

# Cyclospora Infection: A Review

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## Abstract

*Cyclospora is a coccidian parasite responsible for a syndrome of acute and chronic diarrhoea. The organism first came to worldwide attention in 1990 following the publication of three reports. The largest series of cases and the first clinical description of the illness associated with this organism came from Kathmandu where travellers and expatriates were noted to have prolonged diarrhoea with a previously undescribed organism. The organism has been identified as a coccidian both by observation of sporulation and subsequent molecular phylogenetic analysis. Cyclospora organisms appear as non-refractile double-walled spheres, 8-10 microns in diameter. The organism floats in Sheather's sucrose solution and appears variably red on the modified acid-fast stain. It can also be identified on plain wet mounts. Since its first description, Cyclospora has been noted in an increasing number of countries throughout the world. Water-borne transmission has been implicated in several studies. There is a distinct seasonality in Cyclospora outbreaks and cases. In Nepal, the organism has occurred in virtually identical seasonal outbreaks since 1989. The clinical illness associated with Cyclospora is characterized by diarrhoea, nausea, anorexia and weight loss, which may persist for weeks to months if untreated. Evidence of malabsorption of D-xylose has been noted and small bowel biopsies revealed moderately severe villous atrophy and crypt hyperplasia. Successful treatment with trimethoprim-sulfamethoxazole has been identified, but to date no alternative treatment exists for the sulfa allergic patient.*

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## Definition

Cyclosporiasis is an intestinal infection with the coccidian organism *Cyclospora*. Infection is associated with diarrhoea, fatigue, anorexia, and a prolonged course in the absence of treatment.

## History

The intestinal organism *Cyclospora* first came to worldwide attention in 1990-1991, following the publication of three reports.<sup>1-3</sup> The largest series of cases, and the first clinical description of the illness associated with this organism, came from the Canadian International Water and Energy Consultants (CIWEC) Clinic in Kathmandu.<sup>3</sup> Shlim et al<sup>3</sup> reported on a series of 55 cases that had been diagnosed in a distinct outbreak from May through November of 1989. The unknown organism, 8-10 microns in size and resembling a large *Cryptosporidium*, was associated with cases of prolonged diarrhoea, anorexia, fatigue, and weight loss, and was not cured by the usual antiparasitic medications. The illness was shown to be associated with the presence of the new organism, and spontaneous remission was noted when the organism disappeared from the stool exams. The publication of this report came on the heels of a report by Long et al<sup>2</sup> at the Centers for Disease Control (CDC), who reported on the morphologic characteristics of an identical-ap-

pearing organism that had been identified in 8 unrelated patients over the last two years.

The newly-identified particle had a prokaryotic appearance and was felt to resemble a blue-green algae or Cyanobacterium. The internal organelles resembled the photosynthesizing organelles of the blue-green algae, and the organism autofluoresced under ultraviolet epifluorescence, characteristics of blue-green algae. However, there were also aspects of the appearance that were not characteristic of algae, and the organism was usually referred to as a "Cyanobacteria-like body" or CLB.<sup>4</sup>

It soon became apparent that this newly-described organism, the CLB, had been identified before. Soave et al<sup>5</sup> in New York described round 8-9 micron organisms in the stool of immunocompetent travellers to Mexico and Haiti who presented with gastrointestinal symptoms. They called the organism a "big *Cryptosporidium*". Researchers in Haiti, treating patients with AIDS, noted a similar appearing organism as early as 1983, according to a report published in 1994.<sup>6</sup>

Researchers in Peru studying *Cryptosporidiosis* in Peruvian children first noted a "large *Cryptosporidium*-like organism" during studies taking place from 1985-1987.<sup>7</sup>

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The first published report of this organism, however, is most likely the report by Ashford<sup>6</sup> describing a previously undescribed oocyst-like body in three patients in Papua New Guinea in 1979, which fits the current clinical and microscopic characteristics of *Cyclospora*.

The uncertainty surrounding the taxonomic classification of CLB was resolved with the report by Ortega et al<sup>7</sup> that the organism had been shown to sporulate while incubating in a potassium dichromate solution. Two sporozoites were noted, and the organism most closely resembled a previously identified organism known as *Cyclospora*. These researchers proposed the name "*Cyclospora cayetanensis*" after the university in Lima where this research had been done.

### Parasitology

*Cyclospora* appears under the microscope as non-refractile, double-walled spheres, 8-10 microns in diameter. Microscopists familiar with the organism can easily identify it on plain wet mounts. The organism floats in Sheather's sucrose solution. On a modified acid-fast stain *Cyclospora* appears variably red; some organisms resist the stain and appear as "ghosts." The organism tends to cling to mucus strands when mucus is present. *Cyclospora* demonstrates an intense blue autofluorescence under ultraviolet light. Most patients infected with *Cyclospora* will show only a few organisms on direct stool exam, and the diagnosis might only be made after formalin-ethyl acetate concentration. Specimens preserved in formalin for a few days may resist subsequent attempts at concentration. Unlike some intestinal parasites, *Cyclosporas* are almost always present in the stool of patients with the disease; the organism was identified in stool exams 96% of the time in infected patients.<sup>3</sup>

Ten per cent to 20% of *Cyclospora* organisms incubated in a potassium dichromate solution at temperatures of 25°C to 32°C will sporulate after 5 days. Complete sporulation with the appearance of sporozoites within sporocysts occurs between 7 and 12 days in culture. Sporulation produces 2 sporocysts, which rupture to reveal two crescent-shaped sporozoites measuring 1.2 by 9.0 microns.<sup>7</sup> The sporozoites within the sporocyst have a membrane-bound nucleus and micronemes characteristic of coccidia of the phylum Apicomplexa (Family Eimeriidae). Molecular phylogenetic analysis has also confirmed that *Cyclospora* is a coccidian closely related to *Eimeria* species and distinct from *Isospora* and *Cryptosporidium*.<sup>9</sup>

### Epidemiology

#### Incidence

Since 1991, *Cyclospora* has been noted in an increasing number of countries throughout the world. Published case reports and clinical studies include the following:

United States,<sup>1,2,10-16</sup> Haiti,<sup>5,6,17</sup> Peru,<sup>7</sup> Papua New Guinea,<sup>8</sup> Mexico,<sup>5,18-20</sup> Puerto Rico,<sup>21</sup> India,<sup>19,22,23</sup> Guatemala,<sup>22</sup> Morocco,<sup>22</sup> Pakistan,<sup>23</sup> South Africa,<sup>24</sup> Dominican Republic,<sup>19,23</sup> Malaysia,<sup>19</sup> Thailand, Nepal,<sup>1,3,25,26</sup> Cambodia,<sup>18,27</sup> the Solomon Islands,<sup>27</sup> Vietnam,<sup>23</sup> and Indonesia.<sup>23</sup> The organism is found both in immunocompetent and immunosuppressed patients.

An outbreak of *Cyclospora* infection affecting approximately 1100 individuals (75% laboratory-confirmed) occurred in the United States and Canada in late spring, early summer, of 1996.<sup>10,11</sup> Both event related and sporadic cases were noted in Ontario, Canada and 14 states and the District of Columbia during this period.

There are few studies of the prevalence of this infection in specific populations. In Nepal, *Cyclospora* was noted to infect approximately 7% of the American Embassy community during the 1992 *Cyclospora* season, and accounted for 11% of the diarrhoea cases at the CIWEC Clinic.<sup>25</sup>

In a review of 6525 stool specimens at Chicago hospitals from 1989 to 1991, 34 were positive for *Cyclospora*, representing a 0.2% prevalence in the population studied.<sup>16</sup> In a prospective study of 1042 stool specimens from diarrhoea patients in Massachusetts submitted from May to November 1993, 3 specimens were positive for *Cyclospora*.<sup>14</sup> These three patients had no history of foreign travel, and were not infected with HIV.

Among indigenous populations, only two countries have been surveyed. In Peru, Ortega et al<sup>28</sup> found *Cyclospora* in 6% and 18% of Peruvian children under the age of 30 months who submitted weekly stool exams in two separate studies lasting 18 and 24 months respectively. In Nepal, Hoge et al<sup>29</sup> studied 124 children aged 6 months to 5 years who presented with diarrhoea at a local clinic. *Cyclospora* was found in 5% of the children with diarrhoea compared to 2% among 103 non-diarrhoea controls. The mean age of children with *Cyclospora* was 34 months, and no cases were found in children less than 18 months of age, suggesting possible protection from breast-feeding. Among 184 stool samples reviewed at a local hospital in Nepal, 6 (3%) were found to have *Cyclospora*.<sup>1</sup>

#### Transmission

The transmission of *Cyclospora* is presumed to be fecal-oral, although there is no clear evidence yet of person-to-person transmission. Water-borne transmission of *Cyclospora* is implicated in several studies. An outbreak of *Cyclospora* among hospital staff of Cook County Hospital (Chicago) in the summer of 1990 implicated the water supply of a hospital building.<sup>1,13</sup> Water was further implicated in a case-control study in Kathmandu by Hoge et al.<sup>25</sup> Patients with *Cyclospora*

were more likely than non-diarrhoea controls to have drunk untreated water in the week before their illness. *Cyclospora* was also identified in a sample of water from the home of a *Cyclospora* patient who had drunk the water untreated.<sup>25</sup> Unboiled milk was also implicated in this study, but it is not known whether this was due to actual transmission by the milk, or adulteration with untreated water. In Utah, a single case of *Cyclospora* was associated with exposure to milk-contaminated sewage from a dairy.<sup>30</sup>

A point source outbreak was identified in a British Gurkha soldier camp in Pokhara, Nepal, where 6 confirmed cases of *Cyclospora* were noted.<sup>26</sup> The water supply for the camp was routinely chlorinated and the chlorine levels were monitored daily. Despite adequate chlorination of the water, *Cyclospora* was identified in a sample taken from the water storage tank. A patient and 3 family members in Peru who drank unchlorinated canal water developed *Cyclospora* diarrhoea. Interestingly, *Cyclospora* was also found in the stool of a duck bred by the same family.<sup>21</sup>

There is also evidence that *Cyclospora* may be food-borne. It was identified on a head of lettuce in Nepal in 1990.<sup>1</sup> A pilot for an American airline who regularly flew the route from New York to Haiti developed *Cyclospora* diarrhoea after eating airline food prepared in a Haitian kitchen.<sup>17</sup> Preliminary investigations of the multistate outbreak of infection in 1996 suggested an association between risk for *Cyclospora* infection and the consumption of raspberries imported from Guatemala.<sup>11</sup>

#### *Seasonality*

There appears to be a distinct seasonality in *Cyclospora* outbreaks and cases. In Nepal, the organism has occurred in virtually identical seasonal outbreaks since 1989. No *Cyclospora* cases are seen in Nepal between December and March each year. The outbreaks begin in the hot dry season preceding the monsoon rains, and the peak coincides with the weeks of maximal rainfall. Other enteric pathogens also reach a peak in June each year in Nepal. However, all other enteric pathogens are present in Nepal throughout the year.

In Peru, an analysis of 5 years of data shows cases from January to July, with a peak from April to June.<sup>7</sup> Among the 9 cases reported by Pollok et al<sup>27</sup> in travellers from India, Nepal, Pakistan, Cambodia, the Solomon Islands, and Mexico, all of the travel took place between May and October.<sup>27</sup> Cases in non-travellers identified at Cornell University Medical College in New York City appear to occur each year in the late spring and early summer.<sup>15</sup> Community-acquired cases in Massachusetts were noted only in May and June.<sup>14</sup> There were two outbreaks in 1995, one in Palm Beach County, Florida, and one in Westchester County, New York, which occurred in the late spring and early summer. The 1996 North American

outbreak was noted to occur as well during this season.

#### **Pathogenicity**

Evidence that *Cyclospora* can cause diarrhoea comes from a number of studies. The initial report from Nepal found that the organism was present when people were ill, and recovery was associated with disappearance of the organism.<sup>3</sup> A subsequent case-control study conducted in Nepal from May to August of 1992 by Hoge and Shlim provided further evidence that *Cyclospora* was associated with diarrhoea. *Cyclospora* was found in 11% of 964 diarrhoeal patients, but in only 1 of 96 asymptomatic controls. This one patient, however, developed *Cyclospora* diarrhoea three days later.

The clinical illness associated with *Cyclospora* suggested that the organism was a small bowel pathogen. Upper gastrointestinal symptoms are predominant, such as nausea, anorexia, and eructation, and there is an absence of tenesmus and dysentery. There is invariably malabsorption of D-xylose, and weight loss is almost universal.<sup>31</sup> In 1991, Connor et al<sup>32</sup> performed upper gastrointestinal endoscopy on 9 patients in Nepal identified as having *Cyclospora* diarrhoea. Five of the nine *Cyclospora* patients had moderate to marked erythema of the distal duodenum. Duodenal aspirates were obtained and *Cyclospora* was noted adherent to mucous in two of the nine *Cyclospora* patients. The histopathology in small bowel biopsies revealed epithelial disarray with acute and chronic inflammation, partial villous atrophy, and crypt hyperplasia in all *Cyclospora* patients. Although organisms were not found within enterocytes either by light or electron microscopy in this study, Bendall et al<sup>22</sup> performed blind jejunal biopsies with a Crosby capsule on two patients with *Cyclospora* diarrhoea<sup>22</sup> and both biopsies showed pathologic changes similar to the Nepal patients; electron microscopy showed what appeared to be intracellular sporozoites. Subsequent electron microscopical evaluation of small bowel biopsies revealed the asexual stages of *Cyclospora* organisms within the enterocytes (Connor, unpublished observations).

Little is known about whether individuals can develop immunity to *Cyclospora*. AIDS patients studied in Haiti were noted to have recurrent disease.<sup>6</sup> Hoge et al<sup>25</sup> noted that expatriate patients in Nepal could have *Cyclospora* infections in two successive years.<sup>25</sup> They also noted, however, that expatriate *Cyclospora* patients had lived in Nepal for significantly less time than expatriate controls (median 11 months versus 23 months,  $P < 0.0001$ ), suggesting that immunity can develop over time. Long et al<sup>4</sup> reported on some preliminary investigations suggesting that an antibody response can be found in the serum of *Cyclospora* patients.<sup>4</sup> Confirmation of this observation, however, has not yet been

published.

### Clinical Manifestations

Cyclospora infection among foreign residents and travellers to Nepal produces a characteristic illness that can often be recognized clinically. As many as 30% of patients report an abrupt onset of a severe gastroenteritis associated with fever, vomiting, and frequent watery diarrhoea. This acute phase subsides after a few days, and a characteristic pattern of unusually severe fatigue, anorexia, and intermittent diarrhoea and nausea ensues. The symptoms can be consistent from day to day, or intermittent, with remissions and exacerbations occurring every few days. Increased upper intestinal gas and bloating is frequently noted. In some patients, diarrhoea is not prominent; anorexia and fatigue may be the presenting symptoms. Weight loss is usual, with one study estimating the mean weight loss associated with untreated infections at 3.6 kg.<sup>3</sup>

Untreated cases persist for several weeks. In the first Nepal study, the average length of symptoms was 6 weeks, with a range of 4 to 107 days.<sup>3</sup> A second study in Nepal in 1992 found that the median length of illness was 7 weeks, compared to a median duration of 9 days among non-Cyclospora diarrhoea patients ( $P < 0.0001$ ).<sup>25</sup> Among 5 patients in Chicago who had follow-up of their Cyclospora illness, the organism could be found 8 weeks after the onset of illness.<sup>13</sup> Other reports support the fact that the illness associated with Cyclospora has a prolonged course, ranging from 4 to 8 weeks.<sup>18,27</sup>

The incubation period of Cyclospora is thought to be a matter of days, based on observations in Nepal that five expatriates developed illness associated with Cyclospora within 2 to 11 days after returning to Nepal from a prolonged leave.<sup>3</sup> In the Cook County outbreak, symptoms began 1 to 7 days after probable exposure.<sup>13</sup>

### Treatment

In the 1989 outbreak in Nepal, there was no difference between treated and untreated patients, both in clinical course or duration of illness. Thirty-four Cyclospora patients underwent 78 courses of antimicrobials including norfloxacin, metronidazole, tinidazole, and quina-crone.<sup>3</sup> An open trial of azithromycin on 7 patients in Nepal also showed no apparent benefit.<sup>33</sup>

In 1993, Madico et al<sup>34</sup> reported that 5 patients with Cyclospora in Peru were successfully treated with Trimethoprim-sulfamethoxazole with resolution of symptoms and clearance of the organism. Wurtz et al<sup>16</sup> also reported in 1993 that oral Trimethoprim-sulfamethoxazole had attenuated symptoms in an AIDS patient with Cyclospora diarrhoea in 1987.

In 1994, Pape and colleagues<sup>6</sup> reported on their experience of using Trimethoprim-sulfamethoxazole in an open trial on AIDS patients infected with Cyclospora in

Haiti. Using a dose of 160 mg Trimethoprim and 800 mg Sulfamethoxazole q.i.d. for 10 days, they noted that diarrhoea and abdominal cramps stopped within 2.5 days (range 1 to 5 days) and stools re-examined at days 5 and 10 were all negative for Cyclospora. Recurrent Cyclospora infection was frequent, but responded to a second course of treatment. Trimethoprim-sulfamethoxazole prophylaxis three times per week was effective in preventing relapse in most patients followed for 7 months. It may be that the frequent use of Trimethoprim-sulfamethoxazole for toxoplasmosis and *Pneumocystis carinii* pneumonia prophylaxis may decrease the rate of Cyclospora in the AIDS population.

Hoge et al<sup>35</sup> performed a double-blind, placebo-controlled trial of Trimethoprim-sulfamethoxazole (160 mg Trimethoprim and 800 mg Sulfamethoxazole) for Cyclospora infections among immunocompetent patients in Nepal. Forty patients were entered into the study; 21 were given Trimethoprim-sulfamethoxazole b.i.d. for 7 days, and 19 were given placebo. After 3 days, Cyclospora was still present in 71% of the treatment group and 100% of the placebo group. However, after 7 days, only 1/16 patients (6%) in the treatment group was still positive for Cyclospora, compared with 15/17 (88%) of the placebo controls. The one patient who remained positive at 7 days responded to an additional 7-day course of Trimethoprim-sulfamethoxazole. In all patients, eradication of the organism was associated with clinical improvement, and no relapse was noted in an additional 7-day follow-up. This study confirmed the efficacy of Trimethoprim-sulfamethoxazole for Cyclosporiasis. A 7-day course may not be sufficient to eradicate the organism in all cases. The authors of the study noted that recognition of Cyclospora as an emerging pathogen may have coincided with a decreased use of Trimethoprim-sulfamethoxazole in the treatment of traveller's diarrhoea in favour of fluoroquinolone treatment.

Treatment regimens for patients who are allergic to sulfa drugs have not yet been identified.

### Prevention

Travellers to Cyclospora-endemic areas should be aware of the higher risk during the late spring and summer. There is evidence that Cyclospora may not be inactivated by chlorination,<sup>26</sup> and since *Cryptosporidium* is also highly resistant to halogens—both chlorine and iodine—drinking water treated only by halogens may not be safe during Cyclospora season. Boiling appears to kill Cyclospora. These facts have implications for trekkers in Nepal in the late spring, where drinking water is routinely treated with iodine, and boiling is often impractical. Cyclospora infection was not epidemiologically linked to lettuce in Hoge's study,<sup>25</sup> but since Cyclospora was found on a head of lettuce in Nepal,<sup>1</sup> salads may also

represent a potential risk factor. Salad greens soaked in an iodine solution for disinfection may not be rendered safe from *Cyclospora*, and salads may have to be avoided in *Cyclospora* season. Swimming in chlorinated swimming pools in Nepal was not implicated in acquiring *Cyclospora*.<sup>25</sup>

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