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CASE REPORT

Non-O1, Non-O139 *Vibrio cholerae* (NOVC) Bacteremia: Case Report and Literature Review, 2015–2019

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Abstract: Non-O1, non-O139 *Vibrio cholerae* (NOVC) does not agglutinate with O1 and O139 antisera and can cause intestinal and extraintestinal infections in immunocompromised individuals. NOVC bacteremia has the highest mortality among NOVC infections, and the number of reports has increased in recent years. Nevertheless, some clinicians are poorly informed about this disease. Herein, we describe a documented case of NOVC bacteremia in a male patient with impaired liver function. Blood cultures revealed the presence of *V. cholerae*, but this strain showed self-coagulation on the serum agglutination test. To our knowledge, this phenomenon is unreported among cases of NOVC infections. This pathogen was finally confirmed as NOVC via PCR. Because the patient worked as a garbage transporter, he was likely infected after contact with contaminated water through a foot wound. The patient developed septic shock shortly after admission and ultimately died from the illness. This paper reviews 23 cases of NOVC bacteremia from 2015 to 2019. To improve the accuracy of identifying NOVC and analyze its virulence factors, relevant detection methods were reviewed and analyzed.

Keywords: bacteremia, non-O1/non-O139 *Vibrio cholerae*, *V. cholerae*, virulence factors

Introduction

Vibrio cholerae (*V. cholerae*) is a halophilic, facultative, anaerobic, gram-negative, comma-shaped bacillus that is ubiquitous in aquatic and estuarine environments.[1] The non-O1, non-O139 *V. cholerae* (NOVC) strains cannot cause cholera because they do not produce the cholera toxins; however, recent literature has reported that NOVC causes gastroenteritis and some extraintestinal infections.[2] NOVC bacteremia has the highest mortality rates among NOVC infections and usually occurs in immunocompromised patients and those with underlying liver disease.[3] However, the epidemiology, clinical manifestations and pathogenesis of NOVC bacteremia are unclear. Currently, no definitive guidelines exist for treating NOVC bacteremia.[4] Therefore, clinicians should increase their knowledge of NOVC bacteremia to promptly diagnose and treat patients.

Here, we present a case of NOVC bacteremia in a patient with impaired liver function and summarize the available literature on NOVC bacteremia. Using the search terms: "non-O1", "non-O139" and "Vibrio cholera" in PubMed from January 2015 to October 2019, we found 87 articles related to NOVC. Based on the title or abstract, 20 articles reported cases of NOVC-associated bacteremia; 18 of these articles were in English and were eventually included.

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Case Report

A 47-year-old man was admitted to the emergency department for painful swelling of the face and right lower limb for 2 days. He did not significantly improve after anti-allergy treatment. Later, he appeared listless, and his family found large ecchymosis and blisters on his lower limbs. On the way to our hospital, the patient fell into a coma. The patient was mute and had a past medical history of impaired liver function. He worked as a garbage transporter.

On arrival, his body temperature was 38.1°C, heart rate was 78 beats per minute, blood pressure was 88/60 mmHg and oxygen saturation was 98% in room air. His physical examination revealed jaundice of the sclera and skin mucous membranes across his entire body except for the swelling and ecchymosis of both lower limbs. Additionally, a round black scab of ~0.5 cm was observed on the right foot. His blood glucose was only 0.9 mmol/L at admission.

No obvious abnormality was found on the computed tomography of the head or the arteriovenous ultrasonography of the lower extremities. Laboratory tests (Table 1) revealed a normal white blood cell count but with an increased neutrophil percentage (86.7%) and elevated procalcitonin (PCT) level (61.0 ng/mL). The alanine transaminase (ALT), aspartate transaminase (AST), urea, creatinine and pro-B-type natriuretic peptide (pro-BNP; 7248.5 pg/mL) were significantly increased. The prothrombin time and activated partial thromboplastin time (APTT) showed a prolonged coagulation function. Systemic infection was suspected based on the patient's clinical manifestations and laboratory examinations. Blood cultures were immediately sent for microbiological examination (two sets each in aerobic and anaerobic bottles) using an automated blood culture system (BACTEC FX, BD Becton, Dickinson and Company). Empirical parenteral treatment was initiated with piperacillin tazobactam (4.5 g every 6 h) and vancomycin (1 g every 12 h).

After positive intravenous fluid and supportive therapy, the patient regained consciousness. However, 6 hours after admission, the patient's clinical status again deteriorated. Arterial blood analysis showed severe metabolic acidosis. A retest of the blood (Table 1) revealed leukopenia, erythrocytopenia, thrombopenia and elevated liver enzymes. In addition, his APTT was significantly prolonged, and his fibrinogen showed a decreased coagulation function. During hospitalization, his urine volume was only 5 mL, and his blood potassium (6.47 mmol/L) was significantly increased. The patient ultimately died despite endotracheal intubation and cardiopulmonary resuscitation.

After 10 h of blood culture, gram-negative curved or straight rods were detected from all four blood culture bottles. Hemolytic, oxidase-positive colonies grew on the blood agar after 24 h of incubation (Figure 1). Blood culturing on thiosulfate-citrate-bile salt-sucrose agar revealed large yellow colonies. The strain was identified as *V. cholerae* (Vitek 2 Compact: 98%, biotype profile number: 0027601151502221) and subsequently confirmed

Table 1 Changes of Main Laboratory Results at Admission and After 6 Hours of Admission

		On Admission	After 6 Hours	Normal Range
Blood routine test	WBC	6.35	0.83	(3.50–9.50) $\times 10^9$/L
	RBC	4.31	2.33	(4.30–5.80) $\times 10^{12}$/L
	HGB	158	82	(130–175) g/L
	PLT	29	5	(125–350) $\times 10^9$/L
Liver and renal function	ALT	243.4	196.6	(13–69) U/L
	AST	688.1	1069.1	(0–45) U/L
	Urea	9.70	7.36	(2.1–7.2) mmol/L
	CREA	247.3	246.6	(44–132) umol/L
Blood coagulation function	PT	26.5	52.0	(8.0–14.0) s
	PT-INR	2.36	4.73	
	APTT	60.5	>170	(25.0–31.3) s
	TT	21.5	23.7	(15–21) s
	FIB	1.94	0.86	(2.0–4.0) g/L

Abbreviations: WBC, white blood cell count; RBC, red blood cell count; HGB, hemoglobin; PLT, platelet count; ALT, alanine transaminase; AST, aspartate transaminase; CREA, creatinine; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen.

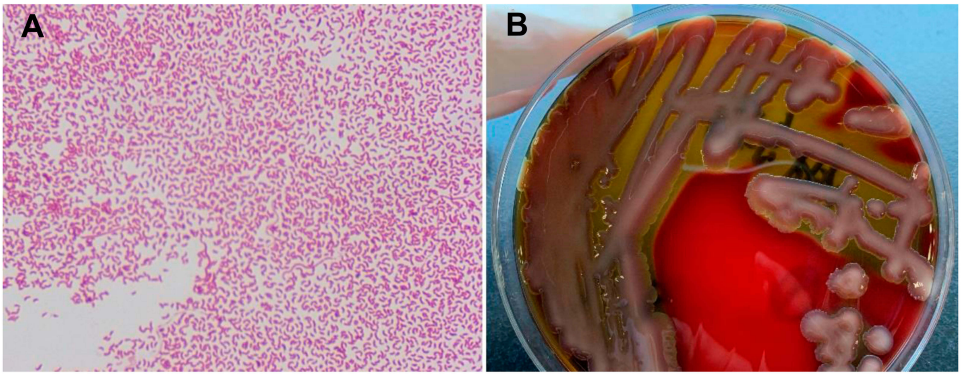

Figure 1 (**A**) Gram stain showing Gram-negative curved bacilli (×1000). (**B**) Blood agar showing β-hemolytic colonies.

by matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF-MS, BioMerieux) with a 99% confidence level.

A serum agglutination test was performed to classify the serotype of the pathogen. The pathogen showed self-coagulation in normal saline, which gradually weakened after several passages. The strain showed no agglutination with the O1 or O139 antisera; thus, NOVC was suspected and later confirmed via PCR by the Microbiology Laboratory of Jiangsu Provincial Center for Disease Control and Prevention. Antimicrobial susceptibility of the strain was analyzed using disk diffusion tests (Oxoid) on Muller-Hinton agar (BioMerieux) as per the Clinical and Laboratory Standards Institute guidelines. The test results showed that the strain was susceptible to penicillins, cephems, carbapenems, aminoglycosides, quinolones, and trimethoprim-sulfamethoxazole.

Discussion

Epidemiology

NOVC bacteria are usually nonpathogenic or asymptomatic colonizers in humans.[3] However, cases of NOVC-associated infections continue to be reported worldwide.[5] NOVC causes gastroenteritis[6] and is related to extraintestinal infections, including skin and wound infections, otitis, bacteremia, biliary tract and urinary tract infections, pneumonia, peritonitis and meningitis.[4,7,8] Statistical analysis of 83 NOVC-infected patients in Taiwan from 2009–2014 showed that gastroenteritis was the most common illness due to NOVC (accounting for 54.2%), followed by biliary tract infection (14.5%) and primary bacteremia (13.3%).[9] Gastroenteritis can be mild to severe for both sporadic and break cases, but the prognosis of all cases is favorable. Although NOVC bacteremia is uncommon, its mortality is the highest among infections caused by this strain.[1] Therefore, the case reports and research progress made in recent years must be systematically summarized.

Our review included 23 cases of NOVC bacteremia described in 18 reports from 2015–2019 (Table 2).[1–5,7,10-21] The male-to-female ratio was 3.6:1, and the median age was 56 years. The youngest patient developed this disease at only 3 days of age, and the oldest patient was 83 years old. Of the patients with NOVC bacteremia, 39.1% (9/23) died.

Risk Factors

A literature review showed that most patients had an underlying disease (91.3%, 21/23), and a few had multiple predisposing conditions. The most frequently documented risk factors were liver cirrhosis or hepatitis, diabetes mellitus, malignancy, and biliary tract disease. Other risk factors included alcohol abuse, localized cellulitis, prolonged corticosteroid therapy, and pulmonary diseases such as chronic obstructive pulmonary disease. These risk factors indicated that immunocompromised individuals were more susceptible to NOVC.[12] The patient in our study had a degree of hepatic impairment, which was in accordance with the susceptibility factors of NOVC infection. The review showed that middle-aged men were at high risk for NOVC infection. Abdelhafiz et al[20] noted that NOVC should be included in the differential diagnoses of invasive infections.

Clinical Manifestations

The clinical manifestations of bacteremic patients varied. The disease may present as hypothermia or hyperthermia, chills, diarrhea, abdominal pain, vomiting, jaundice, and inappetence.[18] Swelling or pain in the lower limbs were the first symptoms in some patients, as in the case we reported. A retrospective study found that patients who developed septic shock had a significantly increased risk of death.[2]

Table 2 Reports of Bacteremia Caused by NOVC in Recent Five Years

Year	Country	Age (Years)	Gender	Risk Factors	Mode of Transmission	Clinical Presentation	Treatment	Clinical Outcome	Ref. no.
2015	USA	54	M	Multiple myeloma	A trip to Haiti	Diffuse abdominal pain, nausea, vomiting, and diarrhea	Piperacillin-tazobactam, levofloxacin	Death	[10]
2015	France	70	M	Hepatitis A	Seafood consumption	Fever, watery diarrhea, abdominal pain, vomiting and dizziness	Ceftriaxone, ciprofloxacin	Recover	[1]
2015	China	11 days	F	None	Contaminated food and paraphernalia (most likely)	Fever, lethargy, and a refusal to feed	Sulbenicillin, metronidazole	Recover	[11]
2016	India	6.5	F	Burkitt's lymphoma	Not found	Abdominal pain, vomiting	Cefepime-tazobactam, teicoplanin, ciprofloxacin	Death	[12]
2016	India	56	F	Diabetes mellitus	Not found	Chills, swelling of the right lower leg	Piperacillin-tazobactam, imipenem	Death	
2016	India	72	M	Not mentioned	Not found	Fever, chills, nausea, dizziness	Not mentioned	Recover	
2016	Netherlands	50	M	Tuberculosis, COPD	Seafood consumption	Hypothermic, right ankle pain	Ciprofloxacin, cefotaxime	Death	[13]
2016	Netherlands	60	M	Heart disease, diabetes mellitus	Seafood consumption	Diarrhea, fever, mild jaundice	Ciprofloxacin	Recover	
2016	Netherlands	70	M	Heart failure, chronic cholangitis	Not found	Fever, coughing, dyspnea, dizziness, and decreased appetite	Ceftriaxone, gentamicin, amoxicillin-clavulanic acid	Recover	
2016	Austria	80	M	Ichthyosis cutis, several episodes of cellulitis	Contact with contaminated water through a wound	Swelling and pain in left lower leg, fever, dyspnea	Piperacillin-tazobactam, clindamycin, doxycycline	Death	[14]
2016	Greece	43	M	Liver cirrhosis, alcohol abuse	Not certain	Poor nutrition, icteric sclera, ascites, diffuse bleeding of the oral mucosa and bullous lesions of extremities.	Cefotaxime, metronidazole	Death	[15]
2016	Pakistan	3 days	M	Very low birth weight	Goat's milk	Fever and chills	Not mentioned	Death	[16]
2017	Canada	66	M	Biliary obstruction, benign pancreatic tumor	Seafood consumption	Epigastric pain, emesis and fever	Ciprofloxacin, doxycycline	Recover	[17]
2017	Saudi Arabia	62	M	Diabetes mellitus, cholecystectomy for chronic calculous cholecystitis	Not found	Fever, epigastric pain, intermittent vomiting	Piperacillin-tazobactam, ciprofloxacin	Recover	[7]
2017	Italy	83	M	COPD, cholecystectomy, and hypertension	Contact with contaminated water, and seafood consumption	Fever, cough, mild jaundice, and abdominal pain	Ceftriaxone, azithromycin	Recover	[3]
2018	Pakistan	2 months	M	Neonatal jaundice, cataract	Not certain	Fever and abdominal pain	Cefotaxime, amikacin	Death	[18]

2018	Belgium	45	M	Klatskin tumor	Contact with contaminated water	Fever, epigastric pain, nausea, anorexia	Piperacillin-tazobactam, ciprofloxacin	Recover	[5]
2018	China	47	M	Hepatitis B cirrhosis	Not mentioned	Fever, chills and diarrhea	Ceftazidime	Recover	[19]
2018	China	47	M	Hepatitis B cirrhosis, hepatocellular carcinoma	Not mentioned	Fever, chills, abdominal distension, edema of both lower limbs	Moxifloxacin	Recover	
2018	Lebanon	74	F	Pancreatic adenocarcinoma with liver metastasis, diabetes mellitus	Not certain	Fever, nausea, vomiting, and abdominal pain	Ciprofloxacin	Recover	[2]
2019	USA	62	M	Chronic hepatitis C with liver cirrhosis	Not found	Right leg swelling, fatigue and chills	Ceftriaxone, doxycycline	Recover	[4]
2019	Saudi Arabia	54	M	Hypertension, diabetes mellitus, right lower limb cellulitis, ischemic heart disease, atrial fibrillation and old stroke	Not certain	Fever, confusion, right leg pain, bullae and pus discharge from the sole of the right foot.	Meropenem, vancomycin, tigecycline	Death	[20]
2019	USA	63	F	Chronic lower extremity lymphedema, hypertension, osteoarthritis, restless leg syndrome	Contact with contaminated water through a chronic wound	Left leg pain and discoloration, haemorrhagic blisters with foul-smelling discharge	Doxycycline	Recover	[21]

Abbreviations: M, male; F: female.

Therefore, early diagnosis and timely treatment can improve the prognosis of NOVC patients.

Mode of Transmission

The modes of infection in patients with bacteremia can be divided into endogenous and exogenous infections. NOVC bacteremia is strongly related to exposure to coastal or estuarine water or consumption of seafood, particularly oysters.[22,23] Many NOVC stains have been isolated in the coastal waters of countries such as Germany, India, South Korea, and France.[24–27] Our review found that 47.8% of patients (11/23) had a possible source of infection; 6 cases were attributed to consuming seafood and 4 to contaminated water. Two cases presented swelling or pain in the lower leg after contact with contaminated water through a wound. Given our patient's workplace and the wound on his right foot, our patient was likely infected in the same manner. Some studies found that NOVC isolation varied seasonally, peaking during the summer (69%, especially June and July) and monsoons (46.5%) and decreasing in the winter (15.5%).[9,25] An increasing abundance of NOVC may lead to an escalating incidence of NOVC-associated human infections as water surface temperatures rise.[24,28] Therefore, people should be educated on the hazards of exposure to coastal and estuarine waters and consuming raw seafood to prevent small-scale outbreaks. In our review, 52.0% of patients denied consuming raw seafood or being exposed to coastal and estuarine waters; therefore, other possible sources of transmission must be determined.

Pathogenesis

To our knowledge, the NOVC pathogenesis remains unknown. Shanley et al hypothesized that NOVC caused bacteremia by spreading from the small intestine or skin wounds into the blood and lymphatic system.[4] Patients with liver cirrhosis are susceptible to NOVC bacteremia because of increased intestinal permeability, altered iron metabolism, and impaired phagocytosis and complement.[1] Previous studies revealed that several virulence factors were involved in the NOVC pathogenicity and invasiveness. NOVC strains typically did not carry the main virulence factors (cholera toxin and toxin-coregulated pilus), but clinical isolates expressed various synergistic factors, including hemolysin (*hlyA*), repeats in toxin (*rtx*), hemagglutinin protease (*hapA*), toxin regulatory gene (*toxR*), outer membrane proteins (*omp*), and the type III (T3SS) and type VI (T6SS) secretion systems.[29,30] Furthermore, several new virulence gene variants were reported in some environmental NOVC strains.[23]

A study suggested that NOVC can release outer membrane vesicles that induce miR-146a to induce colonization.[31] T3SS has also been demonstrated to facilitate colonization[32] and enhance the virulence of NOVC isolates.[6] In addition, hemolysin expression may contribute to the ability of NOVC isolates to invade the bloodstream in immunocompromised individuals.[33]

Treatment

Our review showed significant heterogeneity in antimicrobial therapies. Wong et al analyzed the antibiotic use and outcome patterns of 763 patients in the Cholera and Other Vibrio Illness Surveillance system and found that quinolone use may reduce the risk of death in patients with NOVC.[34] In addition, dual-agent therapy (combining a third-generation cephalosporin with a tetracycline or fluoroquinolone) was recommended for sicker patients with NOVC septicemia or septic shock.[35] However, recent studies discovered increased antimicrobial resistance among environmental and clinical NOVC isolates.[36] Thus, antimicrobial treatment in patients with NOVC bacteremia must be based on antibiotic susceptibility testing.

NOVC Identification Methods

Detecting and accurately identifying pathogens from blood cultures is important for patients with bacteremia. Commercial identification systems based on biochemical reactions (eg, the Vitek 2 Compact and API 20E), mass spectrometry (eg, MALDI-TOF-MS) and gene sequencing are commonly used to identify NOVC. MALDI-TOF-MS analyzes the expression of intrinsic proteins and variations in the mass:charge ratio (m/z) of these proteins to identify pathogens. Gene sequencing is performed by sequencing the conserved bacterial 16S rRNA gene region and comparing the sequences with those in the NCBI database. Serum agglutination testing is performed to classify *V. cholerae* according to its serotype and outer membrane O-antigen composition. However, if the strains self-coagulate (as did our strain), serum agglutination testing is not applicable. PCR can then be used, which is based on the *V. cholerae*-specific outer membrane protein gene (*ompW*) and the O-antigen *rfb* genes specific for both O1 and O139.[22] NOVC can be confirmed by *ompW* expression and the absence of O1-*rfb* and O139-*rfb* genes. Furthermore, the virulence genes and synergistic factors can be subjected to multiplex PCR,[37] and pulsed-field gel electrophoresis and multilocus sequence typing can be used to determine the heterogeneity of the strains.[19]

Conclusion

NOVC should be included in the differential diagnoses of bacteremia patients, especially in immunocompromised individuals such as those with liver cirrhosis or hepatitis and diabetes mellitus. Exposure to coastal and estuarine waters and consuming raw seafood are sources of transmission for this pathogen. Given the different clinical manifestations and high mortality that NOVC bacteremia causes, timely examination of blood cultures and accurate identification of this strain are important for its diagnosis. Timely and adequate antimicrobial therapy can improve the outcomes of patients with NOVC bacteremia.

Ethics and Consent Statement

Written informed consent was provided by the patient's relative to allow the case details to be published, and our study was approved by the Ethics Committee at Jiangsu Province Hospital.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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