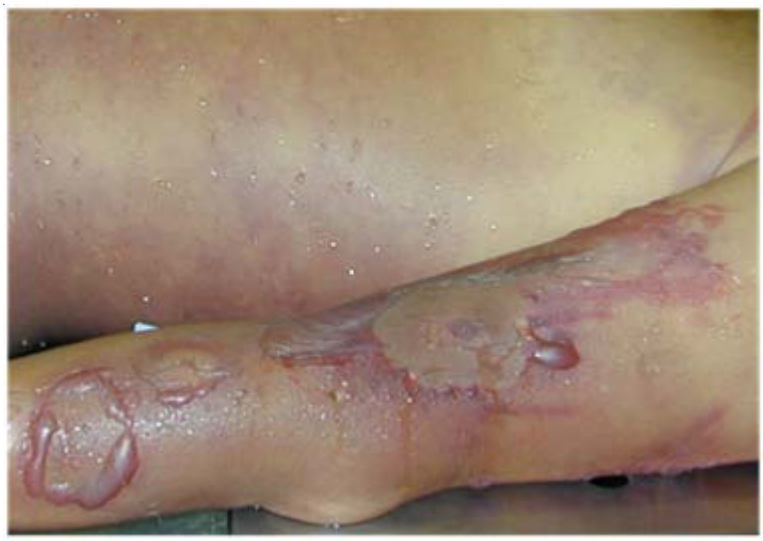

Figure 1. Several hemorrhagic blebs were seen. The trunk and left arm were swollen and purplish discoloration.

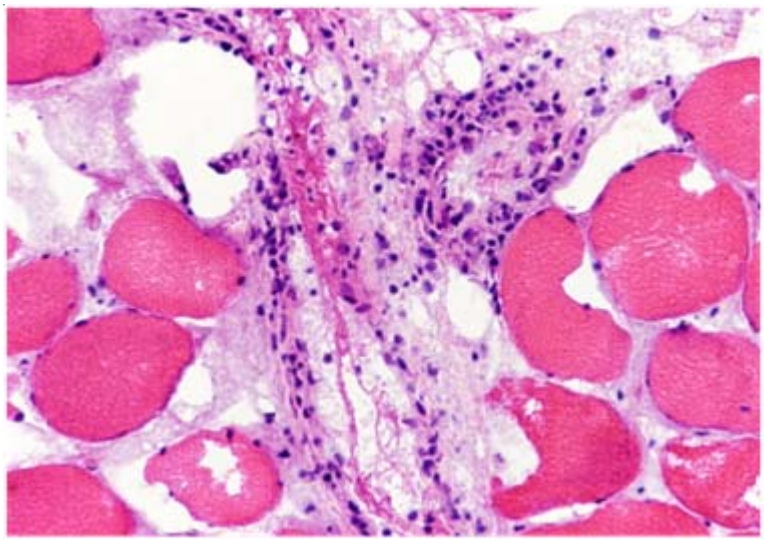

Figure 2. The perimysial vessels were occluded by microthrombi. Polymorphonuclear cell infiltrations were seen in the vicinity of the vessels. Muscle fibers were separated by interstitial edema. Some muscle fibers also had myolysis (haematoxylin and eosin, 400x).

Patient 2, a 47-year old Thai male with underlying cirrhosis developed severe progressive bilateral leg pain and swelling 12 hours prior to hospital arrival. At emergency room, he had altered consciousness, peripheral cyanosis, severe hypotension, swelling of both legs and decrement of both dorsalis pedis and femoral pulses. Laboratory investigations revealed severe hypoglycemia and severe metabolic acidosis. His abnormal blood chemistry results included blood urea nitrogen 31 mg/dL, creatinine 4.3 mg/dL, creatinine kinase 35,040 U/L, creatinine kinase-MB 68.13 U/L and elevated liver enzymes (AST 724 U/L, ALT 137 U/L, GGT 434 U/L, ALP 302 U/L). His serum potassium was 5.6 mEq/L and went up to 11.4 mEq/L prior to his death. He also had thrombocytopenia (platelets 25,000/mm^3) and prolonged coagulogram (PT 47.9 seconds, aPTT >180 seconds). Doppler ultrasound of both legs revealed persistent active femoral to posterior tibial pulses, and thus no arterial occlusion or reperfusion injury. He expired one hour after arrival. Two pre-mortem blood cultures later yielded *V. vulnificus*. The autopsy was performed four hours after his death. The liver and spleen were enlarged. Multiple petechiae were noted at pericardium and myocardium. Abnormal findings included moderate lung congestion with hemorrhage, cirrhotic liver, and multifocal coagulative necrosis with fibrosis of pancreas. The diaphragmatic muscle show acute monophasic muscle necrosis and endomysial edema without microthrombi, polymorphonuclear cells or bacterial clump (**Figure 3**).

Discussion

V. vulnificus, naturally inhabits warm-temperature estuarine water and is notorious for causing limb-threatening and rapidly fatal infections. In Thailand, septicemia due to *V. vulnificus* is not a reportable disease and has never been critically reviewed for case characteristics and risk factors. A 6-year surveillance between 2001 and 2006 by the Thai Ministry of Health among government-based hospitals identified 6-12 cases per year or an average of 0.016 case per 100,000 population per year [7]. *V. vulnificus* septicemia often causes rapid onset of limb swelling and hemorrhagic bullous skin lesions followed by septic shock with deadly disseminated intravascular coagulation. The clinical presentations could be similar to other bacteria such as *Aeromonas hydrophila* [8]. The major routes of *V. vulnificus* infection include ingestion, which often results in self-limited gastroenteritis, and wound contact, which causes soft tissue infection. Secondary invasive skin and soft tissue infection after bacterial ingestion is also common. Infection related to the consumption of undercooked oyster was most commonly reported [4, 9]. We, however, identified in this series that undercooked shellfish, commonly served in Thailand, may also be an important source of this pathogen. The mortality rate of *V. vulnificus* septicemia may be up to 50% or more within a few days despite receiving antimicrobial management [10, 11]. In accordance to our series, 58.6% of patients died within 24 hours after hospital arrival. The mortality rates

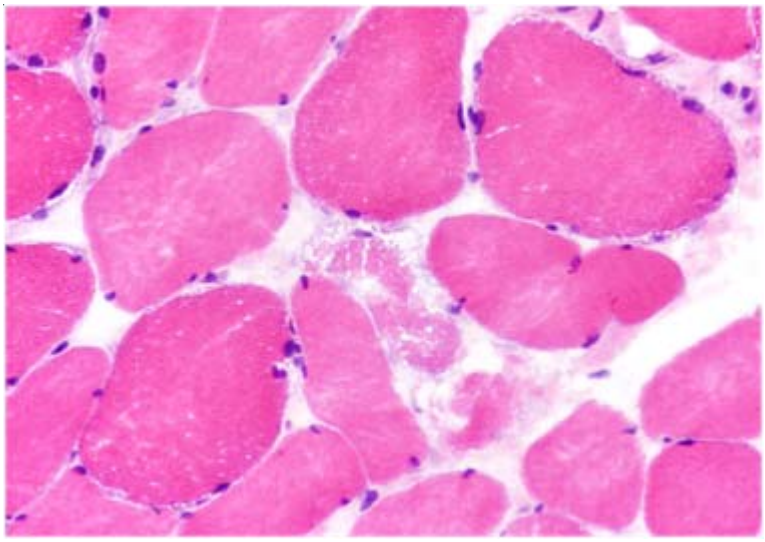

Figure 3. The diaphragmatic muscle demonstrated myolysis without polymorphonuclear cell infiltration. Endomysial edema was seen without microthrombi (haematoxylin and eosin, 400x).

among patients who presented primarily with skin and soft tissue manifestations versus other symptoms were not significantly different. Although male patients usually had a higher prevalence for acquiring *V. vulnificus* infection, we showed in this series that male and female patients had no significant difference in mortality rate. Early onset of shock among these patients was also no predictor of death.

Although *V. vulnificus* infection cases and their severity have been increasingly seen and identified, the pathogenic mechanism remains not completely understood. Multiple factors attributed to *V. vulnificus* pathogenesis include bacterial components and excessive host iron [12, 13]. It has been documented that increased iron levels may enhance bacterial growth rates and deteriorate phagocytic function of neutrophils [14]. Predisposing factors that contribute to a higher mortality are underlying chronic liver diseases and other factors that compromise immunity such as diabetes mellitus, alcoholism and steroid use [2, 4, 10, 11]. Despite being generally susceptible to several antimicrobial agents, treatment of *V. vulnificus* infection usually requires adequate early surgical debridement or fasciotomy of affected tissues or, in severe cases, limb amputation as a life-saving procedure [15, 16]. Two fatal cases in our series developed acute massive rhabdomyolysis, a condition with severe muscle fiber damage, resulting in progressive muscle pain, hyperkalemia, and elevated creatinine kinase. The cellular contents, such as myoglobin, were then released to the bloodstream and broken down to potentially toxic compounds that could injure kidney and result in acute renal failure. This is a rare complication of *V. vulnificus* infection and has only been described for one case, to our knowledge, in the English literature since the year 1990 [17].

Septicemia due to *V. vulnificus* is obviously a life-threatening disease with very high mortality rate as demonstrated in our series. In addition to avoiding consumption of undercooked seafood, populations who are at risk of contracting *V. vulnificus* should be aware that activities with exposure to warm marine environments also appear to be associated with non-foodborne *V. vulnificus* infection [5]. It is therefore important for healthcare personnel, particularly among coastal communities, to recognize this disease, rapidly and accurately identify the causative bacterium and start prompt aggressive treatment to prevent impending mortality due to *V. vulnificus* septicemia. We also recommend early surgical consultation in most cases.

Acknowledgements

The authors thank the Departments of Microbiology and Pathology, and the Division of Medical Records for their kind help, and are supported by the Siriraj Research Development Fund. All the authors declare that there is no conflict of interest in this work.

References

1. Farmer JJ. 3rd *Vibrio* ("*Beneckea*") *vulnificus*, the bacterium associated with sepsis, septicemia, and the sea. Lancet 1979; 2: 903.
2. Hsueh PR, Lin CY, Tang HJ, Lee HC, Liu JW, Liu YC, et al. *Vibrio vulnificus* in Taiwan. Emerg Infect Dis. 2004; 10:1363-8.
3. Liu JW, Lee IK, Tang HJ, Ko WC, Lee HC, Liu YC, et al. Prognostic factors and antibiotics in *Vibrio vulnificus* septicemia. Arch Intern Med. 2006; 166: 2117-23.
4. Haq SM, Dayal HH. Chronic liver disease and consumption of raw oysters: a potentially lethal combination-a review of *Vibrio vulnificus* septicemia. Am J Gastroenterol. 2005; 100:1195-9.
5. Dechet AM, Yu PA, Koram N, Painter J. Nonfoodborne *Vibrio* infections: an important cause of morbidity and mortality in the United States, 1997-2006. Clin Infect Dis. 2008; 46:970-6.
6. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing; eighteenth informational supplement. CLSI document M100-S18. Pensylvania: CLSI; 2008.
7. Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health (Thailand). Weekly Epidemiological Surveillance Report. Ministry of Public Health; 2006.
8. Tsai YH, Hsu RW, Huang TJ, Hsu WH, Huang KC, Li YY, et al. Necrotizing soft-tissue infections and sepsis caused by *Vibrio vulnificus* compared with those caused by *Aeromonas* species. J Bone Joint Surg Am. 2007; 89:631-6.
9. Jones MK, Oliver JD. *Vibrio vulnificus*: disease and pathogenesis. Infect Immun. 2009; 77:1723-33.
10. Chiang SR, Chuang YC. *Vibrio vulnificus* infection: clinical manifestations, pathogenesis, and antimicrobial therapy. J Microbiol Immunol Infect. 2003; 36:81-8.
11. Oliver JD. Wound infections caused by *Vibrio vulnificus* and other marine bacteria. Epidemiol Infect. 2005; 133:383-91.
12. Strom MS, Paranjpye RN. Epidemiology and pathogenesis of *Vibrio vulnificus*. Microbes Infect.

2000; 2: 177-88.
13. Gulig PA, Bourdage KL, Starks AM. Molecular pathogenesis of *Vibrio vulnificus*. J Microbiol. 2005; 43:118-31.
14. Hor LI, Chang TT, Wang ST. Survival of *Vibrio vulnificus* in whole blood from patients with chronic liver diseases: association with phagocytosis by neutrophils and serum ferritin levels. J Infect Dis. 1999; 179:275-8.
15. Halow KD, Harner RC, Fontenelle LJ. Primary skin infections secondary to *Vibrio vulnificus*: the role of operative intervention. J Am Coll Surg. 1996; 183: 329-34.
16. Kuo YL, Shieh SJ, Chiu HY, Lee JW. Necrotizing fasciitis caused by *Vibrio vulnificus*: epidemiology, clinical findings, treatment and prevention. Eur J Clin Microbiol Infect Dis. 2007; 26:785-92.
17. Fernandez A, Justiniani FR. Massive rhabdomyolysis: a rare presentation of primary *Vibrio vulnificus* septicemia. Am J Med. 1990; 89:535-6.