IJID Regions 3 (2022) 76–78

Contents lists available at ScienceDirect

IJID Regions

journal homepage: www.elsevier.com/locate/ijregi

Case Report

Favourable outcomes of non-O1, non-O139 *Vibrio cholerae* bacteraemia in vulnerable populations: a case series

Fatma Al-Farsi[a,*], Turkiya Al-Siyabi[b], Badriya Al-Adawi[b], Amal Al-Tai[c]

[a] *Medical Microbiology Residency Programme, Oman Medical Specialty Board, Muscat, Oman*
[b] *Department of Microbiology and Immunology, Sultan Qaboos University Hospital, Muscat, Oman*
[c] *Department of Microbiology, The Royal Hospital, Muscat, Oman*

ARTICLE INFO

Keywords:
Vibrio cholerae
Non-O1
Bacteraemia
Liver cirrhosis

ABSTRACT

Background: Non-O1, non-O139 *Vibrio cholerae* (NOVC) bacteraemia is an uncommon infection and could be associated with life-threatening conditions in susceptible hosts. Definitive management guidelines are lacking.
Aim: To describe the clinical spectrum, treatment practices and outcome of NOVC bacteraemia.
Methods: Eight patients with NOVC bacteraemia admitted to two large tertiary care hospitals in Oman were identified over a 10-year period (2010–2020). Data were extracted retrospectively from the hospital patient data management.
Results: Six (75.0%) patients were male, and the median age of patients was 67.5 years. The majority of cases (87.5%) were not associated with travel and no clear sources were identified. All patients had predisposing factors including diabetes mellitus, chronic liver disease or malignancies. Gastrointestinal symptoms were the predominant manifestations in 75.0% of cases, but diarrhoea was only reported in one patient.
Conclusions: Early presentation (median interval from symptom onset to presentation 1.5 days), appropriate management and highly susceptible isolates may have contributed to the favourable outcome, as there were no cases of death or severe course of infection. All patients were discharged home after a median of 9 days of hospitalization.

Introduction

Cholera is caused by the Gram-negative bacterium Vibrio cholerae, commonly found in aquatic environments. The main symptom is acute watery diarrhoea. Serogroups O1 and O139 produce the toxin responsible for severe gastroenteritis, and are associated with epidemic cholera (Harris et al., 2012). *V. cholerae* belonging to other serogroups are collectively designated as 'non-O1, non-O139 *Vibrio cholerae*' (NOVC), which often cause sporadic self-limiting gastroenteritis (Deshayes et al., 2015). NOVC bacteraemia is an uncommon infection; however, more extra-intestinal infections associated with these serogroups have been reported in recent years. Invasive, life-threatening NOVC bacteraemia is mainly seen in high-risk hosts such as immuno-suppressed patients and those with underlying liver disease (Chen et al., 2015). Oman is free of endemic cholera, and the majority of cases are imported. Non-O1/O139 strains were occasionally isolated from environmental samples upon epidemiological investigations of indigenous *V. cholera* O1 cases reported between 2000 and 2003 (Ministry of Health Sultanate of Oman, 2017). The authors have observed an increase in the number of NOVC bacteraemias in their setting recently. As such, and in view of the lack of definitive management guidelines, all NOVC bacteraemia cases from two main tertiary care hospitals over the past 10 years were reviewed in order to examine infection risk factors, clinical spectrum, treatment practices and outcome. It is hoped that this may add to local and global knowledge.

Methods

Patients and study period

This was a retrospective, multi-centre, observational study. The medical records of all patients who had a positive blood culture with NOVC between January 2010 and December 2020 at the Royal Hospital (RH) or Sultan Qaboos University Hospital (SQUH), the two main tertiary care hospitals in Muscat, Oman, were reviewed. Demographic data, travel history, presence of co-morbidities, clinical presentations, investigations, management and outcomes were obtained from the Al-Shifa and TrackCare hospital information systems at RH and SQUH, respectively.

* Corresponding author: Medical Microbiology Residency Programme, Oman Medical Specialty Board, Al Azaiba, 130 Muscat, Oman.
E-mail address: f.alfarsi09@gmail.com (F. Al-Farsi).

https://doi.org/10.1016/j.ijregi.2022.03.006
Received 2 November 2021; Received in revised form 21 February 2022; Accepted 8 March 2022

Microbiological investigations

Blood cultures were collected using BACTEC aerobic and anaerobic blood culture bottles, and incubated in the BACTEC machine for 5 days. Any positive blood culture bottles were subjected to Gram staining and subcultured on to various solid culture media in accordance with standard laboratory procedures.

Organisms were identified using Phoenix (Becton Dickinson, Franklin Lakes, NJ, USA), API 20E (bioMérieux, Marcy l'Etoile, France) and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF, Bruker, Billerica, MA, USA). MALDI-TOF was introduced at SQUH and RH in 2017 and 2020, respectively. All isolates were sent to the national reference laboratory (Central Public Health Laboratory) for further confirmation and serotyping. Serotyping was performed using slide agglutination (Remel Agglutinating Sera, *Vibrio cholerae*).

Antimicrobial susceptibility testing was performed using the disc diffusion method, and interpreted based on the guidelines of the Clinical and Laboratory Standards Institute (Clinical and Laboratory Standards Institute, 2016).

Results

Nine patients were admitted to SQUH and RH between January 2010 and December 2020 with NOVC bacteraemia (Table 1). One patient was excluded as confirmation of the serotyping result was not documented. As such, eight patients were included in this study. The median age of patients was 67.5 years (range 64–80 years), and six were male. None of the patients had a recent history of overseas travel prior to admission, except for one patient who had been to India. Seven patients had no significant exposure to water or seafood. One patient had a history of traditional wet cupping, known as 'Hijama' locally, to relieve lower limb pain. Four patients had diabetes, and three patients (37.5%) had chronic liver disease. Three patients (37.5%) had solid organ malignancy (pancreatic, renal and thyroid cancer), but none of them were on chemotherapy at the time of presentation. All cases were community acquired and occurred between the months of August and December, except for one case that occurred in April.

Clinical presentations

Abdominal pain and fever were the most common presenting symptoms in six (75.0%) patients, with a median interval of 1.5 days (range 1–21 days) between symptom onset and presentation. One patient experienced diarrhoea and one presented with left foot cellulitis 4 days after cupping therapy. Of the eight cases, two (25.0%) had hypotension (blood pressure <90/60 mmHg) on initial presentation, which responded to intravenous fluids. Acute ascending cholangitis was identified as the source of bacteraemia in four (50.0%) patients; one of these cases was complicated by multiple pyogenic liver abscesses.

Laboratory investigations

Leukocytosis was found in three cases, and the median C-reactive protein (CRP) was 183 (range 14–371) mg/L at presentation. Two patients had a deranged coagulation profile, and two patients had acute kidney injury. Antimicrobial susceptibility testing was performed for the eight isolates. They were generally susceptible to all tested antibiotics, including ampicillin (8/8), amoxicillin-clavulanic acid (3/3), cefuroxime (3/3), ceftriaxone (2/2), ceftazidime (2/2), cefotaxime (4/4), piperacillin-tazobactam (3/3), meropenem (4/4), ciprofloxacin (5/5), trimethoprim-sulfamethoxazole (8/8), ciprofloxacin (5/5), tetracycline (5/5) gentamicin (3/3) and amikacin (3/3).

Table 1
Patient characteristics.

Case	Age (years)	Month/year of presentation	Risk factors	Presenting symptoms	Source of bacteraemia	Empirical therapy	Targeted therapy: IV/PO	Duration of therapy (days)
1	64	12/2011	HCV liver cirrhosis	Fever, abdominal pain	Unclear	FEP	Cipro/Cipro	14
2	64	10/2014	Renal cell cancer/travel to India	Abdominal pain, N/V	Unclear	Pip-Taz	Mero/AMC	15
3	69	8/2015	HCV liver cirrhosis	Fever, leg pain	Cellulitis	Pip-Taz /Van/CM	Mero+Cipro/Cipro	23
4	70	10/2018	DM, pancreatic cancer	Fever, abdominal pain, N/V	Cholangitis	Pip-Taz	Doxy/AZM	12
5	68	4/2019	DM, pancreatic and thyroid cancer	Fever, abdominal pain	Unclear	Pip-Taz	Cipro	15
6	80	9/2020	Cholangiocarcinoma	Fever, jaundice	Cholangitis	Pip-Taz	Cipro	10
7	67	10/2020	DM	Fever, jaundice	Cholangitis	Pip-Taz/Mero	Doxy	24
8	65	11/2020	DM, HBV liver cirrhosis	Fever, abdominal pain	Cholangitis	CRO	CRO/TMP-SMX	7

HCV, hepatitis C virus; N/V, nausea/vomiting; DM, diabetes mellitus; HBV, hepatitis B virus; FEP, cefepime; Cipro, ciprofloxacin; Mero, meropenem; Pip/Taz, piperacillin-tazobactam; AMC, amoxicillin-clavulanate; Van, vancomycin; CM, Clindamycin; Doxy, doxycycline; CRO, ceftriaxone; AZM, azithromycin; TMP-SMX, trimethoprim-sulfamethoxazole; IV, intravenous; PO, oral.

Treatment

Piperacillin-tazobactam was used empirically for six (75.0%) patients, which was upgraded to meropenem in three patients due to worsening inflammatory markers or continuous fever. One (12.5%) patient with cellulitis received meropenem, vancomycin and clindamycin as empirical therapy. Ciprofloxacin was used as targeted therapy for four patients. Other patients were de-escalated to trimethoprim-sulfamethoxazole, doxycycline, azithromycin or amoxicillin-clavulanate. The median duration of antibiotic therapy was 14.5 days (range 7–24 days).

Progression and outcome

All patients had a favourable outcome, improved clinically and were discharged home after a median of 9 days of hospitalization (range 5–12 days). None of the patients required intensive care or inotropic support. One (12.5%) patient had an incidental finding of cholangiocarcinoma with liver metastasis that required follow-up and referral to oncology.

Discussion

The number of NOVC bacteraemias has increased in recent years due to ongoing climate change, human behaviours, aging and a growing number of susceptible hosts in the world population (Vezzulli et al., 2020). All patients were aged >60 years and had at least one risk factor, including diabetes mellitus, pre-existing liver disease or malignancy. This is consistent with previous studies showing that people with diabetes mellitus, pre-existing liver disease and malignancies are at high risk of invasive vibrio infections (Chen et al., 2015; Li et al., 2020). Although NOVC are associated with exposure to the aquatic environment or consumption of seafood, the source of bacteraemia remained unclear in seven of eight (87.5%) patients in this study, similar to previous results (Deshayes et al., 2015; Engel et al., 2016; Shanley et al., 2019). This may suggest that other routes of infection, such as asymptomatic human carriage, may act as an endogenous or exogenous source of infection. This is supported by a local epidemiological investigation in which NOVC were isolated from asymptomatic carriers upon investigation of *V. cholera* O1 cases (Patel et al., 2006). In the present cohort, cupping therapy was reported in one case, which could be the source of NOVC bacteraemia secondary to cellulitis. Tissue or wound samples for culture were not obtained as surgical intervention was not required and clinical improvement was achieved by medical therapy alone. Soft tissue infections associated with cupping therapy have been reported due to *Pseudomonas* spp. and *Mycobacterium massiliense* (Lee et al., 2014; Alajmi et al., 2021).

Abdominal pain and fever were the predominant presenting symptoms in the study cases. Diarrhoea only manifested in one case. Stool culture was submitted, but it was not tested for the presence of *V. cholerae* as this was not requested specifically.

There were no deaths among the study patients despite the presence of comorbidities. All patients had good outcomes, did not require admission to an intensive care unit, and were hospitalized for <2 weeks. This differs from previous studies which showed significant mortality (8–17%) in Taiwan, China and Australia (Trubiano et al., 2014; Chen et al., 2015; Li et al., 2020). Early presentation (median interval from symptom onset to presentation 1.5 days), appropriate antimicrobial therapy, highly susceptible isolates and (possibly) low-virulence strains may have contributed to the favourable outcome in the cases in the present study.

The study isolates were generally susceptible to all primary tested antibiotics, in contrast to some studies which demonstrated the emergence of multi-drug resistance (Dua et al., 2018; Morita et al., 2020). There is significant heterogeneity in antimicrobial therapy used for NOVC bacteraemia, and there are no established guidelines for the management of such infections. In the present case series, piperacillin-tazobactam was started empirically in six patients, but then upgraded to meropenem or switched to ciprofloxacin in four of these patients due to slow clinical response or worsening inflammatory parameters despite in-vitro susceptibility. There was no clear reason for such failure of clinical response. Antimicrobial therapy should be guided by antimicrobial susceptibility results. Ciprofloxacin showed a good clinical response, but this should be assessed in a larger study.

In conclusion, NOVC are widely present in the environment. Although the source of infection was not identified in most of the study cases, patients with predisposing risk factors, such as diabetes mellitus, liver cirrhosis and immunosuppression, should be warned about the risks of unusual infections that may arise from exposure to aquatic environments. Early presentation, prompt diagnosis and appropriate antimicrobial therapy can improve patient outcomes and prevent a severe course of infection. Ciprofloxacin appears to be an appropriate targeted therapeutic option for NOVC bacteraemia, but this should be evaluated in a larger study.

Conflict of interest statement

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

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

Ethical approval for this study was obtained from Scientific Research Committee at RH (SRC#71/2021) and SQUH (MREC #2590).

References

Alajmi T, Aljulaihim A, Alzahrani M, Aljuhayyiam S. Necrotizing fasciitis following wet cupping: a case report. Cureus 2021;13:e14039.
Chen Y-T, Tang H-J, Chao C-M, Lai C-C. Clinical manifestations of non-O1 Vibrio cholerae infections. PLoS One 2015;10.
Clinical and Laboratory Standards Institute. Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria. 3rd ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2016 M45.
Deshayes S, Daurel C, Cattoir V, Parienti J-J, Quilici M-L, de La Blanchardière A. Non-O1, non-O139 Vibrio cholerae bacteraemia: case report and literature review. SpringerPlus 2015;4:575.
Dua P, Karmakar A, Ghosh C. Virulence gene profiles, biofilm formation, and antimicrobial resistance of Vibrio cholerae non-O1/non-O139 bacteria isolated from West Bengal. India. Heliyon 2018;4:e01040.
Engel MF, Muijsken MA, Mooi-Kokenberg E, Kuijper EJ, van Westerloo DJ. Vibrio cholerae non-O1 bacteraemia: description of three cases in the Netherlands and a literature review. EuroSurveillance 2016;21:30197 pii=.
Harris JB, LaRocque RC, Qadri F, Ryan ET, Calderwood SB. Cholera. Lancet 2012;379:2466–76.
Lee SY, Sin JI, Yoo HK, Kim TS, Sung KY. Cutaneous Mycobacterium massiliense infection associated with cupping therapy. Clin Exp Dermatol 2014;39:904–7.
Li X, Wu Y, Sun X, Ma J, Li X, Liu C, et al. Non-O1/non-O139 Vibrio cholerae bacteraemia in mainland China from 2005 to 2019: clinical, epidemiological and genetic characteristics. Epidemiol Infect 2020;148:e186.
Ministry of Health Sultanate of Oman. Manual on communicable diseases. 3rd ed. Muscat: Ministry of Health Sultanate of Oman; 2017.
Morita D, Takahashi E, Morita M, Ohnishi M, Mizuno T, Miyoshi S-I, et al. Genomic characterization of antibiotic resistance-encoding genes in clinical isolates of Vibrio cholerae non-O1/non-O139 strains from Kolkata, India: generation of novel types of genomic islands containing plural antibiotic resistance genes. Microbiol Immunol 2020;64:435–44.
Patel PK, Bawikar S, John M, Al-Awaidy ST. Atypical cases of cholera due to serogroup O1 in the native population of Oman and its relation to non-O1/O139. Saudi Med J 2006;27:897–8.
Shanley J, Kanj A, El Zein S, Tabaja H, Trzcinski B, Horman J, et al. Non-O1, non-O139 Vibrio cholerae bacteremia in an urban academic medical center in the United States. IDCases 2019;15:e00527.
Trubiano JA, Lee JYH, Valcanis M, Gregory J, Sutton BA, Holmes NE. Non-O1, non-O139 Vibrio cholerae bacteraemia in an Australian population. Intern Med. J 2014;44:508–11.
Vezzulli L, Baker-Austin C, Kirschner A, Pruzzo C, Martinez-Urtaza J. Global emergence of environmental non-O1/O139 Vibrio cholerae infections linked with climate change: a neglected research field? Environ Microbiol 2020;22:4342–55.