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Case report

A case report of *Vibrio vulnificus* sepsis in a diabetic patient

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ABSTRACT

Vibrio vulnificus is a facultative anaerobic, alkalophilic, halophilic, mesophilic, Gram-negative bacterium that can cause severe wound infection, sepsis and diarrhea. This paper reported a case of 85-year-old male patient infected with *Vibrio vulnificus* due to being stabbed by a sea shrimp. This patient also had diabetes with a long history of alcoholism. Due to bacterial pathogenicity and the patient's underlying diseases, his condition deteriorated rapidly. Based on the rapid diagnosis of *Vibrio vulnificus* using the next-generation sequencing (NGS) technology and blood culture method, as well as the selection of the most effective antibiotics via drug sensitivity test, this patient underwent precise antimicrobial treatment, thorough debridement and drainage within the shortest possible time, and thus the prognosis of this patient was greatly improved. In this paper, we have systematically explored the epidemiology, clinical features, diagnosis and treatment of *Vibrio vulnificus* infection, thus providing a practical reference for the clinicians to quickly identify and treat possible *Vibrio vulnificus* infection in diabetic patients after contacting with sea water or seafood.

1. Introduction

Vibrio vulnificus (V. vulnificus) exists as a free-living bacterium inhabiting in estuarine and marine environments. Wound infections often result from exposure of a wound to brackish water containing *V. vulnificus*, which may occur in the context of handling seafood or due to aquatic recreation. *V. vulnificus* infection has been reported all over the world. In China，it is reported that *V. vulnificus* infection mainly occurs in Hong Kong, Taiwan and inland coastal cities [1–4].

Most cases of *V. vulnificus* infection occur from March to November, especially in summer with a sea surface water temperature of 23–29 °C or an optimal growth temperature of 37 °C [2,5,6]; only a few individual cases occur after exposed to cold sea water [1,4,7]. Three *V. vulnificus* biotypes have been identified: biotype I, biotype II and biotype III [8–10]. However, at present, there is no test or set of tests that can be used to clearly distinguish among three biotypes. These biotypes are correlated with the 5 well-supported *V. vulnificus* phylogenetic groups or lineages in the phylogenetic studies by Roig FJ et al. [11], namely, biotype I strains are found

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primarily in lineage I (but also lineages II, IV, and V); biotype II strains in lineage II; and biotype III strains in lineage III. Infections caused by *V. vulnificus* are most common in patients with chronic underlying medical conditions. In the case of medical conditions that predispose to infection, even minor skin breaks can lead to severe wound infections. Therefore, early diagnosis and treatment are crucial to improve the prognosis of patients.

2. Case presentation

An 85-year-oldman was admitted to our hospital due to skin ulceration in the left upper limb, lethargy and fever for 1 day on August 11, 2022. The patient was stabbed in the left upper limb one day ago while cleaning sea shrimps and then developed drowsiness and

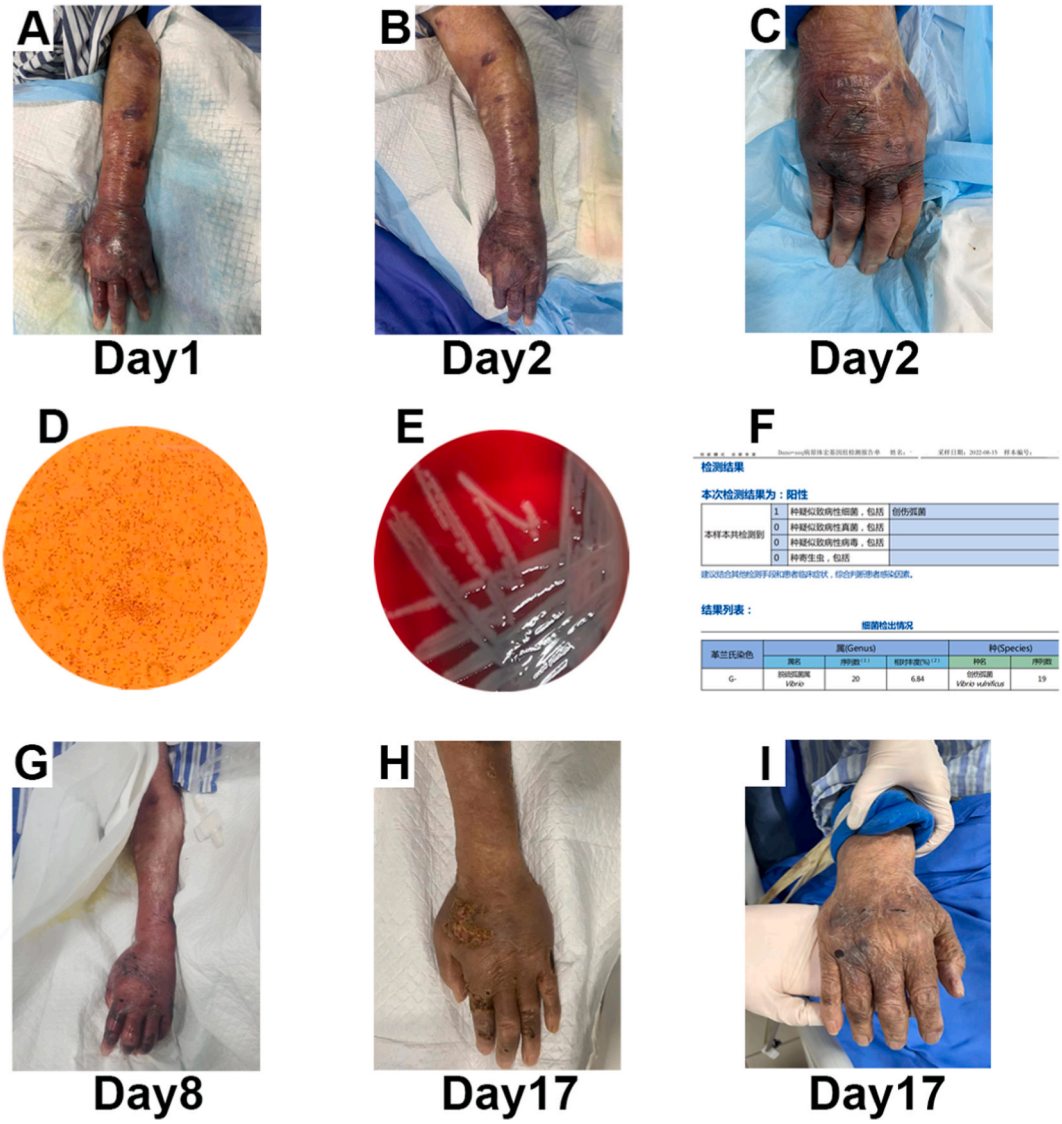

Fig. 1. (A) The left upper limb was swollen, with tension blisters and dark purple ecchymoses at the blister bases in the patient with *V. vulnificus* sepsis on the 1st day of admission. (B) The ulceration and oedema in the left limb of the patient with *V. vulnificus* sepsis were improved slightly after antibiotic treatment and debridement and drainage on the 2nd day of admission. (C) On the 3rd day, the skin on the back of the right hand was swollen, the petechiae with tension blisters were observed, and the skin was incised for decompression and debridement. (D) Direct microscopic examination of bacteria in blood culture of this patient. (E) Colony growth in the blood AGAR plate.
(F) Detection of *V. vulnificus* extracted from blood of this patient using NGS technology. (G) The ulceration and swelling of skin in the left upper limb of the patient with *V. vulnificus* sepsis on the 8th day of admission were alleviated significantly. (H) On the 17th day, the skin in the left upper limb of this patient with *V. vulnificus* sepsis showed no obvious swelling, the ulceration was improved significantly, and granulation tissue was seen at the base of ulceration. (I) The skin lesions on the back of the right hand healed well on the 17th day. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

fever, with a maximum body temperature of 38.8 °C. The skin in the left upper limb was ulcerated, red and swollen, with petechiae and ecchymosis scattered on the skin of the whole body. Laboratory test results were as follows: White blood cell count (WBC) 11.77×10^9/L, procalcitonin (PCT) > 100 ng/mL, and lactate (Lac) 4.28 mmol/L. At first, cultures of blood, secretions and fluid seeping from the broken blisters on the skin in the left upper limb as well as antibiotic sensitivity test were carried out respectively. Considering the fact that the results of the above examinations would usually be obtained 5 days later, and the patient's condition was critical due to uncontrolled infection, we performed metagenomic analysis of pathogens in blood sample using the next-generation sequencing (NGS). Based on the Oxford Nanopore's third-generation single-molecule sequencing platform and combining with efficient genomic nucleic acid extraction and database construction, this detection item was to conduct single-molecule DNA sequencing via detecting the changes in electric current in biological nanopores to predict the base composition. After bioinformatics analysis, the sequencing results were compared with professional medical microbiology database, so as to obtain the species information of all microorganisms in the sample. Then this patient was treated with anti-infection (azithromycin and tienam), rehydration, pressure promotion and anticoagulation. In the next day, a laboratory physician reported that the blood culture was positive for Gram-negative bacilli, thus the patient was admitted to the emergency intensive care unit (EICU) for further diagnosis and treatment of septic shock. This patient had a history of diabetes for more than 20 years and a long-term history of alcoholism. On the 1st day after being admitted to the EICU, this patient was lethargic, with a low spirit; his left hand and forearm had large areas of fluid exudation, local tension blisters, dark purple ecchymoses at the base, slightly cool ends of the five fingers, extensive swelling from the proximal end of the middle segment to the wrist (Fig. 1A), and scattered petechiae and ecchymosis were observed on the skin of the whole body. This patient was treated with meropenem and levofloxacin for anti-infection, norepinephrine and vasopressin for maintaining blood pressure, argatroban for anticoagulation and ulinastatin for inhibiting inflammatory mediators, scavenging free oxygen base, stabilizing lysosomal membrane and improving circulation and organ function, etc. At the same time, multiple incisions were made to decompress and drain the blisters on the skin in the left upper limb, and the operation process was as follows: after the unbroken tension blisters were disinfected with iodophor, the blister fluid was aspirated with a syringe, and the wound was washed with 3% hydrogen peroxide. Gentamicin and magnesium sulfate were externally applied for creating an environment unfavourable for bacterial reproduction and survival and reducing inflammatory response mediators and bacterial toxins. Shortly after admission, this patient had unstable blood pressure and poor oxygenation, thus he immediately underwent tracheal intubation and was connected to a ventilator.

On the 2nd day, the patient still had fever, with slight improvement of the ulceration and oedema in the left limb (Fig. 1B), but the skin on the back of the right hand was swollen, with new petechiae and tension blisters (Fig. 1C), and dark purple skin on the neck appeared as patchy ecchymosis. Infection indicators such as PCT and high-sensitivity C-reactive protein (hCRP) levels were still high. Since the patient had a long-term history of diabetes and alcohol addiction, and a stab wound caused by a sea shrimp before admission, and the blood culture showed positive Gram-negative bacilli, the possibility of *V. vulnificus* infection was considered. Therefore, this patient was treated additionally with doxycycline, which was more sensitive to *V. vulnificus* infection.

On the 3rd day, blood culture identification and antibiotic sensitivity test revealed positivity for *V. vulnificus* (Fig. 1D and E). Under the microscope, *V. vulnificus* appeared as a comma-like, flagellate, spore-free, facultative anaerobic bacterium. The culture medium was inoculated into 5% sheep blood AGAR plate and cultured at 35 °C and 5% CO_2. The colonies were round and slightly convex, moist, gray, opaque and grass-green β-hemolytic colonies, and could grow under both aerobic and anaerobic conditions. After 48 hours of culture, the center of the colony was thickened and protruded, and the secondary edge was concave. On the same day, the results of metagenomic analysis of pathogens in blood sample using NGS indicated *V. vulnificus* with a sequence number of 19 (Fig. 1F). We have uploaded the next-generation sequencing (NGS) data associated with this study into a public repository, NCBI Sequence Read Archive (SRA), (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA940738; accession number: PRJNA940738). BioMerieux automatic microbial identification and drug sensitivity analysis system was used for drug sensitivity test. Since *V. vulnificus* is a kind of Gram-negative bacteria, the drug sensitive card for Gram-negative bacteria was used to conduct drug sensitivity test. The results of in vitro antibiotic sensitivity test of 3 isolates of *V. vulnificus* showed that *V. vulnificus* was sensitive to levofloxacin, ciprofloxacin, meropenem, imipenem, cefzoxime, ceftazidime and cotrimoxazole, and resistant to cefzolin respectively.

On the 4th day, the liver function reexamination revealed an alanine aminotransferase (ALT) level of 2295 U/L and an aspartate aminotransferase (AST) level of 1273 U/L. This patient had no previous history of liver disease, and his liver enzyme levels were normal on admission. At 2 days after the application of doxycycline, the liver enzyme levels were increased sharply, so the possibility of drug-induced liver damage was considered, and the doxycycline was then discontinued.

On the 8th day, the patient's body temperature was normal, and significantly alleviated skin ulceration and redness were observed in both upper limbs (Fig. 1G). Laboratory tests: WBC 9.09×10^9/L; PCT 2.68 ng/mL; Lac 1.74 mmol/L; biochemical test: ALT 281 U/L, AST 44 U/L. Sedation was stopped, and this patient was conscious and passed the spontaneous breathing trial (SBT). This patient was extubated and then underwent noninvasive ventilator-assisted ventilation.

On the 17th day, the patient had no fever, and various vital signs tended to be stable. The swelling and ulceration in the affected limbs were significantly improved, and granulation tissues at the base of ulcers was seen (Fig. 1H and I). The patient's symptoms were improved, and thus he was transferred to a general ward.

3. Discussion

V. vulnificus sepsis is sporadic all year round and has been on the rise in recent years [1], with obvious seasonality and regionality. *V. vulnificus* sepsis mostly occurs in summer, with a seawater temperature between 23 °C and 29 °C [6–8]. This case occurred in August, which is in line with the seasonal characteristics of *V. vulnificus* infection. People usually develop the disease due to consumption of *V. vulnificus*-bearing raw seafood and exposure of limb wounds to brackish water containing bacteria, which can cause severe wound

infection, sepsis, and diarrhea [12–14]. The number of cases with *V. vulnificus* infection in wounds has increased significantly in recent years [1,15], most often in the context of handling seafood or due to aquatic recreation [16,17]. The infected patient in this case had a definite history of being stabbed by a sea shrimp before admission. Infections caused by *V. vulnificus* are commonly seen in patients with chronic underlying diseases, and people with the following conditions are at increased risk of infection with *V. vulnificus* [13,16,18]: ① alcoholic cirrhosis; ② underlying liver disease including cirrhosis and chronic hepatitis; ③ alcoholism without definite liver disease; ④ hereditary haemochromatosis; ⑤ chronic diseases such as diabetes, rheumatoid arthritis, thalassemia major, chronic renal failure and lymphoma. In the case of a medical condition that predisposes to infection, even minor skin breaks can lead to severe wound infections. It is concerned that men have a significantly higher risk of serious infection than women, especially older men [19]. The patient in this case was an elderly man, with a long-term history of diabetes and alcohol addiction, who had low immune function, belonging to the susceptible group of *V. vulnificus*. The reason why the diabetic patients are prone to *V. vulnificus* sepsis is mainly due to diabetes-induced disorder in glucose and lipid metabolism, which leads to reduced protein synthesis, among which, reduced globulin synthesis can decrease the immune function of the body. In such a case, if there is an invasion of *V. vulnificus*, it is very easy to cause suppurative infection. Moreover, a high level of glucose can create a favorable condition for the growth of *V. vulnificus*, which can invade the body, grow rapidly, multiply in large numbers and easily spread, thus promoting bacteremia in a short of time. Therefore, the *V. vulnificus* infection in diabetic patients is often more severe than that in healthy people, and the spread rate is faster. If not timely and effectively treated, *V. vulnificus* infection can often lead to serious complications such as bacteremia and sepsis.

The pathogenic mechanism of *V. vulnificus* is very complex and is related to the following potential factors: ① formation of an antiphagocytic polysaccharide capsule [20]; ② multifunctional-autoprocessing repeats-in-toxin and other toxins [21,22]; ③ availability of iron and iron-acquisition systems, the *V. vulnificus* proliferation depends partially upon the available iron [23–25], and the organism growth in human serum has a direct correlation with the transferrin-iron saturation percentage; if the transferrin-iron saturation is greater than 70%, the bacteria will enter into a nearly exponential growth phase [23].

V. vulnificus infection is divided into three main clinical subtypes: primary sepsis (ie, sepsis without a clear septic source), wound infection, and gastroenteritis [26–28]. This case is characterized by wound infection: the left upper limb of this patient was stabbed by a sea shrimp and thus got infected, which manifested as skin cellulitis in the upper limbs. The disease has rapid onset and progression and will rapidly develop into septic shock and MOF, etc. A report by the US FDA shows that the fatality rate of *V. vulnificus* infection in the United States is as high as 50%. It was reported that in China, 50–70% of patients die of septic shock or MOF within 48 hours [29]. Therefore, early identification, standardized and effective diagnosis and treatment are particularly important to improve the survival rate of patients with *V. vulnificus* infection. In the early stage of *V. vulnificus* infection, the isolation of *V. vulnificus* from blood and wound culture is the gold standard for clinical diagnosis. For patients with presumed *V. vulnificus* sepsis, antibiotic treatment should be started immediately, and aggressive comprehensive treatment in the ICU should be initiated to reduce the incidence of septic shock and MOF. In the selection of antibiotics, the US Center for Disease Control and Prevention recommends third-generation cephalosporins + tetracyclines regimen for the treatment of *V. vulnificus* infection. However, in recent years, A study has shown that *V. vulnificus* has become resistant to various antibiotics to varying degrees worldwide, and there is a significant difference in drug resistance among *V. vulnificus* from different sea areas [30], and there is no unified conclusion on the selection of antimicrobial drugs. Treatment of *V. vulnificus* sepsis should follow the principles of early, adequate and combined use of antibiotics. The patients with severe wound infections require aggressive debridement of necrotic tissues in addition to intravenous antibiotics, because the necrotic tissues provide a breeding ground for the reproduction of *V. vulnificus*. Surgical debridement or amputation is an effective means to remove the infection focus and prevent further spread of infection. In this case, we made multiple incisions to perform decompression and drainage in the swollen upper limbs of this patient in the early stage; firstly, the unbroken tension blisters were sterilized with iodophor, and a syringe was used to aspirate the blister fluid (pale bloody exudate); then the wound was washed with 3% hydrogen peroxide; eventually the wound healed well, and amputation was avoided. Hydrogen peroxide is a strong oxidizing disinfectant for external use, which can oxidize the nucleic acids, proteins, lipids, normal cells and microorganisms. A study reported that exogenous administration of hydrogen peroxide at a concentration of 100 μmol/L can significantly increase the expression of TNF-α in human middle ear epithelial cells [31]; it has been reported that 3% hydrogen peroxide is perfused into the stomach of mice, which significantly increases the expressions of TNF-α, IL-1β and IL-5 in the jejunum tissue [32]; when the intracellular transport of hydrogen peroxide is inhibited, the activation of nuclear factor κB signaling pathway in KC is blocked [33]. These findings elucidate the important role of hydrogen peroxide in promoting inflammatory responses. It was firstly reported in 2015 that V. *vulnificus* is highly sensitive to hydrogen peroxide and can be lysed by hydrogen peroxide.

The clinical manifestations of *V. vulnificus* infection are atypical and easily misdiagnosed. This disease progresses rapidly, with a high mortality rate. Rapid identification of skin damage and early and timely treatment are the keys for successful treatment of this disease. In this case, rapid aetiological diagnosis, positive blood culture and identification of antibiotic susceptibility helped us in implementing precise antimicrobial therapy, thorough debridement and drainage in the shortest possible time, thus the patient's prognosis was greatly improved. We can gain valuable experiences from treatment of this case, in addition to timely treatment and accurate antibiotic selection, the most important thing is that thorough debridement should be performed. Clinical workers should strengthen the cognition of *V. vulnificus*, pay attention to the medical history of the patient and susceptible population such as patients with cirrhosis, diabetes and chronic kidney failure. For the patients with symptoms such as fever and low blood pressure after contacting with sea water, seafood, possible *V. vulnificus* infection should be considered, diagnosed and treated as soon as possible.

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Ethics approval

Written informed consent was obtained from this patient for publication of this case report.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e16521.

References

[1] K.C. Huang, H.H. Weng, T.Y. Yang, T.S. Chang, T.W. Huang, M.S. Lee, Distribution of fatal Vibrio vulnificus necrotizing skin and soft-tissue infections: a systematic review and meta-analysis, Medicine 95 (5) (2016), e2627, https://doi.org/10.1097/MD.0000000000002627.
[2] L. Zhongqiu, L. Caijiao, L. Bingxi, Epidemiological characteristics of 12 cases of Vibrio vulnificus sepsis, China Emerg. Med. 27 (8) (2007) 690–692.
[3] R.L. Shapiro, S. Altekruse, L. Hutwagner, R. Bishop, R. Hammond, S. Wilson, B. Ray, S. Thompson, R.V. Tauxe, P.M. Griffin, The role of Gulf Coast oysters harvested in warmer months in Vibrio vulnificus infections in the United States, 1988-1996. Vibrio Working Group, J. Infect. Dis. 178 (3) (1998) 752–759, https://doi.org/10.1086/515367.
[4] H. Oishi, Y. Ura, S. Mitsumizo, M. Nakashima, A collective review of Vibrio vulnificus infection in Japan, Kansenshogaku Zasshi 80 (6) (2006) 680–689, https://doi.org/10.11150/kansenshogakuzasshi1970.80.680.
[5] L. Zhongqiu, Z. Changlin, H. Weijia, etc. Clinical and epidemiological characteristics of Vibrio vulnificus sepsis, Chin. J. Epidemiol. 24 (10) (2003) 900.
[6] H. Zhao, L. Xu, H. Dong, J. Hu, H. Gao, M. Yang, X. Zhang, X. Chen, J. Fan, W. Ma, Correlations between clinical features and mortality in patients with Vibrio vulnificus infection, PLoS One 10 (8) (2015), e0136019, https://doi.org/10.1371/journal.pone.0136019.
[7] S. Saha, M. Chadha, A. Al Mamun, M. Rahman, K. Sturm-Ramirez, M. Chittaganpitch, S. Pattamadilok, S.J. Olsen, O.D. Sampurno, V. Setiawaty, K.N. Pangesti, G. Samaan, S. Archkhawongs, P. Vongphrachanh, D. Phonekeo, A. Corwin, S. Touch, P. Buchy, N. Chea, P. Kitsutani, Q. Mai le, V.D. Thiem, R. Lin, C. Low, C. C. Kheong, N. Ismail, M.A. Yusof, A. Tandoc 3rd, V. Roque Jr., A. Mishra, A.C. Moen, M.A. Widdowson, J. Partridge, R.B. Lal, Influenza seasonality and vaccination timing in tropical and subtropical areas of southern and south-eastern Asia, Bull. World Health Organ. 92 (5) (2014) 318–330, https://doi.org/10.2471/BLT.13.124412.
[8] N. Bisharat, D.I. Cohen, R.M. Harding, D. Falush, D.W. Crook, T. Peto, M.C. Maiden, Hybrid Vibrio vulnificus, Emerg. Infect. Dis. 11 (1) (2005) 30–35, https://doi.org/10.3201/eid1101.040440.
[9] N. Bisharat, V. Agmon, R. Finkelstein, R. Raz, G. Ben-Dror, L. Lerner, S. Soboh, R. Colodner, D.N. Cameron, D.L. Wykstra, D.L. Swerdlow, J.J. Farmer 3rd, Clinical, epidemiological, and microbiological features of Vibrio vulnificus biogroup 3 causing outbreaks of wound infection and bacteraemia in Israel. Israel Vibrio Study Group, Lancet 354 (9188) (1999) 1421–1424, https://doi.org/10.1016/s0140-6736(99)02471-x.
[10] Y.Y. Broza, Y. Danin-Poleg, L. Lerner, L. Valinsky, M. Broza, Y. Kashi, Epidemiologic study of Vibrio vulnificus infections by using variable number tandem repeats, Emerg. Infect. Dis. 15 (8) (2009) 1282–1285, https://doi.org/10.3201/eid1508.080839.
[11] F.J. Roig, F. González-Candelas, E. Sanjuán, B. Fouz, E.J. Feil, C. Llorens, C. Baker-Austin, J.D. Oliver, Y. Danin-Poleg, C.J. Gibas, Y. Kashi, P.A. Gulig, S. S. Morrison, C. Amaro, Phylogeny of *Vibrio vulnificus* from the analysis of the core-genome: implications for intra-species taxonomy, Front. Microbiol. 8 (5 Jan. 2018) 2613, https://doi.org/10.3389/fmicb.2017.02613.
[12] J.G. Morris Jr., R.E. Black, Cholera and other vibrioses in the United States, N. Engl. J. Med. 312 (6) (1985) 343–350, https://doi.org/10.1056/NEJM198502073120604.
[13] P.A. Blake, M.H. Merson, R.E. Weaver, D.G. Hollis, P.C. Heublein, Disease caused by a marine Vibrio. Clinical characteristics and epidemiology, N. Engl. J. Med. 300 (1) (1979) 1–5, https://doi.org/10.1056/NEJM197901043000101.
[14] N.A. Daniels, Vibrio vulnificus oysters: pearls and perils, Clin. Infect. Dis. 52 (6) (2011) 788–792, https://doi.org/10.1093/cid/ciq251.
[15] C. Baker-Austin, J.D. Oliver, Vibrio vulnificus: new insights into a deadly opportunistic pathogen, Environ. Microbiol. 20 (2) (2018) 423–430, https://doi.org/10.1111/1462-2920.13955.
[16] A.M. Dechet, P.A. Yu, N. Koram, J. Painter, Nonfoodborne Vibrio infections: an important cause of morbidity and mortality in the United States, 1997-2006, Clin. Infect. Dis. 46 (7) (2008) 970–976, https://doi.org/10.1086/529148.
[17] J.S. Yoder, M.C. Hlavsa, G.F. Craun, V. Hill, V. Roberts, P.A. Yu, L.A. Hicks, N.T. Alexander, R.L. Calderon, S.L. Roy, M.J. Beach, Centers for Disease Control and Prevention (CDC), Surveillance for waterborne disease and outbreaks associated with recreational water use and other aquatic facility-associated health events–United States, 2005-2006, MMWR Surveill. Summ. 57 (9) (2008) 1–29. PMID: 18784642.
[18] C.O. Tacket, F. Brenner, P.A. Blake, Clinical features and an epidemiological study of Vibrio vulnificus infections, J. Infect. Dis. 149 (4) (1984) 558–561, https://doi.org/10.1093/infdis/149.4.558.

[19] S.H. Lee, B.H. Chung, W.C. Lee, Retrospective analysis of epidemiological aspects of Vibrio vulnificus infections in Korea in 2001-2010, Jpn. J. Infect. Dis. 66 (4) (2013) 331–333, https://doi.org/10.7883/yoken.66.331.
[20] A.C. Wright, L.M. Simpson, J.D. Oliver, J.G. Morris Jr., Phenotypic evaluation of acapsular transposon mutants of Vibrio vulnificus, Infect. Immun. 58 (6) (1990) 1769–1773, https://doi.org/10.1128/iai.58.6.1769-1773.1990.
[21] K.J. Chung, E.J. Cho, M.K. Kim, Y.R. Kim, S.H. Kim, H.Y. Yang, K.C. Chung, S.E. Lee, J.H. Rhee, H.E. Choy, T.H. Lee, RtxA1-induced expression of the small GTPase Rac2 plays a key role in the pathogenicity of Vibrio vulnificus, J. Infect. Dis. 201 (1) (2010) 97–105, https://doi.org/10.1086/648612.
[22] C. Baker-Austin, J.D. Oliver, Vibrio vulnificus: new insights into a deadly opportunistic pathogen, Environ. Microbiol. 20 (2) (2018) 423–430, https://doi.org/10.1111/1462-2920.13955.
[23] C.E. Brennt, A.C. Wright, S.K. Dutta, J.G. Morris Jr., Growth of Vibrio vulnificus in serum from alcoholics: association with high transferrin iron saturation, J. Infect. Dis. 164 (5) (1991) 1030–1032, https://doi.org/10.1093/infdis/164.5.1030.
[24] C.M. Kim, R.Y. Park, M.H. Choi, H.Y. Sun, S.H. Shin, Ferrophilic characteristics of Vibrio vulnificus and potential usefulness of iron chelation therapy, J. Infect. Dis. 195 (1) (2007) 90–98, https://doi.org/10.1086/509822.
[25] C.M. Kim, Y.J. Park, S.H. Shin, A widespread deferoxamine-mediated iron-uptake system in Vibrio vulnificus, J. Infect. Dis. 196 (10) (2007) 1537–1545, https://doi.org/10.1086/523108.
[26] R.L. Shapiro, S. Altekruse, L. Hutwagner, R. Bishop, R. Hammond, S. Wilson, B. Ray, S. Thompson, R.V. Tauxe, P.M. Griffin, The role of Gulf Coast oysters harvested in warmer months in Vibrio vulnificus infections in the United States, 1988-1996. Vibrio Working Group, J. Infect. Dis. 178 (3) (1998) 752–759, https://doi.org/10.1086/515367.
[27] J. Humphrey, L. Richey, A case series of Vibrio vulnificus infections in New Orleans, Louisiana, J. La. State Med. Soc. 164 (4) (2012) 197–201, 203-4. PMID: 22953457.
[28] L. Zhongqiu, L. Caijiao, H. Guangliang, Epidemiological characteristics and clinical diagnosis and treatment of 34 patients with Vibrio vulnificus sepsis, Chin. J. Emerg. Med. 18 (7) (2009) 732–736.
[29] L. Zhongqiu, H. Guangliang, Advances in diagnosis and treatment of Vibrio vulnificus sepsis, J. Clin. Surg. 19 (3) (2011) 159–163.
[30] P. Serratore, E. Zavatta, E. Fiocchi, E. Serafini, A. Serraino, F. Giacometti, G. Bignami, Preliminary study on the antimicrobial susceptibility pattern related to the genotype of *Vibrio vulnificus* strains isolated in the north-western Adriatic Sea coastal area, Ital. J. Food Saf. 6 (4) (2017) 6843, https://doi.org/10.4081/ijfs.2017.6843.
[31] J.J. Song, H.W. Lim, K. Kim, K.M. Kim, S. Cho, S.W. Chae, Effect of caffeic acid phenethyl ester (CAPE) on H_2O_2 induced oxidative and inflammatory responses in human middle ear epithelial cells, Int. J. Pediatr. Otorhinolaryngol. 76 (5) (2012) 675–679, https://doi.org/10.1016/j.ijporl.2012.01.041.
[32] Z. Cui, J. Yin, L. Wang, L. He, Y. Yin, T. Li, Effects of pro-inflammatory cytokines and antioxidants expression in the jejunum of mice induced by hydrogen peroxide, Int. Immunopharm. 31 (2016) 9–14, https://doi.org/10.1016/j.intimp.2015.12.012.
[33] M. Hara-Chikuma, H. Satooka, S. Watanabe, T. Honda, Y. Miyachi, T. Watanabe, A.S. Verkman, Aquaporin-3-mediated hydrogen peroxide transport is required for NF-κB signalling in keratinocytes and development of psoriasis, Nat. Commun. 6 (2015) 7454, https://doi.org/10.1038/ncomms8454.