

## Acute, severe cryptosporidiosis in an immunocompetent pediatric patient

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### Abstract

Severe diarrheal illness in children can be attributed to a number of different microbiological agents. Without appropriate microbiological testing of stool samples, patients who present with multiple days of severe diarrhea might have a delay in proper diagnosis and treatment. Here, we report a case of an immunocompetent pediatric patient presenting with acute cryptosporidiosis. Humans and bovine species are known hosts of cryptosporidium and several studies have evaluated the zoonotic transmission of cryptosporidium from cattle to humans. Adding diagnostic tests for cryptosporidium like Ziehl-Neelsen staining of stool or fecal rapid antigen detection techniques should be considered in the workup of patients presenting with undifferentiated, severe diarrheal illness, especially in those who have close contact with livestock.

### Introduction

Diarrheal diseases are the second most common cause of death in children under the age of 5 years worldwide.<sup>1</sup> Nearly 375 million episodes of acute diarrhea occur each year in the United States, causing more than 900,000 hospitalizations and up to 6000 deaths.<sup>2-5</sup> *Cryptosporidium* spp. are oocyst-forming parasitic protozoa that are transmitted fecal-orally, causing diarrheal illness. The most common mode of transmission of cryptosporidium is thought to be exposure to contaminated water, however, contact with cattle has also been identified as a risk factor for cryptosporidiosis.<sup>6</sup> The symptoms of acute cryptosporidiosis include severe, watery diarrhea, eventually leading to dehydration, malabsorption, and malnutrition.<sup>7</sup> Without appropriate microbiological testing of stool samples, patients who are immunocompromised may have symptoms that persist for weeks, delaying

proper treatment. It is a well-known cause of severe diarrhea in immunocompromised patients, especially those with acquired immune deficiency syndrome (AIDS) or X-linked hyper-immunoglobulin M (IgM) syndrome type 1.<sup>8</sup> We are reporting a case of severe cryptosporidiosis in an immunocompetent pediatric patient.

### Case Report

An 11-year-old female presented with a seven-day history of nausea, vomiting, colicky abdominal pain, and profuse diarrhea. Prior to presentation she vomited approximately ten times per day and had up to six episodes of non-bloody, non-mucous, watery diarrhea daily. The patient's mother stated that her symptoms had been progressively getting worse since the initial onset of diarrhea. The patient presented to her primary care physician on the second day of symptoms and was diagnosed with acute gastroenteritis. No medications were administered at that time and the patient was recommended to drink fluids to avoid dehydration. On the fifth day of symptoms, the patient presented to a local urgent care center, where she was given a shot of ceftriaxone and a prescription for promethazine. The patient experienced slight improvement in her symptoms for one day, but quickly worsened the next day. On the seventh day, the patient returned to the urgent care clinic, at which time she was admitted for further work up. On initial physical examination, she showed signs of moderate to severe dehydration, including sunken eyes, excessive thirst, and dry mucus membranes. The patient was afebrile with a heart rate of 86 beats per minute, respiratory rate of 22 per min, and a blood pressure of 105/65 mmHg. The patient also reported a 13-lb weight loss since the onset of symptoms. The patient was cooperative during examination, and showed signs of lethargy and fatigue. Pulmonary and cardiac examinations were normal. Abdominal examination revealed a soft, diffusely tender, non-distended abdomen with hyperactive bowel sounds and no rebound tenderness. No lymphadenopathy was present on examination.

Laboratory workup at the emergency department revealed a white blood cell count of 8400 cells/uL with 64% neutrophils, 18% lymphocytes, 14.8% monocytes, 2.2% eosinophils, and 0.4% basophils. Blood biochemistry showed an elevated lipase (112 U/L), severe hypokalemia (2.6 mMOL/L), low CO<sub>2</sub> (19 mMOL/L), and high blood urea nitrogen (28 mg/dL). All other results of complete blood count and comprehensive metabolic panel studies were within normal limits. The patient was immediately started on IV fluids (D5 ½ NS), ondansetron,

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Key words: *Cryptosporidium*; immune status; pediatric.

Acknowledgments: the authors would like to thank Dr. Jerry Kirkland and Dr. Micah Boyer for their contribution to the clinical care of this patient.

Contributions: all authors listed contributed to the drafting, review and final approval of the manuscript.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 12 January 2016.

Accepted for publication: 20 April 2016.

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Licensee PAGEPress, Italy  
Clinics and Practice 2016; 6:837  
doi:10.4081/cp.2016.837

oral electrolyte replacement protocol and was admitted to the pediatric floor. Upon admission, the patient was made nil *per os* except for medications. While in the emergency department, stool samples were sent for routine studies, including culture, white blood cells (WBC) count, ova and parasite studies, and occult blood. The patient's stool was also tested for *Clostridium difficile* at this time. An arterial blood gas was unable to be successfully performed due to patient distress. In the emergency department, the patient also received an abdominal computed tomography (CT) scan with oral and intravenous contrast, as well as a right upper quadrant ultrasound and urine analysis to rule out acute abdominal pathology.

Stool cultures revealed normal enteric flora and no growth of *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, or *Escherichia coli* O157:H7. Stool exam showed many WBCs present, no ova or parasites, and negative occult blood and *C. difficile* antigens. The CT scan revealed multiple moderately large mesenteric lymph nodes, with no other apparent pathology. Ultrasound revealed gallbladder sludge without gallstone shadowing or sonographic evidence of acute cholecystitis. Urinalysis was positive for trace protein and ketones, and negative of leukocyte esterase and nitrites.

On the third day of hospitalization the patient showed no clinical signs of improve-

ment. Nursing staff reported that the patient had 10-15 episodes of loose stools per day amounting to 1900 mL of fluid. The patient was also recorded to have 1-2 episodes of vomiting per day. The nursing staff also recorded that the patient was passing her oral potassium replacement medication in her stool less than one hour from administration. The patient was then switched to the IV electrolyte replacement protocol. At this time, additional stool studies were ordered to include testing for *Norovirus*, *Rotavirus*, *Adenovirus*, *Giardia*, and *Cryptosporidium* antigens, as well as stool anion gap.

Results of the stool immunoassay antigen testing were received the same day and reported as positive for cryptosporidium. Speciation was not performed due to limited capability of the testing modality. The results for the stool anion gap were never reported, likely due to miscommunication with the order process. Infectious disease was consulted, and HIV testing was ordered and determined to be negative. Immunoglobulin studies were then performed to rule out other immunodeficiencies, which were also all found to be normal. A three-day treatment of nitazoxanide (500 mg twice daily) was initiated upon diagnosis, and the patient saw significant clinical improvement by the second day of treatment. The patient was discharged from the hospital three days after the nitazoxanide regimen was finished and she tolerated an oral diet. A copy of the patient's discharge summary was sent to her primary care physician, and parents were instructed to have the patient follow up within the week.

Upon diagnosis, the patient and her family were questioned further about her history and possible exposure to transmitting agents for cryptosporidium. It was reported that five days before the onset of diarrhea, the family purchased two calves from a local livestock show. One of the calves had died soon after birth of an unknown cause. The patient and her family had bottle-fed both calves in their backyard and the patient was directly involved in bottle-feeding each calf. The patient and her family reported brief exposure at a public pool during the week prior to the onset of symptoms.

## Discussion and Conclusions

*Cryptosporidium* spp. are among several known causes of diarrheal outbreaks and has been associated with contamination of recreational water sources and consumption of contaminated water.<sup>9</sup> Humans and bovine species are among the known hosts of cryptosporidium and several studies have evaluated the zoonotic transmission of cryptosporidium from bovines to humans.<sup>9,10</sup> Previous studies have

suggested that newborn calves are the only major reservoir for *C. parvum* infections in humans with nearly 75% of newborn calves up to two months of age being infected with the protozoa.<sup>11</sup> A previous study also found a causal relationship between bottle-feeding newborn calves and an outbreak of cryptosporidium.<sup>12</sup>

In the reported patient, the onset of symptoms began 5 days after the patient's family acquired two newborn calves, which the patient actively participated in bottle-feeding. One of the calves passed away soon after birth, possibly from cryptosporidiosis. The patient had an otherwise negative travel and social history, suggesting that she acquired the protozoa from bottle-feeding the deceased calf. Each of the family members, including the patient's twin sister, participated in bottle-feeding the calf, however, only the reported patient had severe symptoms, while the other family members experienced mild, self-limited symptoms, which is expected in immunocompetent hosts. This raises the question of how much the level of inoculum affects the severity of symptoms in cryptosporidiosis.

Several studies have suggested that the severity of cryptosporidiosis is dependent on the immune status of the patient, with more impaired immune statuses being associated with more severe symptoms.<sup>7,13</sup> In immunocompetent patients, the symptoms are usually self-limited, lasting approximately 5-10 days, and only require supportive rehydration and replacement of lost sodium, potassium, bicarbonate, and glucose.<sup>7</sup> However, in patients who are immunocompromised, cryptosporidiosis can cause severe, cholera-like illness or chronic diarrhea, eventually leading to wasting, malabsorption, and long-term negative effects on growth, weight gain, and physical and cognitive development in children.<sup>14</sup> Additionally, one older study asserted that in primate models for cryptosporium, the level of inoculum did not affect severity or duration of disease.<sup>15</sup> However, there have been no studies confirming this trend in humans.

In children, the only antiparasitic drug that has been proven to be effective is nitazoxanide, administered twice daily with food for 3 days at a dose of 500 mg (>12 years of age), 200 mg (4-11 years of age), or 100 mg (1-3 years of age).<sup>7</sup> Nitazoxanide is only approved for use in pediatric patients who are non-immunodeficient, and has been found to reduce the duration of diarrhea and oocyte shedding.<sup>16</sup> One study stated, that given the safety of nitazoxanide and the potential chronic negative sequelae associated with prolonged cryptosporidiosis, children should be administered this medication in most suspected cases.<sup>7</sup>

This same study stated that adults with HIV should be given a higher dose of nitazoxanide (500-1000 mg) twice daily until clinical symp-

toms resolve, oocysts are eliminated from the stool and the CD4 T-cell count recovers to greater than 100 cells/mm<sup>3</sup>.<sup>7</sup> However, in adults with HIV only the use of highly active antiretroviral therapy has been proven to ultimately reduce the frequency and severity of cryptosporidium.<sup>16</sup>

Few other treatment options exist for cryptosporidium regardless of immune status. Paromomycin, an aminoglycoside antibiotic that targets bacterial ribosomes, was the first drug tested against cryptosporidium in humans.<sup>16</sup> However, it appears to offer only modest activity against cryptosporidium and has only been tested in small clinical trials with inconclusive evidence.<sup>16,17</sup> Pyvinium pamoate, an anthelmintic drug, may be a candidate for clinical trials as it has been found to have activity against cryptosporidium in cell culture and in neonatal mouse models.<sup>16</sup> Parenteral octreotide can be used to alleviate the symptoms of severe diarrhea, however, it does not offer any curative response to this disease.

To date, there have been no studies published that describe immunocompetent pediatric patients that present with prolonged illness in acute cryptosporidiosis in the United States. Cryptosporidiosis commonly affects both immunocompetent and immunocompromised individuals, but patients typically present in characteristic ways based on the patients' immune status. The reported patient presented paradoxically with severe symptoms and an immunocompetent state. Based on this presentation, the most likely explanation is that her severe symptoms were due to a higher inoculum of the protozoa, rather than her immune status, which she received during her active involvement in the care and feeding of her family's two calves.

Therefore, in immunocompetent patients presenting with multiple days of severe diarrhea and negative routine stool studies, it is important to keep cryptosporidiosis in the differential diagnosis. This is most relevant in any patients who have direct contact or involvement with livestock and, in particular, cattle. Thus, we recommend adding a diagnostic test for cryptosporidium to the laboratory workup of any patient presenting with an undifferentiated, severe diarrheal illness, especially in those who have close contact with cattle.

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