CASE REPORT

Cholera gravis associated with acute renal failure in a traveler from Haiti to the United States

Andrés Reyes-Corcho*, Richard W. Pinsker, Samir Sarkar, Farshad Bagheri, Mahendra C. Patel, Pablo Lam, Argentina González

Department of Internal Medicine, Jamaica Hospital Medical Center, 89th Avenue and Van Wyck Expressway Jamaica, NY 11418, USA

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Summary  Cholera is a gastroenteric disease caused by epidemic or pandemic Vibrio cholerae which still is responsible for over 100,000 annual deaths worldwide. Since October 2010, Haiti experienced a cholera outbreak affecting more than 300,000 persons. Few imported cases related to the Haitian epidemic have been reported so far in the United States and Canada. We presented a patient who developed cholera gravis soon after arrival at New York City from Haiti. The patient needed admission to an Intensive Care Unit, for vigorous intravenous hydration, antibiotic therapy, and hemodialysis due to refractory oliguric renal failure. The patient was discharged the day 6 after admission and V. cholerae O1 was isolated from the stool culture. Cholera can be a life-threatening disease; early recognition based on travel history and clinical features is the cornerstone for successful management.

Introduction

Cholera is an infectious disease caused by Vibrio cholerae (V. cholerae) whose course can vary from a mild diarrheal syndrome to a rapidly fatal malady called cholera gravis. From the classic epidemiological description by John Snow during the epidemic of cholera in London, to the isolation of the V. cholerae by Robert Koch in 1883 and the consecutive observation of Filippo Pacini (he named the bacterium V. cholerae) and Sambhu Nath De (he characterized the cholera toxin) in 1959, the disease has caused seven pandemics and it is endemic in over 50 countries.1 It is estimated that at least 5–7 million persons develop clinical cholera each year, resulting in approximately 100,000 to 120,000 deaths.2 The current seventh cholera pandemic began in 1961 in Celebes, Indonesia. From 1991
Cholera gravis associated with acute renal failure in a traveler

A 76-years-old African-American male was brought from John F Kennedy airport to the Emergency Department at Jamaica Hospital Medical Center in the city of New York, because of multiple episodes of watery painless diarrhea, severe weakness, dizziness, and muscle cramps. The patient had nausea and one episode of clear vomiting, denied fever, chills, shortness of breath or headache, but said that he had not urinated for hours. The symptoms started after he embarked on a flight from Haiti where he spent 3 weeks. The patient stated that he visited several relatives at the suburban area of Port-au-Prince, but denied any direct contact with sick individuals. The patient had essential hypertension controlled with lisinopril. He had no history of alcohol, tobacco or drug use and was not using any other medication at the time the symptoms started.

On examination, the patient seemed somnolent with critical ill appearance, marked mucous membrane dryness, sunken-glassy eyes and a positive skin turgor sign. The extremities were cool with weak peripheral pulse. The blood pressure was 70/20 with tachycardia. The lungs were clear and there was tachypnea of 28 breaths per minute. There was mild abdominal tenderness on deep palpation without organomegaly.

Upon arrival vigorous intravenous hydration was started, 4 × 1000 ml of normal saline were given followed by a continuous infusion of Ringer’s lactate plus potassium at 200 ml/kg of body weight during the first 24 h. A Foley catheter was placed and no urinary output was obtained. A central venous line was inserted in the right subclavian vein after several unsuccessful attempts to insert a peripheral line due to vascular collapse secondary to severe hypovolemia. The patient was admitted at the Medical Intensive Care Unit (MICU) and cholera was suspected based on the travel history and the severity of the clinical manifestation. Doxycycline 300 mg was given orally.

At the time the patient was admitted to the Intensive Care Unit, the laboratory findings were consistent with neutrophilic leukocytosis of 20.8 K/µL (4.8–10.8 K/µL), anion gap metabolic acidosis (pH: 7.16 [7.35–7.45]), high lactic acid level (6.8 [0.5–2.2 mmol/L]), low bicarbonate (16 [21–28 mEq/L]), hypokalemia (3.1 [3.6–5.0 mEq/L]) and azotemia, BUN: 23 [5–20 mg/dL], creatinine 2.7 [0.6–1.2 mg/dL].

During the first 24 h after admission the patient was severely ill, episodes of diarrhea were too frequent to count, a flexi-seal was placed and 9 L of liquid "water-rice" diarrhea was collected during the next 24 h after admission (Fig. 1). Blood pressure improved with the continuous intravenous hydration. On the second day, the main concern was the deterioration of renal function, even when the patient clinically reached the euvoletic status, the urinary output was 200 ml in 24 h, there were worsening azotemia (BUN/creatinine 31/7.3 mg/dL) and persistent metabolic acidosis. Oligoanuric acute kidney injury was suspected and two sessions of hemodialysis were completed successfully.

During the third day, the patient consumed solid food and oral fluid. No episode of diarrhea occurred and the total urinary output was 2680 ml. The laboratory abnormalities returned progressively to normal, and he was

Figure 1 Typical “rice water” diarrhea collected in a flexi-seal bag. The patient had profuse diarrhea exceeding 9 L in 24 h.
discharged after 6 days of hospitalization. Finally, stool culture was positive for *V. cholerae* O1.

**Discussion**

Cholera is an extremely virulent disease, even when 75% of infected individuals do not develop clinical disease; after a short incubation period of 1–3 days, 20% of the symptomatic patient may have sudden onset of profuse painless watery diarrhea, shortly progressing to severe volume and electrolyte depletion. Clinical symptoms parallel volume contraction, and at 10% loss of the normal body weight, oliguria, absent peripheral pulses, sunken eyes and wrinkle skin may be identified. If untreated, cholera will become in a life-threatening condition in a few hours, including serious complications such as coma, renal failure due to acute tubular necrosis and refractory shock. Few cases may develop a malignant toxemic form (cholera sicca or cholera siderans) before the classical symptoms of vomiting and diarrheas appear, usually with high mortality. Early recognition based on the travel history and clinical features are essential. Mortality rate of appropriately treated patients is usually less than 1%; but, may reach 2.1%–7% as has occurred in the recent cholera epidemic in Haiti.3

Cholera is the prototype of “secretory diarrhea” resulting from increased chloride secretion, decreased sodium absorption, or increased mucosal permeability. Although most of the upper small bowel infection, cholera is a relatively noninvasive and noninflammatory disease, causing watery diarrhea, which may contain more than 10⁹ organisms per milliliter. Patients with severe cholera may shed more than 10¹³ organism per day.7,8 Other causes of noninvasive diarrhea such as enterotoxigenic *Escherichia coli*, *Bacillus cereus*, caliciviruses (including noroviruses), and rotavirus in infants, should be included in the differential diagnosis.9

Cholera is a toxin-mediated disease and the classical watery diarrhea is mainly due to the action of cholera toxin (CT), a potent protein enterotoxin produced by the organism in the small intestine, first postulated by Robert Koch in 1886 after the isolation of *V. cholerae* from a stool sample originated in Egypt. The hallmark of this toxin is the perturbation of the adenylate cyclase pathway, with the secondary increase in cyclic AMP in the epithelial cells and the rise of fluid secretion; however, the activation of prostaglandins and neural histamine receptors by the toxin, may play a role in the mechanism of the disease.10 Two chromosomal segments: CTXφ (virulence cassette) and VPI are responsible for the production of CT and the regulation of virulence genes and colonization factors in the toxigenic strains.11 Current evidence suggests the existence of a novel extracellular toxin called: W07, 10 times more potent than CT, which can be produced by *V. cholerae* W07, a serogroup O1 variant despite the absence of the virulence genes from its genome.12

Of the approximately 200 serogroups of *V. cholerae*, only serogroups O1 and O139 have epidemic potential. *V. cholerae* O1 biotype El Tor responsible for the 7th cholera pandemic started in Indonesia in 1961, is also the etiology of the current epidemic in Haiti; nevertheless, several variations suggest the existence of “El Tor hybrid strain” a clonal genotype phylogenetically related to CIRS 101 strain, one of the highest virulent *V. cholerae* O1 from India.3,13

Compared with previous strains, there is some evidence that the hybrid strain in Haiti causes more asymptomatic cases, persists longer in the environment, and exists in higher concentration of bacteria in feces, including asymptomatic cases.3

This Gram-negative, rod-shaped, waterborne bacterium persists in the environment, and is associated with brackish estuarine water, especially in areas where fresh and salt water intermix. The bacterium becomes hyperinfectious following passage through the human intestine, facilitating explosive outbreaks and epidemics among susceptible populations.7,14 Several conditions including poverty, malnutrition, unsafe water and foods, tropical hypochlorhydria syndrome associated with *Helicobacter pylori* infection, ages over 2 years, persons with type O blood group and immunological naive individuals have been recognized as potential risk factors for cholera and severe disease.10,14,15

The diagnosis of *V. cholerae* infection may be confirmed by the classic “shooting star” movement of organisms when looking at a wet mount of fresh stool under a dark field microscope, and its serotype can be determined by immobilization with specific antiserum. Isolation of the virbio in culture of stool or rectal swab requires the use of selective medium such as thiosulfate-citrate-bile-salt-sucrose (TCBS), permitting typing and susceptibility testing. An antigen detection cholera dipstick assay is available commercially for the use in the field at resource-limited areas.10,14

Hydration is the corner stone of the treatment of cholera and it is the only effective way to prevent death secondary to hypovolemic shock. Euvolemia should first rapidly be restored, and adequate hydration should then be maintained to replace ongoing loss of body fluids. Mild cases can be treated with the standard oral replacement formulas. Rapid correction of severe hypovolemia is life-saving in patient with significant fluid deficit (>10% of body weight). In these cases, the recommended rate of intravenous hydration is 100–200 ml/kg, allowing the safety replacement of the total fluid deficit in the first 3–6 h of therapy. Due to the concomitant bicarbonate deficit, acidosis and hypokalemia, Ringer’s lactate with extra potassium is the solution of choice; normal saline could be a reasonable alternative if the first is not available. Intra-venous hydration should be continued until the resolution of the hypovolemia, or until the patient can ingest hydration solutions by mouth.9,10

As occurred in our patient, renal complication can be present in the course of cholera and other gastrointestinal infections. Oligoanuric acute kidney injury, tubulointerstitial nephritis and persistent metabolic acidosis, could be a potential complication of the infection itself or secondary to volume depletion. Renal replacement therapies (hemodialysis and peritoneal dialysis) must be considered as therapeutic options in patients with acute renal failure.16

The administration of antibiotics has a secondary role in the treatment of cholera.17 The WHO recommends the use of antibiotics for cholera patients with severe dehydration
and serious disease. However, there is an increasing trend to use antibiotics during cholera epidemics in certain regions of the world. It is postulated that early treatment with effective oral antimicrobials eradicates vibrios, may reduce the stool volume by 50% and stops diarrhea within 48 h.18

Increasing resistance to tetracycline, nalidixic acid and trimethoprim/sulfamethoxazole is reported continuously, suggesting avoiding these drugs in cases associated with the Haiti epidemic, and region with high burden of V. cholerae O139 infection.3 Several mechanisms are responsible for this phenomenon: production of extended-spectrum beta-lactamases, enhanced multi-drug efflux pump activity, plasmid-mediated fluoroquinolone resistance, and chromosomal mutations have been described as the most commons ones.19 The selection of the antibiotic should consider the regional susceptibility pattern. Azithromycin 1000 mg or doxycycline 300 mg (one dose) appears to be the best choices. In a published study, 1 g of azithromycin in a single dose was superior to ciprofloxacin in clinical and bacteriological response.20

Quality of sanitation and health infrastructures are essential for containing the spread of cholera worldwide. Provision of safe water and facilities for sanitary disposal of feces, improved nutrition, and attention to food preparation and storage, provide a significant reduction in the risk of cholera transmission.

There are two oral cholera vaccines on the market (not in the USA); both are killed whole cell vaccines. Dukoral (licensed in over 60 countries) also contains the nontoxic (recombinant) B subunit of the CT which stimulates anti-toxic and antibacterial immunity, and has been shown to have 85% of protective efficacy.3 Two oral live attenuated vaccines are undergoing clinical trials. The immunomodulatory property of the CT-B represents a potential tool for the development of new oral vaccine candidates.10,12

**Conflict of interest**

The authors declare no conflict of interest regarding this article.

**References**


