DOI: 10.7860/JCDR/2020/43621.13647

Original Article

Paediatrics Section

Clinical Characteristics, Laboratory Profile and Outcome of Children with *Vibrio Cholerae* Gastroenteritis (Both O1 and Non-O1/Non-O139) and *Vibrio Cholerae* (Non-O1/Non-O139) Bacteraemia- A Retrospective Single Centre Study

LEENATH THOMAS[1], SHALINI ANANDAN[2], VALSAN PHILIP VERGHESE[3], VEERARAGHAVAN BALAJI[4], S MAHASAMPATH GOWRI[5], ANILA CHACKO[6], ANU PUNNEN[7], WINSLEY ROSE[8]

ABSTRACT

Introduction: *Vibrio cholerae* (*V. cholerae*) infection (O1, O139, and non-O1/non-O139) in children can occur in the form of gastroenteritis and bacteraemia.

Aim: To describe and compare the clinical characteristics, laboratory profile and outcome of children with gastroenteritis due to *V. cholerae* O1, O139 and *V. cholerae* non-O1/non-O139 and to present a case series describing the clinical and laboratory profile and outcome of children with *V. cholerae* non-O1/non-O139 bacteraemia.

Materials and Methods: A retrospective study was conducted on the medical records of children under 15 years of age in whom *V. cholerae* was identified in stool culture or blood culture. The children who presented from January 2010 to November 2018 in Christian Medical College and Hospital, Vellore, India were included. The following details were noted: symptoms and signs (including vital signs and state of dehydration) at presentation, co-morbidities, anthropometry, complete blood counts, serum electrolytes, creatinine, reports of stool culture, blood culture and antibiotic susceptibility, details of treatment given (including hospital admission, IV fluids and antibiotics) and outcome. The group-wise comparison for continuous variables was done using Independent t-test. The categorical data among the groups were compared using the chi-square test.

Results: Among the 8990 stool cultures and 1,23,005 blood cultures done in children during the study period for various reasons, *V. cholerae* had grown in stool culture of 105 children and blood culture of six children. Children with *V. cholerae* O1 were more tachypnoeic/acidotic (44.8% vs. 10.0%; p<0.001), had dehydration and shock (65.5% vs. 6.6%; p<0.001) at presentation and required hospital admission more often (87.3% vs. 18.1%, p<0.001) compared to *V. cholerae* non-O1/non-O139. Both isolates in stool culture were susceptible to cefotaxime, norfloxacin and tetracycline. All six children with *V. cholerae* non-O1/non-O139 bacteraemia had co-morbidities and 66% of them had chronic liver disease. About 50% of these children (n=3) succumbed to the illness in the first week of illness itself and 2 of them were infants.

Conclusion: The gastroenteritis due to *V. cholerae* O1 was more severe than that with *V. cholerae* non-O1/non-O139. Children with chronic liver disease and immunodeficiency were particularly susceptible to non-O1/non-139 *V. cholerae* bacteraemia.

Keywords: Antibiotic susceptibility, Blood culture, Cholera

INTRODUCTION

Vibrio cholerae (*V. cholerae*) is a halophilic, highly motile, curved (comma-shaped), gram-negative bacillus belonging to the family Vibrionaceae [1,2]. There are over 200 serotypes classified based on lipopolysaccharide O-antigen [3]. Among them, serogroup O1 and serogroup O139 (O139 is found only in Asia) causes cholera, a form of severe watery diarrhoea, which can lead to dehydration if left untreated [4]. The other serogroups which do not agglutinate with serum from cholera patients were named as non-O1/non-O139 *V. cholerae* and these serogroups causes a diarrheal disease which is less severe than cholera [4].

In 2016, globally, cholera was the third leading cause of mortality due to diarrhoea among all ages (including children), responsible for about 107,290 deaths [5]. Cholera has been an important public health problem in India for many years. Between 2010 to 2015, as per surveillance by the Integrated Disease Surveillance Program, 24 states of India reported cholera and 13 states were classified as endemic [6].

Cholera is an extremely virulent disease with an incubation period for *V. cholerae* O1 infection ranging from 12 hours to 5 days [7]. *V. cholerae* non-O1/non-O139 are non-pathogenic or are asymptomatic colonisers in human beings [8,9]. The incubation period for gastroenteritis is 12 hours to 3 days (up to one week) [10]. The illness severity ranges from mild to severe watery diarrhoea along with other non-specific symptoms [4,10].

Bacteraemia or septicaemia due to *V. cholerae* O1 or O139 is extremely rare. In literature, there is only one case report of *V. cholerae* O1 bacteraemia in the paediatric age group and another one case report of a neonate with *V. cholerae* O139 bacteraemia [11,12]. There are a few case reports of bacteraemia due to non-O1/non-O139 *V. cholerae* and all the affected children were either neonates or the patients with some form of co-morbidities like nephrotic syndrome, Fanconi's anaemia and thalassaemia [13-20]. Apart from these 8 case reports, the present authors couldn't find any case reports or case series about *V. cholerae* bacteraemia in children. The usual presentation in a child with bacteraemia would be with fever, lethargy, and hypotension [4].

There are a few studies and case reports in the literature which has investigated the clinical features and outcome of either *V. cholerae* O1 or *V. cholerae* non-O1/non-O139, but has not compared against each other [21-23]. Hence the present study was conducted with an aim to compare the clinical characteristics, laboratory profile and outcome of children with gastroenteritis due to *V. cholerae* O1 or O139 (also called as cholera) and *V. cholerae* non-O1/non-O139 and to describe the clinical and laboratory profile and outcome of children bacteraemia due to *V. cholerae* non-O1/non-O139.

MATERIALS AND METHODS

This retrospective study was conducted in Christian Medical College and Hospital (tertiary care institute), after the approval from the Institutional Review Board (IRB: 11536 dated 26.09.2018). All children below 15 years of age who had *V. cholerae* isolated from the blood (bacteraemia) and/or stool (gastroenteritis) between January 2010 and November 2018 were included in the study. The data was collected during January 2019 to March 2019 of the children who reported to the institute between January 2010 and November 2018. The following details were noted: symptoms and signs (including vital signs and state of dehydration) at presentation, co-morbidities, anthropometry, complete blood counts, serum electrolytes, creatinine, reports of stool culture, blood culture and antibiotic susceptibility, details of treatment given (including hospital admission, IV fluids and antibiotics) and outcome. When any of the clinical or laboratory details mentioned above were missing in the records, those variables were excluded from calculations. As this is a retrospective study, no sample size calculation was done. When we considered dehydration and shock as the most important clinical feature of gastroenteritis, there was sufficient power of 99.3% to detect the difference among the groups. The standard of practice in the microbiology laboratory of this institution is as follows: stool samples sent for culture were studied for macroscopic appearance and a hanging drop done if it was watery. The sample was then plated on to Blood agar, MacConkey agar, Desoxycholate Citrate Agar, Xylose Lysine Desoxycholate Agar and if watery a Thiosulphate citrate Bile salts Sucrose Agar was added with Alkaline Peptone Water. The plates were incubated at 37ºC aerobically for 18 hours. Any suspicious colonies were followed-up with preliminary screening biochemical media and confirmed for identity using specific antisera. Antimicrobial susceptibility testing was done by the Kirby Bauer technique and results interpreted using Clinical and Laboratory Standards Institute (CLSI) guidelines [24].

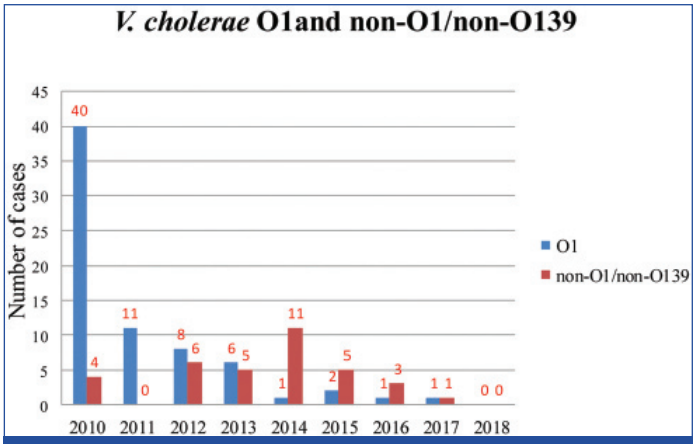
Blood cultures were done using BacT Alert 3D system (Biomerieux) and identification using conventional media and biochemical reactions. The details of clinical features, laboratory profile, treatment and outcome were collected from the medical records.

STATISTICAL ANALYSIS

All the analysis was performed using STATA /IC 15.0 (Copyright 1985-2017 StataCorp LLC, Statistics/Data Analysis, StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA). Data were summarised using mean (SD)/median (IQR) for continuous variables and categorical data were expressed as frequency and percentage. The group-wise comparison for continuous variables was done using Independent t-test. The categorical data among the groups were compared using the chi-square test.

RESULTS

The total number of stool cultures and blood cultures done in children during the study period were 8,990 and 1,23,005, respectively. *V. cholerae* had grown in the stool culture of 105 children and the blood culture of six children. None of the children had both stool and blood culture positivity. The year-wise detection of *V. cholerae* gastroenteritis cases shows that the incidence of *V. cholerae* gastroenteritis is in a decreasing trend [Table/Fig-1].



[Table/Fig-1]: Trend of *V. cholerae* O1 and non-O1/non-O139 gastroenteritis from 2010 to 2018.

Vibrio Cholerae Gastroenteritis

There were 68 (64.7%) boys and 37 (35.2%) girls. *V. cholerae* O1 had grown in stools of 70 children, *V. cholerae* non-O1/non-O139 in 35 and *V. cholerae* O139 in none. The median age at diagnosis was 2.85 years (IQR: 1.4 to 6.0 years) for children with *V. cholerae* O1 and 1.3 years (IQR: 0.9 to 3.3 years) for children with *V. cholerae* non-O1/non-O139 (p-0.005) [Table/Fig-2].

Co-morbidities were present in 17/56 (30.3%) children with *V. cholerae* O1 and 8/30 (26.6%) with *V. cholerae* non-O1/non-O139 (p-0.71) [Table/Fig-2]. The most common co-morbidity was protein energy malnutrition (n=5), followed by iron deficiency anaemia (n=4), leukaemia (on chemotherapy) (n=4), and post bone marrow transplant (on immunosuppression) (n=2).

The children with gastroenteritis with *V. cholerae* O1 had a significantly lower potassium level (p-0.04), and bicarbonate (p-0.02) and a higher creatinine (p-0.007) than *V. cholerae* non-O1/non-O139 [Table/Fig-3].

Among the 70 children with stool culture positive for *V. cholerae* O1, 50 had stool hanging drop test done and 16 out of 50 (32%) was positive. Six out of 35 with *V. cholerae* non-O1/non-O139 infection had hanging drop test done and 1 (16.6%) was positive (p-0.44).

Thirteen children (18.5%) with *V. cholerae* O1 infection and 11 (31.4%) with *V. cholerae* non-O1/non-O139 infection were co-infected with other bacteria (p-0.139). The bacteria that co-infected with *V. cholerae* O1 were Aeromonas (n=11), Shigella (n=1) and Salmonella C1 (n=1) and that with *V. cholerae* non-O1/non-O139 were Aeromonas (n=5) and Shigella (n=6). However, there was no way to prove which one among the co-infection was responsible for diarrhoea.

Among the positive stool cultures which underwent susceptibility testing, *V. cholerae* O1 was resistant to nalidixic acid and cotrimoxazole in all (17/17) as against *V. cholerae* non-O1/non-O139 where 5/9 (55.5%) were susceptible to nalidixic acid (p 0.001) and 6/9 (66.6%) to cotrimoxazole (p<0.001) [Table/Fig-4].

Among the 105 children, 96 had the details available regarding hospital stay. A total of 55 out of 63 (87.3%) children with *V. cholerae* O1 infection and six out of 33 (18.1%) with *V. cholerae* non-O1/non-O139 required hospital admission (p<0.001). The average duration of hospital stay was 3.27±1.69 days and 4.2±2.17 days for *V. cholerae* O1 and *V. cholerae* non-O1/non-O139 respectively. About 56 out of 63 (88.8%) children with *V. cholerae* O1 and 5 out of 32 (15.1%) with *V. cholerae* non-O1/non-O139 required intravenous fluids administration (p<0.001). The details of inpatient care of 1 child were not available. Among the 63 children with *V. cholerae* O1 infection, 2 required inotropes, 3 required oxygen, 2 required treatments in Intensive Care Unit (ICU) and 1 required ventilation.

A total of 59 out of 63 (93.6%) with *V. cholerae* O1 and 31 out of 32 (96.8%) with *V. cholerae* non-O1/non-O139 gastroenteritis were treated with antibiotics (p-0.362). 39 children among 59 (66.1%) with *V. cholerae* O1 and 8 out of 31 (25.8%) with *V. cholerae* non-

		V. cholera O1 (n=70)		*V. cholerae* non-O1/non-O139 (n=35)		
		Number available on records (n)	Percentage†	Number available on records (n)	Percentage†	p-values
Females (%)		70	29 (41.4%)	35	8 (22.9%)	0.06
Median age in years (IQR)*		70	2.85 (1.4-6.0)	35	1.3 (0.9-3.3)	0.005
Symptoms	Fever	58	21/58 (36.2%)	27	16/27 (59.3%)	0.46
	Vomiting	57	49/57 (85.9%)	27	12/27 (44.4%)	<0.001
	Blood in stools	58	2/58 (3.4%)	27	17/27 (62.9%)	<0.001
	Abdominal pain	58	6/58 (10.3%)	27	2/27 (7.4%)	0.666
	Lethargy/poor feeding	58	30/58 (51.7%)	27	2/27 (7.4%)	<0.001
	Seizures	58	4/58 (6.8%)	27	0/27 (0%)	0.162
	Decrease in urine output	58	23/58 (39.6%)	27	5/27 (18.5%)	0.054
Co morbidities		56	17/56 (30.3%)	30	8/30 (26.6%)	0.719
Respiration	Normal	58	32/58(55.2%)	30	27/30 (90%)	0.001
	Tachypnoeic/acidotic		26/58 (44.8%)		3/30 (10%)	
Degree of dehydration (WHO grading) [25]	No dehydration	58	7/58 (12.0%)	30	26/30 (86.6%)	<0.001
	Some dehydration		13/58 (22.4%)		2/30 (6.6%)	
	Severe dehydration		25/58 (43.1%)		2/30 (6.6%)	
	Shock		13/58 (22.4%)		0	
Weight for age Z score (IQR)		50	-1.75 (-2.61, -0.88)	29	-1.05 (-1.65, -0.34)	0.025
Height for age Z score (IQR)		31	-1.26 (-2.4,0.15)	26	-0.98 (-1.61, -0.98)	0.470

[Table/Fig-2]: Description and comparison of clinical characteristics of the 105 patients with V. cholerae gastroenteritis (O1 and non-O1/non-O139) at presentation to hospital.
p-value <0.05 significant;
*IQR: interquartile range; †Numerator is the number of children having that variable and denominator is the total number of children for whom details are available in medical records
Independent t-test for continuous variables and chi-square test for categorical data was used

		V. cholerae O1 (n=70)		*V. cholerae* non-O1/non-O139 (n=35)		
		Number available on records (n)	Percentage† or SD (as applicable)	Number available on records (n)	Percentage† or SD (as applicable)	p-value
Haemoglobin in g/dL (SD)*		29	10.92 (2.84)	18	10.99 (1.93)	0.928
Total WBC (in cu mm)(IQR)‡		30	12250 (IQR: 10700, 19200)	18	11750 (IQR: 7200, 14800)	0.163
Neutrophils in % (SD)		28	61.89 (19.33)	17	47.29 (24.12)	0.030
Lymphocytes in % (SD)		28	30.11 (17.92)	17	43.12 (23.92)	0.043
Platelet count (lac/cu mm) (SD)		27	4.27 (2.03)	17	2.69 (1.54)	0.008
Sodium (in meq/L) (SD)		56	134.5 (5.2)	11	136.1 (2.9)	0.327
Sodium (in meq/L) (%)	<135	56	27/56 (48.2)	11	3/11 (27.2)	0.309
	135-145		27/56 (48.2)		8/11 (72.7)	
	>145		2/56 (3.5)		0 (0)	
Potassium (in meq/L) (SD)		56	3.23 (0.73)	11	3.7 (0.63)	0.048
Potassium (%)	<3.5	56	41/56 (73.2)	11	4/11 (36.3)	0.092
	3.5-5.0		14/56 (25.0)		7/11 (63.6)	
	>5.0		1/56 (1.7)		0 (0)	
Bicarbonate (in meq/L) (SD)		28	11.57 (4.83)	3	18.33 (1.53)	0.024
Creatinine (in mg/dL) (SD)		39	0.94 (0.55)	12	0.48 (0.23)	0.007
eGFR (in mL/min/1.73 sqm) (SD)		22	52.98 (27.99)	9	95.57 (47.85)	0.005
SGPT (in IU/L) (SD)		4	13.5 (4.36)	8	15.5 (10.41)	

[Table/Fig-3]: Description and comparison of laboratory profile of children with *V. cholerae* gastroenteritis (O1 and non-O1/non-O139).
p-value <0.05 significant
*SD: Standard deviation; †Numerator is the number of children having that variable and denominator is the total number of children for whom details are available in medical records; ‡IQR: Interquartile range
Independent t-test for continuous variables and chi-square test for categorical data

Drug sensitivity	*V. cholerae* O1	*V. cholerae* non-O1/ non-O139	p-value
Cefotaxime, n=26	17/17 (100%)	9/9 (100%)	
Norfloxacin, n=26	17/17 (100%)	9/9 (100%)	
Ampicillin, n=23	13/14 (92.8%)	7/9 (77.7%)	0.295
Tetracycline, n=20	12/12 (100%)	8/8 (100%)	
Nalidixic acid, n=26	0/17 (0%)	5/9 (55.5%)	0.001
Cotrimoxazole, n=26	0/17 (0%)	6/9 (66.6%)	<0.001

[Table/Fig-4]: Drug susceptibility testing of *V. cholerae* isolates from stool culture.
p-value <0.05 significant

O1/non-O139 were given doxycycline alone (p<0.001). Doxycycline or doxycycline combination therapy was given for 57 out of 59 (96.6%) children with *V. cholerae* O1 and nine out of 31 (29.0%) with *V. cholerae* non-O1/non-O139 (p<0.001).

Follow-up details were available for 97 children, 63 with *V. cholerae* O1 and 34 with *V. cholerae* non-O1/non-O139 infection. All the 97 children recovered without any morbidity.

V. Cholera Non-O1/non-O139 Bacteraemia

There were six children with *V. cholerae* bacteraemia. The summary of the six cases is mentioned in [Table/Fig-5]. The age group of

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	15 years	10 years	6 years	7 months	4 days	5 years
Sex	Female	Male	Female	Male	Male	Male
Co-morbidity	Osteosarcoma-left humerus, on chemotherapy for 8 months	Wilson's disease	Acute on chronic liver disease (unclear aetiology)	Neonatal cholestasis	Preterm (30+5 weeks) Only risk of sepsis: spontaneous premature onset of labour	Non Cirrhotic Intrahepatic Portal Hypertension (NCIPH)
Presenting symptoms	Fever	Fever, diarrhoea	Fever, lethargy	Fever, fast breathing, lethargy, irritability	Lethargy, brown nasogastric aspirates, haematochezia	Fever, abdominal pain
Duration of symptoms	1 day	1 day	1 day	1 day	1 day	1 day
Haemodynamic status	Normal	Compensated shock	Hypotensive shock	Hypotensive shock	Hypotensive shock	Normal
Hb (in g%)	9.9	9.1	11.8	9.7	20.2	11.5
Total WBC (in cu mm)	3300	19600	5800	13500	16480	14500
Differential count	N92 L8	N61 L22	N71 L28	N76 L11	N30 L56	N86 L2
Platelet count (in cu mm)	1.14 lac	1.53 lac	45,000	72000	22000	1.09 lac
Sensitive to	Tetracycline, norfloxacin, ofloxacin	cotrimoxazole, ofloxacin, ampicillin, tetracycline, nalidixic acid and cefotaxime	Not done	Not done	Ampicillin, tetracycline, cotrimoxazole, cefotaxime, norfloxacin	Ampicillin, tetracycline, cotrimoxazole, cefotaxime, ofloxacin and ciprofloxacin
Resistant to	Cefotaxime, nalidixic acid, cotrimoxazole	Nil	Not done	Not done	Nalidixic acid	Nil
Treatment given	Ceftriaxone†, Gentamycin	Cefotaxime, followed by ceftriaxone. Doxycycline 1 dose	Meropenem	Cefotaxime followed by Piperacillin/Tazobactam and Amikacin	Meropenem, amikacin	Cefotaxime, doxycycline
Duration	7 days	10 days	3 days	2 days	2 days	10 days
Course of illness	No complications	No complications	Septic shock and DIC*	Septic shock and DIC	Refractory septic shock, MODS‡ and DIC	No complications
Outcome	Cured	Cured	Died on day 4 after admission	Died on day 2 after admission	Died on day 2 after the onset of symptoms	Cured

[Table/Fig-5]: Clinical and laboratory profile and outcome of the 6 cases of *V. cholerae* non-O1/non-O139 septicaemia
*DIC: Disseminated intravascular coagulopathy
†Ceftriaxone was continued as the child had already shown improvement and gentamycin sensitivity was not done
‡MODS: Multiorgan dysfunction syndrome

patients ranged from neonate to adolescent and four out of 6 (66.6%) were males. All patients had significant co-morbidities and the four out of 6 (66.6%) had liver disease. Despite treatment, three out of 6 (50%) succumbed to the illness.

DISCUSSION

Among the 105 children with *V. cholerae* gastroenteritis, *V. cholerae* O1 was predominant (66.6%) compared to *V. cholerae* non-O1/non-O139 (33.3%). A similar distribution was noted by Dutta D et al., in Kolkata, India (83.4 vs. 12.7%) [26].

There was a decreasing trend of *V. cholerae* gastroenteritis (both cholera and non choleragenic infection) over the study period of 2010 to 2018, which seems to be in a continuation of trend from the previous study done by Sebastian T et al., of the same institution (Christian Medical College, Vellore) from 2000 to 2010 [27]. This is probably due to decreased incidence of the disease itself, improvement of hygiene and use of ORS and antibiotics in the early course of the illness. The improvement of case management in a primary or secondary care facility could have reduced the need for referral to a tertiary centre. However incomplete reporting of cholera cases was always there [28].

Dysentery was a significant symptom in children with *V. cholerae* non-O1/non-O139 gastroenteritis (62.9%, p<0.001) with a higher incidence than what was observed in a previous study done in Kolkata, India by Dutta D et al., [26]. The other symptoms like vomiting and lethargy occurred more often in children with *V. cholerae* O1 (p<0.001 for both symptoms) in present study which was comparable to the study done by Clemens JD et al., [29].

At presentation, the children with *V. cholerae* O1 gastroenteritis were significantly tachypnoeic/acidotic, dehydrated and in shock compared to *V. cholerae* non-O1/non-O139 (p<0.001). This is expected when a child passes watery stools at the rate of 10-20 mL/Kg/hour and loses bicarbonate in the stools leading to acidotic breathing, dehydration, and shock [30].

The characteristic motility can be seen in stool hanging drop preparation and examination by dark field microscopy (sensitivity of about 50%) and it was done in about half of the total children (n=56) and only one-third (30.3%) had positive results. This is even lower than what was observed by Clemens JD et al., [29]. In stool cultures, co-infections (or mixed infections) with other bacteria like Aeromonas and Shigella were common in children (23.8%) with either type of vibrio gastroenteritis but there was a higher frequency of co-infection with *V. cholerae* non-O1/non-O139 (31.4% vs. 18.5%; p 0.139), a finding consistent with previous studies [26,31,32]. The children with co-infections had a more severe form of gastroenteritis [33].

Antibiotic susceptibility: Both *V. cholerae* O1 and non-O1/non-O139 isolates were sensitive to cefotaxime, norfloxacin, and tetracycline. While *V. cholerae* O1 were all resistant to nalidixic acid and cotrimoxazole, *V. cholerae* non-O1/non-O139 was partially sensitive to both (p<0.001). The pattern of drug susceptibility is not uniform in different parts of the world, even though there are some similarities [26,34-36].

The children with *V. cholerae* O1 infection were sicker at presentation and required hospital admission (87.3% vs. 18.1%, p<0.001) for management of dehydration, shock, and acidosis.

Almost all the children were treated with antibiotics (93.6% vs. 96.8%). The difference in antibiotic administration was due to the less severe diarrhoea and the presence of blood in stools in children with *V. cholerae* non-O1/non-O139. In our institution, authors continue to use doxycycline as the first-line antibiotic in suspected cholera based on the American Academy of Pediatrics (AAP) recommendation in 2010 of treating paediatric cholera with doxycycline (drug of choice) at a dose 2-4 milligrams/kilogram (mg/kg) in one dose [37].

V. Cholerae Non-O1/Non-O139 Bacteraemia

The youngest was a four-day-old preterm baby and the oldest was a 15-year-old girl. There are case reports in children of all age groups [13-20]. Every patient in this study had some form of significant co-morbidities [Table/Fig-5] which is similar to all the case reports available. The most noticeable fact is four out of 6 (66%) had Chronic Liver Disease (CLD). Chronic liver disease being a significant predisposing factor for *V. cholerae* non-O1/non-O139 bacteraemia has been recorded in various studies in adult population [9,38], but not in paediatric population. Some suggest that patients who are immunocompromised and with CLD should not ingest raw seafood or expose skin wounds to saltwater [4].

Fever and lethargy were the predominant symptoms noted in these 6 patients, similar to all case reports [13-20]. A 66% of children had haemodynamic instability as has been documented before [13-20]. Antibiotic susceptibility of the isolated organism was done in four out of 6 cases. All 4 were susceptible to tetracycline and 3 were susceptible to ampicillin, cefotaxime, and cotrimoxazole. Based on the antibiotic susceptibility pattern, ampicillin, cefotaxime, and tetracycline are reasonable choices of initial empirical antibiotics.

The antibiotics used in different case reports were cefotaxime, penicillin, ampicillin, ciprofloxacin and imipenem [13-16,18]. Among the 3 survivors in the present study, cefotaxime or ceftriaxone were given for seven to 10 days. Based on the available data and study, one of the third generation cephalosporins (cefotaxime or ceftriaxone) seemed to be the most effective treatment [39]. In the case reports, the duration of intravenous antibiotics ranged from 10 days to 1 month [13-16,18]. Fifty percent of children in study succumbed to the illness in the first week of the illness itself. The outcome was unfavourable in younger children (especially infants, n=2) with bacteraemia. Among the 8 case reports available in literature, one child died [17], three survived without sequelae [13,16,20], two had severe neurological sequelae [15,18] and two did not have follow-up details. The younger infants including neonates were the ones who died or suffered severe neurological sequelae. This study has provided a description as well as for the first time, a comparison on clinical characteristics, laboratory profile and outcome of children with gastroenteritis due to *V. cholerae* O1 and *V. cholerae* non-O1/non-O139.

To the best our knowledge, this is the first-ever case series of *V. cholerae* non-O1/non-139 bacteraemia in the paediatric age group.

Limitation(s)

As the data were collected retrospectively from medical records, all the details with respect to clinical characteristics were not available.

CONCLUSION(S)

The gastroenteritis due to *V. cholerae* O1 was more severe than that with *V. cholerae* non-O1/non-O139. However, with appropriate management using fluids and antibiotics the prognosis was good. When diarrhoea due to *V. cholerae* is suspected, cefotaxime, norfloxacin or tetracycline should be the empirical antibiotics and not nalidixic acid or cotrimoxazole. The response to single dose doxycycline was excellent in the index patients.

With regards to *V. cholerae* non-O1/non-139 bacteraemia, children with chronic liver disease and immunodeficiency are particularly susceptible. In spite of administering appropriate antibiotics, 50% of the children succumbed to the illness and the younger ones had the worst outcome.

REFERENCES

[1] Mégraud F, Musso D, Drancourt M, Lehours P. 182-Curved and Spiral Bacilli. In: Cohen J, Powderly WG, Opal SM, editors. Infectious Diseases (Fourth Edition) [Internet]. Elsevier; 2017 [cited 2019 May 2]. Pp. 1600-1610.e2. Available from: http://www.sciencedirect.com/science/article/pii/B9780702062858001829.

[2] Waldor MK, Ryan ET. 216-Vibrio cholerae. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (Eighth Edition) [Internet]. Philadelphia: Content Repository Only!; 2015 [cited 2019 May 2]. Pp. 2471-2479.e2. Available from: http://www.sciencedirect.com/science/article/pii/B9781455748013002162.

[3] Garza JM, Cohen MB. 39-Infectious Diarrhea. In: Wyllie R, Hyams JS, editors. Pediatric Gastrointestinal and Liver Disease (Fourth Edition) [Internet]. Saint Louis: W.B. Saunders; 2011 [cited 2019 May 2]. Pp. 405-422.e5. Available from: http://www.sciencedirect.com/science/article/pii/B9781437707748100399.

[4] Non-O1 and non-O139 Infections | Sources of Infection & Risk Factors | Cholera | CDC [Internet]. 2018 [cited 2019 Apr 26]. Available from: https://www.cdc.gov/cholera/non-01-0139-infections.html.

[5] Troeger C, Blacker BF, Khalil IA, Rao PC, Cao S, Zimsen SR, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018;18(11):1211-28.

[6] Ali M, Gupta SS, Arora N, Khasnobis P, Venkatesh S, Sur D, et al. Identification of burden hotspots and risk factors for cholera in India: An observational study. PLOS ONE. 2017;12(8):e0183100.

[7] Azman AS, Rudolph KE, Cummings DAT, Lessler J. The incubation period of cholera: A systematic review. J Infect. 2013;66(5):432-38.

[8] Routledge Handbook of Water and Health-Google Books [Internet]. [cited 2019 May 3]. Available from: https://books.google.co.in/books?redir_esc=y&id=zhHKCgAAQBAJ&q=vibrio+cholerae#v=snippet&q=vibrio%20cholerae&f=false.

[9] 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. ID Cases. 2019;15:e00527.

[10] Momba AE-L. Vibrio cholerae and Cholera biotypes [Internet]. Global Water Pathogen Project. 2015 [cited 2019 May 5]. Available from: https://www.waterpathogens.org/book/Vibrio.

[11] Bose A, Philip JK, Jesudason M. Neonatal septicemia caused by vibrio choleraeo: 139. Pediatr Infect Dis J. 2000;19(2):166.

[12] Gordon MA, Walsh AL, Rogerson SRK, Magomero KC, Machili CE, Corkill JE, et. Three cases of bacteremia caused by vibrio cholerae O1 in Blantyre, Malawi. 2001;(7). Emerging Infectious Diseases journal-CDC. [cited 2019 May 3]; Available from: https://wwwnc.cdc.gov/eid/article/7/6/01-0629_article.

[13] Thomas M, Cherian T, Raghupathy P. Non-o:1 vibrio cholerae bacteremia and peritonitis in a patient with nephrotic syndrome. Pediatr Infect Dis J. 1996;15(3):276.

[14] Kerketta JA, Paul AC, Balaji V, Kirubakaran C, Jesudason MV, Moses PD. Non-01 Vibrio cholerae septicemia and meningitis in a neonate. Indian J Pediatr. 2002;69(10):909-10.

[15] Hao Y, Wang Y, Bi Z, Sun B, Jin Y, Bai Y, et al. A case of non-O1/non-O139 Vibrio cholerae septicemia and meningitis in a neonate. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2015;35:117-19.

[16] WHO EMRO | Two cases of Vibrio cholerae non-O1/non-O139 septicaemia with favourable outcome in Lebanon | EMHJ. 2011;(17)8: [Internet]. [cited 2019 May 14]. Available from: http://www.emro.who.int/emhj-volume-17/volume-17-issue-8/article14.html.

[17] Sarwar S, Hannan A, Sultana Q, Saleem S, Sohail M, Arshad MU, et al. Non-O1 Vibrio cholerae bacteremia in an infant, first case report from Pakistan. J Infect Dev Ctries. 2016;10(02):188-89.

[18] Rubin LG, Altman J, Epple LK, Yolken RH. Vibrio cholerae meningitis in a neonate. J Pediatr. 1981;98(6):940-42.

[19] Dhar R, Badawi M, Qabazard Z, Albert MJ. Vibrio cholerae (non-O1, non-O139) sepsis in a child with Fanconi anemia. Diagn Microbiol Infect Dis. 2004;50(4):287-89.

[20] Punpanich W, Sirikutt P, Waranawat N. Invasive Vibrio cholerae non-O1 non-0139 infection in a thalassemic child. J Med Assoc Thail Chotmaihet Thangphaet. 2011;94 Suppl3:S226-30.

[21] Colombara DV, Cowgill KD, Faruque ASG. Risk factors for severe cholera among children under five in rural and urban Bangladesh, 2000-2008: A hospital-based surveillance study. PloS One. 2013;8(1):e54395.

[22] Fukuda JM, Yi A, Chaparro L, Campos M, Chea E. Clinical characteristics and risk factors for Vibrio cholerae infection in children. J Pediatr. 1995;126(6):882-86.

[23] A Case of Vibrio cholerae Non-O1/O139 Gastroenteritis. Ann Lab Med. 2004;24(6):386-88.

[24] Kirby-Bauer-Disk-Diffusion-Susceptibility-Test-Protocol-pdf.pdf [Internet]. [cited 2020 Feb 20]. Available from: https://www.asm.org/getattachment/2594ce26-bd44-47f6-8287-0657aa9185ad/Kirby-Bauer-Disk-Diffusion-Susceptibility-Test-Protocol-pdf.pdf.

[25] 9789241506823_Module-4_eng.pdf [Internet]. [cited 2020 Feb 21]. Available from: https://apps.who.int/iris/bitstream/handle/10665/104772/9789241506823_Module-4_eng.pdf;jsessionid=A3C6D41D7CAFD41B777E2BA6B8F5C141?sequence=6.

[26] Dutta D, Chowdhury G, Pazhani GP, Guin S, Dutta S, Ghosh S, et al. Vibrio cholerae Non-O1, Non-O139 Serogroups and Cholera-like Diarrhea, Kolkata, India. Emerg Infect Dis. 2013;19(3):464-67.

[27] Sebastian T, Anandan S, Jeyaseelan V, Jeyaseelan L, Ramanathan K, Veeraraghavan B. Role of seasonality and rainfall in Vibrio cholerae infections: A time series model for 11 years surveillance data. Clin Epidemiol Glob Health. 2015;3(3):144-48.

[28] Kanungo S, Sah B, Lopez A, Sung J, Paisley A, Sur D, et al. Cholera in India: an analysis of reports, 1997-2006. Bull World Health Organ. 2010;88(3):185-91.

[29] Clemens JD, Nair GB, Ahmed T, Qadri F, Holmgren J. Cholera. The Lancet. 2017;390(10101):1539-49.
[30] Harris JB, Ivers LC, Ferraro MJ. Case 19-2011. N Engl J Med. 2011;364(25):2452-61.
[31] Enzensberger R, Besier S, Baumgärtner N, Brade V. Mixed diarrhoeal infection caused by Vibrio cholerae and several other enteric pathogens in a 4-year-old child returning to Germany from Pakistan. Scand J Infect Dis. 2005;37(1):73-75.
[32] Gharibi O, Mirzaei K, Karimi A, Darabi H. Mixed infections of Vibrio cholerae O1 Ogawa EL Tor with Shigella dysenteriae. Pak J Biol Sci PJBS. 2010;13(22):1110-12.
[33] Shrivastava AK, Kumar S, Mohakud NK, Suar M, Sahu PS. Multiple etiologies of infectious diarrhea and concurrent infections in a pediatric outpatient-based screening study in Odisha, India. Gut Pathog. 2017;9(1):16.
[34] Dalsgaard A, Forslund A, Bodhidatta L, Serichantalergs O, Pitarangsi C, Pang L, et al. A high proportion of Vibrio cholerae strains isolated from children with diarrhoea in Bangkok, Thailand are multiple antibiotic resistant and belong to heterogenous non-O1, non-O139 O-serotypes. Epidemiol Infect. 1999;122(2):217-26.
[35] Uppal B, Mehra B, Panda PS, Kumar SK. Antimicrobial susceptibility profile of Vibrio cholerae strains isolated at a tertiary care medical centre in New Delhi, India. Int J Community Med Public Health. 2017;4(3):868-71.
[36] WHO EMRO | Isolation frequency and susceptibility pattern of non-O1 and non-O139 Vibrio cholerae in a tertiary health care laboratory, 1999-2012 | Volume 22, issue 2 | EMHJ volume 22, 2016 [Internet]. [cited 2019 May 4]. Available from: http://www.emro.who.int/emhj-volume-22-2016/volume-22-issue-2/isolation-frequency-and-susceptibility-pattern-of-non-o1-and-non-o139-vibrio-cholerae-in-a-tertiary-health-care-laboratory-19992012.html.
[37] Pediatrics AA of. Recommendations on preventing, treating cholera. AAP News. 2010 Oct 28;E101028-1.
[38] Deshayes S, Daurel C, Cattoir V, Parienti JJ, Quilici ML, de La Blanchardière A. Non-O1, non-O139 Vibrio cholerae bacteraemia: Case report and literature review. SpringerPlus. 2015;4(1):575.
[39] Engel MF, Muijsken MA, Mooi-Kokenberg E, Kuijper EJ, Westerloo DJ van. Vibrio cholerae non-O1 bacteraemia: description of three cases in the Netherlands and a literature review. Eurosurveillance [Internet]. 2016 Apr 14 [cited 2019 May 4];21(15). Available from: http://www.e-sciencecentral.org/articles/SC000015533.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Paediatrics, Christian Medical College, Vellore, Tamil Nadu, India.
2. Professor, Department of Microbiology, Christian Medical College, Vellore, Tamil Nadu, India.
3. Professor, Department of Paediatrics, Christian Medical College, Vellore, Tamil Nadu, India.
4. Professor, Department of Microbiology, Christian Medical College, Vellore, Tamil Nadu, India.
5. Statistician, Department of Biostatistics, Christian Medical College, Vellore, Tamil Nadu, India.
6. Associate Professor, Department of Paediatrics, Christian Medical College, Vellore, Tamil Nadu, India.
7. Assistant Professor, Department of Paediatrics, Christian Medical College, Vellore, Tamil Nadu, India.
8. Professor, Department of Paediatrics, Christian Medical College, Vellore, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Leenath Thomas,
Paediatrics 1 Office, Christian Medical College Hospital, Vellore, Tamil Nadu, India.
E-mail: tvleenath@yahoo.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jan 16, 2020
- Manual Googling: Feb 12, 2020
- iThenticate Software: Mar 27, 2020 (8%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 11, 2020**
Date of Peer Review: **Feb 19, 2020**
Date of Acceptance: **Mar 19, 2020**
Date of Publishing: **Apr 01, 2020**