Cyclospora: An Overview

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... humankind is beset by a greater variety of microbial pathogens than ever before. Some of this, of course, may be due to our increased ability to recognize or identify microbes [1].

Emergence of a "New" Pathogen: Historical Aspects

Popularization of the acid-fast stain in the early 1980s for detecting Cryptosporidium species in stool specimens set the stage for recognition of Cyclospora species. Between 1986 and 1993, there were nine reports linking diarrheal illness in more than 200 immunocompetent and immunocompromised children and adults to an unidentified, acid-fast organism resembling a "large Cryptosporidium" [2–10]. On the basis of electron microscopic studies in 1990 that revealed photosynthesizing organelles within the organism, similar to those of blue-green algae, Long et al. suggested that it was a cyanobacterium similar to Chlorella species [7]. Thus, in addition to being called a large Cryptosporidium, the organism has been called a coccidian-like body or a cyanobacterium-like body (CLB), a blue-green alga, a Cryptosporidium muris–like cyst, a fungal sporule, and a species of Blastocystis.

In 1993, Ortega et al. [11] succeeded in inducing Cyclospora to sporulate and showed that, when mature, it has two sporozoites, each containing two sporozoites. Thus, the organism is the oocyst stage of the coccidian parasite Cyclospora [11]. Detailed electron microscopic studies, which revealed that the Cyclospora sporozoites possess a membrane-bound nucleus and micronemes that are characteristic of the phylum Apicomplexa, provided additional evidence that the organism is a coccidian [11]. With use of molecular phylogenetic analysis, Relman [12] recently confirmed that Cyclospora is a coccidian related to Eimeria species and possibly most closely related to Isospora species [12].

It is of interest that the first report of human cyclospora infection (which had largely gone unnoticed until 1993) came from Papua New Guinea in 1979, before the popularization of acid-fast stained stool smears and the advent of molecular phylogenetic analysis [2, 13]. In that report, Ashford [2] detailed the morphological characteristics of a coccidian-like organism that was present in fecal specimens from two children and one adult; the organism was examined by bright-field microscopy and was found to resemble Isospora species [2].

As with Cryptosporidium, Cyclospora is not a "new" organism but a newly recognized organism that is perhaps emerging as a pathogen. Cyclosporan organisms were first noted in the intestines of moles in 1870 by Eimer, and Schneider created the genus Cyclospora in 1881. In 1902, Schaudinn reported the first life-cycle study, which showed that Cyclospora caryolitica developed in the intestinal epithelia of moles and produced severe enteritis [14]. Cyclosporan species have subsequently been found in snakes, insectivores, and rodents.

Epidemiology

Cyclospora is widely distributed throughout the world; it has been identified in both residents and travelers from various regions including North America, Central America, and South America; the Caribbean islands; Eastern Europe; India; South Africa; and Southeast Asia. Persons of all ages have been infected. Most of the current knowledge of the epidemiology of Cyclospora species is derived primarily from Nepal, Haiti, and Peru because the parasite appears to be endemic in these countries.

Although epidemiological studies have differed in design and thus are not comparable, distinctly different patterns of infection have been described in the areas where the parasite is endemic (table 1). In Kathmandu, Nepal, workers at two clinics for expatriates and tourists have documented an annual surge of cyclosporiasis that coincides with the rainy season (between May and October) [5, 15]. Because of this unique situation, several investigators have been able to conduct numerous large-scale clinical studies that have contributed significantly to our knowledge of the epidemiology, pathogenesis, and treatment of infections due to Cyclospora [5, 15–19].

Prevalence rates of 11% have been documented among non-native adults and children residing in Kathmandu during the rainy season [15]. In a case-control study of the indigenous population (i.e., Nepalese children), Hoge found that 5% of symptomatic children and 2% of asymptomatic children older than 18 months had cyclospora infection, whereas none of 74 children <18 months of age were infected [16].
Before 1995, four or five cases of cyclosporiasis per year were diagnosed at the New York Hospital–Cornell Medical Center in New York, and all infections that were not in travelers occurred between May and August, consistent with the seasonality documented in Nepal. In May, June, and July of 1995, excess numbers of cyclospora infections, primarily in nontravelers, were documented in New York and Florida. Although eating unwashed berries was implicated as a risk factor, it could not be proven. Similar outbreaks are occurring once again in New York and Florida at the time of this writing. Investigations are currently being conducted to determine the sources of infection and whether these clusters are due to point source outbreaks, increased incidence, or increased recognition.

Whether cyclosporiasis is truly uncommon in the United States cannot be determined from the available data. Underdiagnosis of cyclospora infection may be due to the following factors: many physicians have never heard of the parasite; most clinical laboratories do not routinely include Cyclospora as part of the ova and parasite examination; shedding of Cyclospora in stool may be intermittent, as is the case with Isospora; and acid-fast staining, which is insensitive for the detection of Cryptosporidium species, may also be a relatively insensitive technique for detecting Cyclospora.

Two point source outbreaks of cyclosporiasis have been epidemiologically linked to contaminated water. In 1990, 21 employees, including house staff, who attended a party in a Chicago hospital dormitory developed diarrhea; 11 of these persons had documented cyclospora infection [27]. The stirring up of stagnant water in a storage tank after repair of a water pump is believed to have caused contamination of the implicated building’s water supply. Although algae and diatoms were detected in the water, Cyclospora was not found.

An outbreak of diarrhea occurred in June 1994 among British soldiers and dependents stationed in a military detachment in Pokhara, Nepal; an investigation revealed Cyclospora oocysts in a 2-liter water sample taken from a storage tank that fed chlorinated, filtered water to all the homes in the area [19]. During the outbreak, chlorination was found to be adequate, and the water was free of coliforms. Thus, Cyclospora is resistant to chlorination, as is Cryptosporidium, and Cyclospora is not readily detected by methods that are currently used to assure the safety of drinking water supplies.

Data on the outbreaks of cyclospora infection in Chicago and Nepal provide compelling evidence that Cyclospora is acquired through contaminated water [15, 19, 27]. In a report of cyclosporiasis in a man from Utah, contaminated sewage that seeped into his home was implicated as a putative source of infection [28]. Transmission via contaminated food [29], lettuce [15], undercooked meat [2], and raw beef [6] has been suggested but not proven. In Peru, four members of the same family who drank unchlorinated canal water developed cyclosporiasis; in addition, one of the ducks they bred was found to have asymptomatic cyclospora infection [30].

Table 1. Studies on the epidemiology of cyclospora infection.

<table>
<thead>
<tr>
<th>Location [reference]</th>
<th>Study population (age)</th>
<th>No. of persons</th>
<th>Diarrhea present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal [15]</td>
<td>Expatriates and tourists (adults and children)</td>
<td>108/964 (11)</td>
<td>Yes</td>
</tr>
<tr>
<td>Nepal [16]</td>
<td>Nepalese children (&gt;18 mo)</td>
<td>6/124 (5)</td>
<td>Yes</td>
</tr>
<tr>
<td>Nepal [16]</td>
<td>Nepalese children (&gt;18 mo)</td>
<td>2/103 (2)</td>
<td>No</td>
</tr>
<tr>
<td>Peru [11]</td>
<td>Peruvian infants (1 y-2.5 y)</td>
<td>26/147 (18)</td>
<td>No</td>
</tr>
<tr>
<td>Peru [11]</td>
<td>Peruvian infants (1 mo-1.5 y)</td>
<td>15/230 (6)</td>
<td>Yes</td>
</tr>
<tr>
<td>Haiti [20]</td>
<td>HIV-infected adults</td>
<td>51/450 (11)</td>
<td>Yes</td>
</tr>
<tr>
<td>Haiti [20]</td>
<td>Infants (&lt;6 mo)</td>
<td>0/2,000</td>
<td>Yes</td>
</tr>
<tr>
<td>Haiti [20]</td>
<td>Non-HIV-infected adults</td>
<td>0/50</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Over a 34-month period, Pape et al. [20] found that 11% of 450 HIV-infected Haitian adults with chronic diarrhea had cyclospora infection. However, none of 2,000 Haitian infants (mean age, <6 months) with diarrhea or 50 non-HIV-infected adults with diarrhea were found to have cyclosporiasis.

In two separate studies conducted in shantytowns outside Lima, Peru, Ortega et al. [11] found that 18% (26 subjects) and 6% (15 subjects) of children ranging in age from 1 month to >2 years had Cyclospora in their stool specimens. Nine of the 26 subjects in the first study and two of the 15 subjects in the second study presented with diarrhea.

Prevalence studies from Nepal, Haiti, and Peru suggest that, to date, symptomatic infection is more common in children older than 18 months but that younger children may have asymptomatic infection, and the rates of infection are lower among natives than among non-native residents (table 1). Whether the differences in the distribution of symptomatic infections in different age groups and in various geographic areas are due to the acquisition of protective immunity, different exposures, different species or strains, the sensitivity of diagnostic techniques, or other as yet undescribed factors is not known.

Prevalence studies of cyclosporiasis have not been reported from the United States or other developed countries. However, surveys of 1,042 stool specimens received in laboratories in Chicago and 6,525 stool specimens received in laboratories in Burlington, Massachusetts, revealed Cyclospora in 0.5% and 0.3% of samples, respectively [9, 21, 22]; this incidence is similar to that of isosporiasis. Similarly, in a survey of stool samples conducted in the United Kingdom, Cyclospora was identified in 0.1% of 1,333 samples [23].

Although most reported cases of cyclosporiasis that have occurred outside Nepal, Haiti, and Peru have been linked to travel, it appears that documentation of infection in indigenous populations, both in the United States and abroad, is increasing [16, 24–26]. Whether this increase is due to more frequent recognition of the infection or a true change in its incidence is not known.
Direct animal-to-human or person-to-person transmission of *Cyclospora* has not been documented. Reservoirs of infection have also not been identified. Although the seasonality of cyclospora infection is more pronounced than is that of cryptosporidium infection, characteristics of *Cyclospora* and/or host factors that contribute to this phenomenon have not been delineated.

**Taxonomic and Morphological Features of Cyclospora**

The genus *Cyclospora* is in the subclass Coccidia, phylum Apicomplexa. Thus, this genus is taxonomically related to four other coccidian genera that have been described as pathogens in humans: *Cryptosporidium*, *Isospora*, *Toxoplasma*, and *Sarcocystis*. The species name *C. cayetanensis* has been suggested by Ortega et al. [11, 31] and is derived from the Universidad Peruana Cayetano Heredia in Lima, Peru, where studies of this parasite have been conducted. Whether more than one species of *Cyclospora* affects humans has not yet been determined.

The range of hosts for the *Cyclospora* species that have been identified in humans and animals is also known. Cyclosporan species detected in insectivores, reptiles, and rodents are ovoid and slightly larger than the species identified in humans [32].

Coccidia may complete their life cycle within a single host (*Cryptosporidium* species) or require a second host (*Toxoplasma* species) or a period of time outside the host for maturation (*Isospora* species). Although the details of its life cycle in the human host have yet to be fully characterized, *Cyclospora* resembles *Isospora* in that oocysts are excreted unsporulated and require a period of time outside the host for maturation to occur. In the laboratory, sporulation occurs after a 5–11 day incubation in either distilled water or in 2.5% potassium dichromate at temperatures between 25°C and 32°C [11].

*Cyclospora* oocysts are spherical and are 8–10 μm in diameter. When observed by means of light microscopy or phase-contrast microscopy, *Cyclospora* oocysts appear as nonrefractile spheres that contain a cluster of refractile membrane-bound globules [11, 31, 33] (figures 1 and 2). Electron microscopic studies reveal an outer fibrillar coat that is 63 nm thick and a cell wall that is 50 nm thick. Within each oocyst there are two sporocysts, each ~4 μm in diameter with a cell wall that is 62 nm thick.

Two sporozoites are contained within each sporocyst; these sporozoites are 1.2 μm wide and 9.0 μm long and contain a membrane-bound nucleus and micronemes characteristic of the Apicomplexans [11, 31]. In contrast, the spherical *Cryptosporidium* oocyst is half the size of *Cyclospora* and contains four naked sporozoites, whereas the elliptical *Isospora* oocyst is much larger than that of *Cyclospora* and contains two sporocysts, each containing four sporozoites (table 2) (figure 3A, 3B, and 3C).

**Infection Due to Cyclospora**

**Clinical manifestations.** The incubation period for cyclospora infection ranges from 2 to 11 days. In the Chicago outbreak the onset of illness may have occurred as early as 12–24 hours after exposure to the organism, whereas in Nepal, a patient was found to have *Cyclospora* oocysts in a stool sample before the onset of diarrhea [15, 27].

Although cyclosporiasis is said to be clinically indistinguishable from cryptosporidiosis and isosporiasis, clinicians should be aware that diarrhea may not be the presenting or predominant symptom for patients who have cyclospora infection. Clinical manifestations of cyclosporiasis include watery diarrhea that occurs in a relapsing, cyclical pattern, sometimes alternating with constipation. Important associated symptoms include profound fatigue, “indigestion or heartburn”-like symptoms, nausea, abdominal cramps, anorexia, weight loss, and vomiting. A flu-like prodrome with accompanying myalgias and arthralgias may precede the onset of diarrhea. Although the illness is self-limited, it may be prolonged and last for weeks; progressive fatigue, anorexia, and weight loss may overshadow the presenting diarrheal symptoms [9, 21, 24, 34, 35].

Delay in diagnosis (which requires examination of a stool specimen) occurs often because upper gastrointestinal tract signs and symptoms and the symptoms of profound fatigue often predominate over the diarrheal symptoms by the time medical attention is sought. Abnormal xylose absorption has been documented in a small number of *Cyclospora*-infected patients [10, 17].

Among immunocompromised hosts, cyclospora infection has occurred primarily in HIV-infected individuals. Clinical illness due to *Cyclospora* in these patients, like that due to *Cryptosporidium* species, is prolonged and severe and is associated with a high rate of recurrence that can be attenuated with long-term suppressive therapy [20, 24]. In a recent report, Sifuentes-Osornio et al. [24] provided indirect evidence for
Figure 2 (upper left). Fecal wet mount from an immunocompetent host with cyclosporiasis. Numerous refractile globules are present within the spherical *Cyclospora* oocyst. (Bright-field microscopy; original magnification, ×630.) 


Figure 4. Fecal smear showing acid-fast-stained and unstained *Cyclospora* oocysts. Variable staining often indicates the presence of *Cyclospora* (modified Kinyoun stain; original magnification, ×630).

Figure 5. *Cyclospora* appears as bluish-green circles under ultraviolet epifluorescence (courtesy of Dr. Ynes R. Ortega).
biliary tract infection with *Cyclospora* in two patients with AIDS [24]. The life cycle of *Cyclospora talpae* in the liver and bile ducts of moles has been well characterized, indicating that this parasite may have tropism for these tissues [32].

**Histopathology and pathogenesis.** Histological studies of distal duodenal and jejunal aspirates and of biopsied tissues have provided evidence of the following characteristics of *Cyclospora*: it is a human pathogen; the upper small bowel is the site of infection in the immunocompetent host; infection is associated with pronounced histopathologic changes; and the parasite is intracellular [10, 17]. In their controlled study, Connor et al. [17] found inflammatory changes, villous atrophy, and crypt hyperplasia in jejunal tissue from patients with diarrhea and *Cyclospora*-positive stool specimens; however, these findings were not present in asymptomatic controls with negative stool specimens [17].

With use of electron microscopy, Bendall et al. [10] showed that coccidial organisms were present inside vacuoles within the cytoplasm of epithelial cells in jejunal biopsy specimens [10]. This finding has recently been confirmed [36] (Y. R. Ortega, personal communication) and contrasts with the intranuclear location of *Cyclospora* in the small intestines of moles [37]. The pathological changes seen in patients with cyclospora infection are reminiscent of tropical sprue, and the possibility that the parasite may trigger the latter condition has been raised [10]. The pathogenic mechanisms by which *Cyclospora* causes clinical illness are unknown.

**Diagnosis.** The diagnosis of cyclospora infection is based on microscopic detection of oocysts in fecal specimens. Examination of wet mounts of fresh, unpreserved stool by means of bright-field microscopy reveals nonrefractile spheres that are 8–10 μm in diameter and contain numerous refractile globules enclosed within membranes (figure 2). Like the oocysts of *Cryptosporidium* and *Isospora*, the oocysts of *Cyclospora* are acid fast and thus can be seen by using one of the many acid-fast staining techniques, including the modified Ziehl-Nielsen stain or the Kinyoun acid-fast stain. *Cyclospora* cysts have a variable appearance (unstained, pink, or dark red) on acid-fast staining, which is a distinguishing feature of the parasite with some diagnostic usefulness (figures 3A and 4).

Despite their distinct characteristics, *Cyclospora* oocysts may be confused with *Cryptosporidium* oocysts unless their diameter is measured with a micrometer (figures 3A and 3B). *Cyclospora* oocysts are autofluorescent and appear as neon-blue circles when examined with an ultraviolet fluorescence microscope fitted with a 365-nm excitation filter (figure 5); this property appears to wane over time.

The relative sensitivity, specificity, and predictive values of the various techniques for diagnosing cyclospora infection are not known. Whether persons infected with *Cyclospora* shed oocysts intermittently, as do those with isospora infection, is also unknown. It is important to underscore that the rudimentary nature of our diagnostic techniques may in part contribute to underrecognition of cyclospora infection.

In addition to being found in feces, *Cyclospora* has also been detected in jejunal aspirates and biopsy specimens by means of light microscopy and electron microscopy [10, 17, 36]. Antibodies to *Cyclospora* have been detected in infected patients, and antibody titers have been shown to increase during convalescence [33]. The humoral immune response to cyclospora infection has not been characterized in patients with AIDS.

**Treatment.** Trimethoprim-sulfamethoxazole (TMP-SMZ) is the drug of choice for treating cyclospora infection; this has been demonstrated in anecdotal reports, in a large open-label study of HIV-infected patients in Haiti, and in a placebo-controlled trial in Nepal [18, 20, 38]. Pape et al. [20] successfully treated patients infected with HIV and *Cyclospora* with TMP-SMZ (160/800 mg) four times daily for 10 days, followed by secondary prophylaxis with TMP-SMZ (160/800 mg) three times weekly. Hoge et al. [18] showed that TMP-SMZ

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**Table 2. Comparison of *Cyclospora*, *Cryptosporidium*, and *Isospora*.**

<table>
<thead>
<tr>
<th>Variable</th>
<th><em>Cyclospora</em></th>
<th><em>Cryptosporidium</em></th>
<th><em>Isospora</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocyst size (μm)</td>
<td>8–10</td>
<td>4–6</td>
<td>20–30 × 10⁻¹⁹</td>
</tr>
<tr>
<td>No. of sporozoites per sporocyst</td>
<td>2</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>No. of sporozoites</td>
<td>2</td>
<td>4 per oocyst</td>
<td>4</td>
</tr>
<tr>
<td>Acid-fast staining</td>
<td>Variable</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ultraviolet autofluorescence</td>
<td>Blue-green</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Auramine fluorescence</td>
<td>Weak</td>
<td>Bright</td>
<td>Variable</td>
</tr>
</tbody>
</table>

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(160/800 mg) taken twice daily for 7 days was statistically significantly better than placebo for treating cyclospora infection in an expatriate population in Nepal \( (P < .0001) \) [18]. It is noteworthy that cyclosporiasis appears to have emerged in Nepal at a time when, because of growing resistance, quinolones replaced TMP-SMZ for the treatment of bacterial enteritis [18]. Alternative effective therapeutic agents have not yet been identified.

The Future

Has *Cyclospora* been responsible for many of our previously undiagnosed cases of intestinal disease, or has it recently emerged as a pathogen in response to dramatic changes in our environment? Is this organism, which holds great fascination for parasitologists, a passing medical curiosity for the clinician?

The impact of this parasite in terms of enteric illness in different populations, especially children in the developing world, will be determined only if clinicians are aware of its existence. Current concern with cost-effectiveness and the streamlining of medical care must be balanced against our ability to successfully intervene in the spread of a disease that is often associated with significant morbidity in immunocompetent hosts as well as immunocompromised hosts.

Further studies are needed to identify the populations at risk for cyclospora infection; to delineate the modes of spread; to develop inexpensive, reliable diagnostic techniques; and to identify alternative, efficacious agents for therapy and prophylaxis. Only after such studies have been completed will we have a chance of understanding and perhaps conquering this parasite.

Acknowledgment

The author is indebted to Leticia Ramos for her tremendous dedication and competence in identifying *Cyclospora* in fecal specimens.

References


**Suggested Additional Readings**


This test affords you the opportunity to assess your knowledge and understanding of the material presented in the preceding clinical article, "Cyclospora: An Overview," by Rosemary Soave, and to earn continuing medical education (CME) credit.

The Office of Continuing Medical Education, UCLA School of Medicine, is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. The Office of Continuing Medical Education, UCLA School of Medicine, certifies that this continuing medical education activity meets the criteria for 1 credit hour in Category I of the Physician's Recognition Award of the American Medical Association and the California Medical Association Certificate in Continuing Medical Education.

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Certificates of CME credit will be awarded on a per volume (biannual) basis. Each answer card must be submitted within 3 months of the date of the issue.

This program is made possible by an educational grant from Roche Laboratories.

1. On parasitological examination of stool, Cyclospora is most commonly confused with which of these parasites?
   A. Cryptosporidium
   B. Isospora
   C. Blastocystis hominis
   D. Giardia lamblia

2. With respect to treatment, Cyclospora is most closely related to which of these other coccidians?
   A. Cryptosporidium
   B. Isospora
   C. Toxoplasma
   D. Sarcocystis

3. Symptoms of cyclospora infection may include all of the following except
   A. Watery diarrhea
   B. Constipation
   C. Blood-streaked stool
   D. Anorexia

4. All of the following statements about Cyclospora are true except
   A. There is a seasonality to cyclospora infection in that it is most common in the warm, humid months of the year
   B. Cyclospora infection is common in immunocompromised patients, particularly HIV-infected individuals in Haiti
   C. Infection is likely underrecognized because of intermittent shedding of the parasite and insensitivity of detection methods
   D. Oocyst shedding may occur in asymptomatic patients

5. Epidemiological studies of waterborne Cyclospora outbreaks suggest all of the following except
   A. Chlorination of drinking water may not be protective
   B. Cyclospora may accumulate in water storage tanks
   C. Warm, rainy weather may increase the risk of water supply contamination
   D. When coliform counts are within acceptable limits, Cyclospora contamination is unlikely

6. On Kinyoun acid-fast staining, Cyclospora oocysts appear
   A. Dark red
   B. Pink
   C. Unstained
   D. Any of the above

7. Though the two organisms can look similar, features of Cyclospora oocysts that distinguish them from Cryptosporidium oocysts on microscopy include all of the following except
   A. A round shape
   B. The larger size of Cyclospora
   C. Variable staining of oocysts by acid-fast methodology
   D. Blue autofluorescence on ultraviolet fluorescence microscopy

8. The following statements about cyclospora infection are true except
   A. Immunocompetent patients who have had prior infection are immune to recurrence
   B. In immunocompetent patients, untreated infection is self-limited, although symptoms and parasite shedding may persist up to several weeks
   C. Treatment with trimethoprim-sulfamethoxazole for 7 days is effective, and symptoms typically respond within 1–3 days
   D. There is presently no known alternative to trimethoprim-sulfamethoxazole therapy
   E. Infection in patients with AIDS frequently relapses following treatment, unless chronic maintenance therapy is given
9. Identify the true statement regarding human cyclospora infection
   A. Consumption of contaminated water is the only mode of transmission for which epidemiological evidence has thus far been compelling
   B. Transmission through contaminated food (such as lettuce) has been suggested but not demonstrated
   C. Although Cyclospora species have long been recognized as parasites in a variety of animals, no animal vector for the species identified in humans (Cyclospora cayetanensis) is known
   D. All of the above

10. All of the following are true about human cyclospora infection except
   A. Symptoms may begin as a flu-like prodrome
   B. Diarrhea is invariably the principal complaint
   C. Diarrhea is frequently intermittent
   D. Fatigue and malaise may last for weeks after gastrointestinal symptoms have resolved