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# Clinical and laboratory observations

## Azithromycin for treatment of severe *Cryptosporidium* diarrhea in two children with cancer

Sergio L. Vargas, MD, Jerry L. Shenep, MD, Patricia M. Flynn, MD, Ching-Hon Pui, MD, Victor M. Santana, MD, and Walter T. Hughes, MD

From the Departments of Infectious Diseases and Hematology-Oncology, St. Jude Children's Research Hospital, and the Department of Pediatrics, University of Tennessee, Memphis

**Two children with cancer received azithromycin for *Cryptosporidium*-associated diarrhea that was unresponsive to supportive care. One child had choleriform diarrhea requiring daily fluid replacement of up to 65% of his total body weight; the other had protracted diarrhea and wasting. In both cases, administration of azithromycin was followed by prompt clinical improvement. (J PEDIATR 1993;123:154-6)**

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Reprint requests: Sergio L. Vargas, MD, Department of Infectious Diseases, St. Jude Children's Research Hospital, 332 North Lauderdale St., Memphis, TN 38105-2794.

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Best known as a pathogen in patients with the acquired immunodeficiency syndrome,[1] *Cryptosporidium* species can also cause life-threatening illness in other immunocompromised hosts, including patients with cancer who are receiving chemotherapy.[2, 3] Serious *Cryptosporidium* infection is usually manifested as chronic debilitating diarrhea. Although several therapeutic approaches have been investigated, none has proved effective.[2, 4]

Drugs investigated as possible therapies for *Cryptosporidium* infection include diloxanide furoate, furazoli-

done, quinine plus clindamycin, interleukin-2, amprolium, various macrolide antibiotics, and intravenous preparations of immune globulin administered orally.[2,4] Perhaps the most promising of these agents are the macrolide antibiotics. Of the five macrolides tested to date at St. Jude's Children's Research Hospital—clarithromycin, spiramycin, erythromycin, oleandomycin, and azithromycin—Rehg[5,6] found azithromycin to be the most effective in decreasing the parasitic load in the ileum of immunosuppressed experimental animals infected with *Cryptosporidium*.

We recently treated two young children with cancer who had severe *Cryptosporidium*-associated diarrhea that was unresponsive to aggressive supportive care. We selected oral azithromycin for use in this empiric trial because of its safety, availability, and promising results in experimental animals.

## CASE REPORTS

**Patient 1.** A 14-month-old boy with newly diagnosed epithelioid sarcoma of the mediastinum had diarrhea 1 day after completing initial chemotherapy (a 4-day course of ifosfamide, carboplatin, and etoposide) and 8 days after initiation of antibiotic treatment for a *Staphylococcus aureus* infection at the incision site for biopsy of his mediastinal tumor. *Cryptosporidium* oocysts were identified by modified acid-fast stain of stool specimens; no other enteric pathogens were found in bacterial or fungal cultures and results of tests for rotavirus and *Clostridium difficile* toxin were negative. The patient's diarrhea progressively worsened during the ensuing 7 days; fluid requirements increased to a daily volume of 650 ml/kg, necessitating transfer to the intensive care unit. Azithromycin (Zithromax capsules), was administered at a dose of 500 mg (40 mg/kg) orally once daily. A Foley catheter was used to facilitate monitoring of urine output and stool loss. The volume of fluid lost in the feces decreased steadily, and diarrhea resolved during the first 10 days of azithromycin treatment (Figure ). The patient was discharged from the hospital and continued treatment with azithromycin as an outpatient. Stool examinations revealed *Cryptosporidium* organisms on several occasions during the next 2 weeks, although there was no diarrhea. Four days after completing a 3-week course of azithromycin, severe diarrhea and dehydration again developed. Stool examinations revealed *Cryptosporidium* as the sole pathogen. Diarrhea resolved promptly again after resumption of azithromycin therapy. Four consecutive stool examinations done after an additional 2 weeks of azithromycin treatment found no *Cryptosporidium* organisms. Azithromycin (250 mg twice daily) was continued until the patient completed the intensive phase of his chemotherapy regimen. No further episodes of diarrhea occurred, and no adverse effects were associated with azithromycin therapy.

**Patient 2.** A 3-year-old boy with disseminated neuroblastoma was admitted to the hospital with a 1-week history of diarrhea that had begun 33 days after an autologous bone marrow transplant with a preparative regimen consisting of etoposide and carboplatin. The patient had not recently been treated with antibiotics, and his bone marrow function had fully recovered. Both *C. difficile* toxin and *Cryptosporidium* organisms were detected in his stool. The *C. difficile* toxin cleared from the stool after a 7-day oral course of vancomycin, but diarrhea progressively worsened, resulting in a loss of almost 15% of his body weight. He did not respond to intravenous fluid therapy and became listless. Because of *Cryptosporidium* organisms in the stool and the patient's progressive wasting, oral azithromycin therapy was initiated empirically at a daily dose of 500 mg (40 mg/kg). Listlessness and diarrhea improved within 4 days, and the illness resolved during a 10-day period. The dosage of azithromycin was then reduced to 250 mg until a 21-day course was completed. Stool samples were not reexamined.

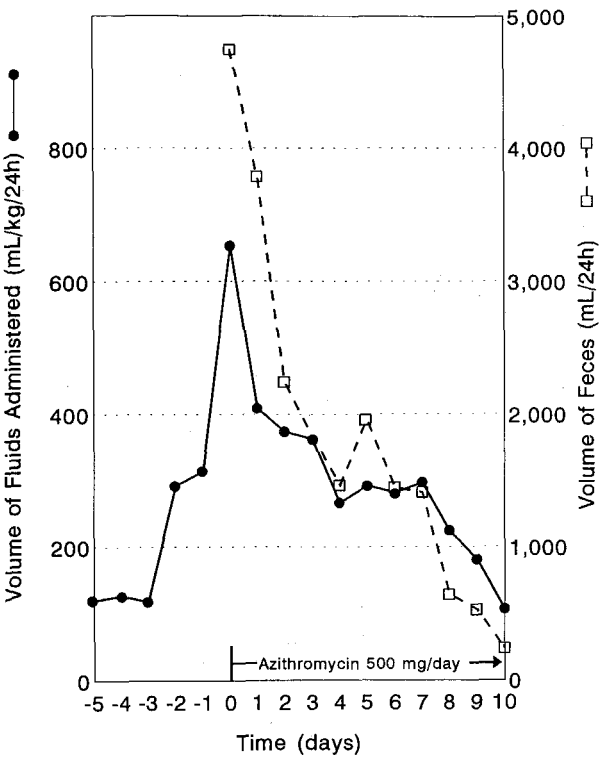


**Figure.** Daily fluid administration and fecal volume in a 13 kg, neutropenic 14-month-old patient with cancer and cryptosporidiosis (patient 1). The patient's diarrhea had substantially abated before recovery of bone marrow function, which began on day 7 of azithromycin therapy.

## DISCUSSION

The degree to which treatment with azithromycin hastened the recovery of these two patients is not certain. Anecdotal reports can be misleading; spiramycin was once thought to be effective for cryptosporidiosis on the basis of anecdotal reports, but this impression was not confirmed in a controlled clinical trial.[2] Nevertheless, the course of infection in these two patients does suggest a beneficial effect of azithromycin, especially in the first patient, who apparently responded to azithromycin, became worse when it was withdrawn, and again improved when the therapy was resumed.

The optimal dosage of azithromycin in children is unknown. The dose that we selected was empiric and may have been unnecessarily high, but there are few data to guide treatment in young children. In addition, the azithromycin preparation that we used contains lactose, which could exacerbate diarrhea in patients with primary or acquired lactose intolerance.[7] Although treatment caused no overt adverse effects in these two patients, use of a preparation that does not contain lactose would be advisable.

The apparent clinical responses to azithromycin observed in these two patients, characterized by rapid normalization of stool output and weight recovery, are concordant with the results of animal experiments and indicate that azithromycin may have a role in the treatment of human *Cryptosporidium*-associated diarrhea. Further assessment of the therapeutic effect of azithromycin in cryptosporidiosis must await the results of a randomized, controlled clinical trial. If the drug should be proved effective, our experience indicates that young children with *Cryptosporidium*-associated diarrhea will tolerate azithromycin well.

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# Evaluation of secondary prophylactic schemes, based on benzathine penicillin G, for rheumatic fever in children

Zilda Maria Alves Meira, MD, Cleonice de Carvalho Coelho Mota, MD, Edward Tonelli, MD, Elzíria Aguiar Nunan, MSc, Ana Margarida Marques C. Mitre, and Nordnei Soares de Paiva C. Moreira

From the Departments of Pediatrics and Pharmaceuticals, the Schools of Medicine and Pharmacy, Federal University of Minas Gerais, Belo Horizonte, Brazil

**Serum concentrations of penicillin were measured in children with rheumatic fever. The adequacy of the values after administration of 1.2 million units of benzathine penicillin G every 2 or 3 weeks was confirmed; the adequacy of a 4-week regimen was questionable. The administration of 0.6 million units every 3 weeks was found to be inadequate to maintain serum levels high enough for the secondary prophylaxis of rheumatic fever. (J PEDIATR 1993;123:156-8)**

The use of benzathine penicillin G is effective for the secondary prophylaxis of rheumatic fever.[1] However, the interval between injections and the optimal dose remain matters of controversy. Because of the discomfort caused by injections, reduction of the time between doses could decrease compliance. In Brazil, the cost of more frequent injections is another factor that could lead families to abandon prophylaxis. Thus the main objective of this study was to identify regimens for secondary prophylaxis of rheumatic fever by using BPG, which could ensure adequate serum levels of penicillin while causing less discomfort to patients.

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Reprint requests: Zilda Maria Alves Meira, MD, Rua Júlio Ferraz, 397, Belo Horizonte—Minas Gerais, 31270, Brazil.
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