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THERAPEUTIC DILEMMA

Optimal Treatment of Campylobacter Dysentery

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The following are contrived case reports that have been created as a teaching case in the area of pediatric pharmacotherapy.

CASE 1

A 9 day old Caucasian female infant was admitted to a general pediatric floor from an outside hospital for a 23 hour observation and treatment of dehydration associated with severe diarrhea. Parents reported frequent stools for 4 days prior to admission with possible hematochezia 1 day prior to admission. Stools were occurring every 15 to 20 minutes at times. No vomiting or fever accompanied the diarrheal episodes. The child's formula was changed 3 days prior to admission with no improvement in symptoms. Her birth history included an uncomplicated vaginal delivery at 38 weeks, with a birth weight of 2.93 kg. No medical problems or abnormalities had been identified prior to this hospital admission. She had no previous contact with sick individuals or exposure to pets. The patient's mother has alpha I antitrypsin deficiency, but no other pertinent family history was identified. On admission, the patient weighed 2.77 kg and the physical exam revealed soft and flat fontanelles, and pink, wet oral mucosa. Bowel sounds were present throughout and the abdomen was soft and non-distended. Stools were sent to the lab for culture and sensitivity. The patient's home formula was continued without modification and intravenous (IV) maintenance fluids were started to aid with hydration. All electrolytes were within normal limits and vital signs remained stable throughout hospitalization. After admission, the patient only had 1 loose stool and was discharged the following day with a suspected viral process and no signs of dehydration. The day following discharge, the patient returned to the hospital's pediatric emergency department (ED) with bloody stools of jelly-like consistency. Stool cultures from the first admission revealed a *Campylobacter jejuni* infection, and the patient was given 1 dose of erythromycin ethylsuccinate suspension (EES) 29 mg (10.5 mg/kg) in the ED and re-admitted to the general pediatrics floor. Maintenance fluids were restarted and the patient's home formula was resumed unchanged. EES (200 mg/5 mL) was initiated at a dose of 30 mg by mouth 3 times daily to provide 32.5 mg/kg/day. The following day, the order for EES was changed to 30 mg by mouth every 6 hours to give a total daily dose of 43.2 mg/kg. On day 3 of the second admission, the patient was dis-

ABBREVIATIONS CDC, Centers for Disease Control and Prevention; ED, emergency department; EES, erythromycin ethylsuccinate suspension; IHPS, Infantile Hypertrophic Pyloric Stenosis; IV, intravenous; PCP, primary care physician; US, United States

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charged home with directions to continue EES at the same dose for 4 more days.

CASE 2

A 7 month old Caucasian male was brought to the ED for a 1 day history of diarrhea, vomiting and fever (up to 103.6°F, orally). The infant was administered 1 oral dose of ondansetron and provided Pedialyte popsicles. A chest x-ray was negative, stool hemoccult was positive, and a culture and sensitivity of the stool was obtained. The patient had good oral intake in the ED and was released to follow up with his primary care physician (PCP) the following morning. At the PCP's appointment, the parents reported that the infant did not drink any liquids overnight, was fussy, and was not acting normally. The infant was urinating, but continued to have hematochezia (9 stools overnight) and fever (up to 104.3°F, orally). The infant was afebrile in the clinic, had a sunken fontanelle and dry oral mucosa, but was in no acute distress. This was an overall healthy infant, born full-term and meeting developmental milestones. The infant did not attend daycare and the family had outside pets, none of which were ill. The infant had no travel history or recent changes in diet. However, he had been diagnosed with enterhemorrhagic *E coli* 5 months previously, which resolved without treatment. His last antibiotic course was 6 weeks earlier for otitis media. He had been previously diagnosed with allergic colitis, thus the infant was taking Alimentum (hypoallergenic formula). The PCP diagnosed mild-moderate dehydration, fever, and hematochezia, and rechecked the stool specimen from the ED. The culture was growing presumptive *campylobacter*, thus the patient was admitted to the hospital for hydration and treatment of *campylobacter* diarrhea. In the hospital, the infant weighed 8.8 kg, was placed on IV maintenance fluids, and encouraged to take fluids by mouth. Acetaminophen was ordered as needed for fever and/or irritability. The basic metabolic panel and complete blood count were normal except for a neutrophil count of 29%, bands 14%, and lymphocytes 47% (white blood count 10.45 m^3). The blood culture was negative. The stool *C difficile* toxin a/b was negative. The stool culture grew *Campylobacter jejuni*. The patient was afebrile and vital signs were normal during admission. The patient initially received 2 doses of erythromycin ethylsuccinate suspension 100 mg (11.4 mg/kg/dose). The next morning he was tolerating his formula with adequate intake, weighed 8.91kg, but still had some diarrhea. He was switched to azithromycin 100 mg ×1 (11.2 mg/kg/dose) and discharged on azithromycin 50 mg daily (5.6 mg/kg/dose) for 4 days of treatment.

DISCUSSION

The most common cause of acute bacterial enterocolitis worldwide is *Campylobacter* infection.[1] Specifically, *Campylobacter jejuni* has been identified as the most common cause of community-acquired enteritis.[2] According to the Centers for Disease Control and Prevention (CDC), there are approximately 2.4 million cases of *Campylobacter* infection in the United States (US) each year, which is nearly 1% of the entire US population.[1] The Foodborne Diseases Active Surveillance Network (FoodNet) surveillance group, a project of the CDC and Emerging Infections Program, has documented 28.4 cases per 100,000 infants.[3] In 2006, FoodNet documented 12.7 cases per 100,000 people in the US, which had decreased from 15 cases per 100,000 people.[4]

California has the highest incidence of infection, with Tennessee having the lowest.[4] Most cases are never diagnosed or reported (no mandatory reporting in the US) since they are generally self-limiting and often mimic viral gastroenteritis. Cases are mostly sporadic and isolated versus regional outbreaks, and occur more commonly during the summer months.[3] *Campylobacter* organisms are found more in infants and young adults than other age groups, and more males acquire the organism than females.[3] In developing countries, *Campylobacter* species contribute significantly to childhood morbidity. Although death is uncommon in the US, it is thought that more than 100 people die each year due to *Campylobacter* infections.[3]

Campylobacter jejuni is a motile, S-shaped gram negative rod that causes an infectious process which is often indistinguishable from illness caused by viruses or other bacterial organisms. This pathogen was historically described as a "vibrio related" organism seen in

animals, and was not isolated from human feces until 1968.[5] Transmission of *C jejuni* occurs through the fecal–oral route, via sexual transmission, exposure to sick animals, such as dogs, cats, hamsters or birds, and by ingestion of raw milk, uncooked poultry, or water from contaminated sources. While exposure to 10,000 *C jejuni* organisms likely cause an infectious process, illness has occurred with as few as 500 organisms.[6,7] FoodNet recently completed a case-controlled study to identify risk factors for *campylobacter* infections.[8] They found that drinking well water or riding in a shopping cart next to meat or poultry were risk factors for infants less than 6 months of age.[8] Visiting or living on a farm, having a pet with diarrhea in the home, and eating vegetables and fruits that were prepared in the home were risks for infants 7-11 months of age.[8] International travel increased the risk of C*ampylobacter* infections in all infants.[8] However, breastfed infants who were less than 6 months of age were less likely to contract the infection than those who were not breastfed.[8]

The incubation period for *C jejuni* is between 1-7 days and initial symptoms may include a prodrome phase, often accompanied by fever, headache, malaise and myalgias. This early prodrome is generally followed by cramping abdominal pain, high fever (up to 104º F), and numerous, often bloody or mucoid loose bowel movements. Infants and young children may have bloody diarrhea without a fever.[9] Mild infections may mimic viral gastroenteritis. Diarrhea may resolve within 2-3 days, but the abdominal pain often persists for several days longer. The illness usually lasts about 7days. About 20% of patients have a relapse or a severe infection.[9] Although this enteritis is generally very acute and self- limiting, complications such as Guillain-Barre syndrome, sepsis, and even death can occur in patients who are at the extreme limits of age or who are immunocompromised.[5] Approximately 40% of Guillain-Barre syndrome cases are secondary to *campylobacter* infections.[3]

Because *Campylobacter* enteritis is often self-limiting, supportive measures and oral fluid restoration are the mainstays of therapy. Anti-motility agents are not indicated for use in gastroenteritis and should not be recommended. Treatment with antibiotics is warranted only in patients with persistent fever, bloody diarrhea for 7 days or more, significant volume loss, and those having 8 or more bowel movements per day.[5] Patients known to be at greater risk of complications may also benefit from antibiotic therapy started early in the course of the illness. While earlier studies were inconclusive about whether or not antibiotic therapy played a role in shortening the actual clinical course of the illness, a recent meta analysis concluded that antibiotic therapy shortened the duration of intestinal symptoms by approximately 1 day.[10-13] Treatment may possibly prevent relapse if administered early as well.[9] Excretion of *Campylobacter* is usually 2-3 weeks without treatment but only 2-3 days with treatment.[9]

If antibiotic treatment is indicated, a macrolide is the drug of choice for *C jejuni* infections. The American Academy of Pediatrics recommends a treatment course of 5-7 days with a macrolide such as erythromycin or azithromycin.[9] Erythromycin is one option that provides an inexpensive, efficacious treatment with minimal potential for toxicity. Although resistance rates are reportedly increasing for erythromycin, they remain less than 5%, supporting its continued utility despite past widespread use for this indication.[1,14] Azithromycin has gained favor for use against *C jejuni* solely based upon drug characteristics. Its once daily dosing, improved tolerability, decreased association of Infantile Hypertrophic Pyloric Stenosis (IHPS) and overall less adverse effects profile versus erythromycin, as well as clinical efficacy, makes it a viable option for therapy. At this time, no comparative pediatric clinical trials of agents are available.

While fluoroquinolones are an alternative choice for therapy against *C jejuni*, increasing resistance rates continue to be reported. The prevalence of ciprofloxacin-resistant *Campylobacter* increased from 13% in 1997 to 19% in 2004.[15] This increased resistance is believed to coincide with the increased use of fluoroquinolones animals used for food worldwide.[1,14] In 1995, the US approved the use of fluoroquinolones in poultry.[16] Although data exist supporting the appropriate use of fluoroquinolones in children less than 18 years of age in certain pediatric disease states, other viable options are available for treating gastrointestinal illness. Aminogly-

cosides, tetracyclines and chloramphenicol are all alternatives for treatment; however, the latter 2 are avoided in infants due to adverse effects. Treatment with aminoglycosides require IV access. Most beta-lactam and trimethoprim antibiotics are naturally resistant to *C jejuni*. Of viable options, azithromycin is the optimal first line treatment of *C jejuni* in children and should be utilized.

Appropriate hand washing techniques and good hygiene are important in preventing the spread of *Campylobacter*. Symptomatic people should neither handle food nor care for others until the diarrhea resolves. Using pasteurized milk and being sure chlorinated water is used in pools, are also important in preventing outbreaks.

The two infants presented did not have any risk factors for *Campylobacter* and no source was found for the infection. The first infant was treated with antibiotics due to the number of stools she was experiencing. The second infant was treated due to the number of stools, as well as elevated fever. Treatment was warranted in both infants based upon symptoms, but azithromycin should have been the initial agent received by both children. Erythromycin should only be utilized in young infants if it is absolutely necessary, due to the risk of developing IHPS.

CONCLUSION

Campylobacter jejuni was isolated from the stools of two infants who presented to the hospital with bloody diarrhea. Bacterial causes should be investigated in infants with persistent diarrheal symptoms, especially bloody diarrhea. The use of antibiotics in patients with *C jejuni* should be evaluated based on the severity of symptoms and overall condition of the patient. While the increasing resistance rates and questionable safety of fluoroquinolones and unfavorable drug characteristics of erythromycin limit their utility in infants, azithromycin remains an efficacious choice with a relatively benign safety profile for treatment of *campylobacter* infections.

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