

8.8.6 Cyclospora and cyclosporiasis 1432

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section 8 Infectious diseases 1432 Control of transmission Primary control is by limiting the opportunity for faecal-oral transmission, both direct and indirect. Symptom-free subjects not in contact with immunocompromised patients can normally be permitted to work if their hygiene is scrupulous. Spread via fomites is possible but this route is limited by the susceptibility of oocysts to desiccation. Patients with AIDS are more susceptible to infection with uncommon species or genotypes and advice may be needed to limit exposure. Contamination of water supplies is inevitable, even in developed countries, and may be the source of some sporadic cases as well as outbreaks. When a public advisory notice is issued to boil water, raising the water just to boiling point is sufficient. In general, bottled water and water from point-of-use filters are unlikely to contain parasites but may carry an increased bacterial load, the health significance of which is uncertain for the immunocompromised. Patients with AIDS and others who are profoundly compromised should be advised never to drink water that has not been boiled or filtered through a suitable device. Users of filters should remember that these devices may concentrate potential pathogens and care is needed in replacing and disposing of filter elements. Hospitals involved in the care of profoundly immunocompromised patients should be particularly vigilant in the management of patients with cryptosporidiosis. Long-term arrangements should be made for the provision of safe water for the immunocompromised to avoid difficulties when a notice to boil water is issued. FURTHER READING Cacciò SM, Putignani L (2014). Epidemiology of human cryptosporidiosis. In: Cacciò SM, Widmer G, editors. *Cryptosporidium: parasite and disease*, pp. 43–79. Springer, Vienna. Chalmers RM, Katzer F (2013). Looking for *Cryptosporidium*: the application of advances in detection and diagnosis. *Trends Parasitol*, 29, 237–51. Checkley W, et al. (2015). A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for *Cryptosporidium*. *Lancet Infect Dis*, 15, 85–94. Hunter PR, Nichols G (2002). Epidemiology and clinical features of *Cryptosporidium* infection in immunocompromised patients. *Clin Microbiol Rev*, 15, 145–54. Sparks H, et al. (2015). Treatment of *Cryptosporidium*: what we know, gaps, and the way forward. *Curr Trop Med Rep*, 2, 181–7. Xiao L (2010). Molecular epidemiology of cryptosporidiosis: an update. *Exp Parasitol*, 24, 80–9. 8.8.6 Cyclospora and cyclosporiasis Paul Kelly and Ralph Lainsont† ESSENTIALS Most species of Cyclospora (Protozoa: Apicomplexa:

Eimeriidae)

are parasites of various reptiles and mammals. *C. cayetanensis*, which probably infects only humans, is transmitted by way of resistant oocysts voided in the faeces and contaminating food or water. Distribution is worldwide, particularly in regions with a low level of hygiene. Clinical presentation is with explosive outbreaks of acute diarrhoea, with this infection now regarded as an important causative agent of traveller's diarrhoea. Diagnosis is dependent on detection of oocysts in faeces by direct examination or in stained faecal smears. Aside from supportive care, treatment with trimethoprim-sulfamethoxazole has proved effective in eliminating the parasite in immunocompetent patients, but relapses are common in those with AIDS. Prevention is by ensuring good general hygiene, and in areas of high endemicity water should be boiled before drinking or use in preparation of fruits/vegetables that are to be eaten raw. Introduction Species of the coccidian genus *Cyclospora* (Protozoa: Apicomplexa: Eimeriidae) have been recorded in invertebrates (millipedes), reptiles (principally snakes), insectivores (moles), rodents, and primates (monkeys and humans). The genome of this parasite has been partially sequenced. Endogenous development of most species is within the epithelial cells of the small intestine, culminating in the production of oocysts, which are voided in the faeces and serve as the means of transmission. Small coccidial oocysts detected in the faeces of patients with diarrhoea in Papua New Guinea almost certainly represented the first discovery of *Cyclospora* in humans in 1979, but the parasite was not identified to generic level. Oocysts of the same parasite, seen by other authors in patients with diarrhoea, were for many years referred to as 'cryptosporidium-like oocysts', 'cyanobacterium-like bodies' (bodies resembling blue-green algae), or even 'fungal spores', and it was not until 1992 that the parasite was named as *Cyclospora cayetanensis*. Life cycle *Cyclospora* species have been most extensively studied in non-human hosts. Asexual reproduction (merogony) (Fig. 8.8.6.1a) is followed by the production of female gametocytes (macrogamonts) (Figs. 8.8.6.1b-f) and male gametocytes (microgamonts) that produce many flagellated gametes (Figs. 8.8.6.1g-j). Following fertilization of the female parasites, the zygotes develop a resistant membrane (Fig. 8.8.6.1k). The resulting oocysts (Fig. 8.8.6.2) are voided, unsporulated, in the host's faeces. During periods varying from a few days to 1 or 2 weeks, depending on the species of *Cyclospora* and ambient temperature, the zygote within the oocyst (Fig. 8.8.6.3a) undergoes division to produce two sporoblasts (Fig. 8.8.6.3b), each of which develops a resistant membrane, the sporocyst (Fig. 8.8.6.3c). Division of each sporoblast then gives rise to two elongate sporozoites, leaving a conspicuous residual body (Figs. 8.8.6.2b and 8.8.6.3c). The sporozoites are the stages that infect the next host when oocysts are ingested with contaminated food or water. † It is with great regret that we report that Ralph Lainson died on 5 May, 2015.

1433 8.8.6 *Cyclospora* and cyclosporiasis Epidemiology Failure to infect a variety of animals experimentally or to detect *C. cayetanensis* in those living in or near houses with human infection has led to the conclusion that humans are the specific host of this coccidian and the sole source of its oocysts. The parasite is globally distributed, although risk of infection is greatest in developing countries with low standards of hygiene where prevalence rates up to 40% (Peru) have been reported. It is particularly prevalent in Central America and southern Asia, and uncommon in southern Africa. Serious outbreaks of acute diarrhoea have been reported across the world, related to consumption of contaminated foods such as raspberries and salads. Oocysts of *C. cayetanensis* have been detected on green leafy vegetables, in sewage, and even in tap water. Airborne and zoonotic transmission is suspected but not confirmed. Clinical features An acute,

watery, and nonbloody diarrhoea is variously accompanied by abdominal pain, steatorrhoea, headache, fever, nausea, and general malaise. The diarrhoea can be persistent and last for several weeks. Asymptomatic infections are known to occur, notably in the indigenous population of developing countries. Infection is more prolonged in immunocompromised hosts, such as in AIDS or in transplant recipients. (a) (f) (g) (i) (j) (k) (h) (b) (c) (d) (e) 10 μ m Fig. 8.8.6.1 Intracellular development in epithelial cells of the ileum (haematoxylin and eosin stained sections) in a typical life cycle of a *Cyclospora* species: (a) segmented meronts; (b–e) developing macrogamonts; (f) mature macrogamont with small wall-forming bodies (arrow) and large wall-forming bodies (arrowhead); (g, h) developing microgamonts; (i, j) mature microgamonts shedding microgametes; (k) intracellular zygote, with developing oocyst wall (OW). From Lainson R (2004). The genus *Cyclospora* (Apicomplexa: Eimeriidae), with a description of *Cyclospora schneideri* n.sp. in the snake *Anilius scytale scytale* (Aniliidae) from Amazonian Brazil—a review. Mem Inst Oswaldo Cruz, 100, 103–110, with permission.

section 8 Infectious diseases 1434 Diagnosis Diagnosis is dependent on the demonstration of oocysts of *C. cayetanensis* in the faeces by direct microscopic examination. Flotation methods, using saturated sugar or aqueous zinc sulphate solutions, are useful in concentrating the oocysts, which measure from 8.0 to 10.0 μ m in diameter (average 8.6 μ m). The living oocysts are autofluorescent using ultraviolet illumination, which is useful for rapid diagnosis. In addition, most diagnostic laboratories use a variety of staining methods to colour the oocysts in faecal smears fixed in 10% formalin: notably, modified Ziehl-Neelsen acid-fast staining and safranin stain. The polymerase chain reaction with primers specific for *C. cayetanensis* also affords a highly sensitive, but more costly, diagnostic technique. There are four other intestinal coccidia that infect humans and may produce similar symptoms, but they are morphologically readily differentiated from *C. cayetanensis* (Fig. 8.8.6.4). *Cryptosporidium* oocysts are only 4.5–5.0 μ m in diameter and they contain four naked sporozoites. *Cystoisospora belli* oocysts are elongated, measure from 25 to 33 μ m in length and from 12 to 16 μ m in width, and have two sporocysts, each of which contains four sporozoites. *Sarcocystis hominis* and *S. suihominis* oocysts are easily differentiated from *C. cayetanensis* oocysts by their larger size (average 16 μ m $\times$ 10.5 μ m) and ellipsoidal shape. Pathology Histology of jejunal biopsies from patients with cyclosporiasis has shown blunting and widening of infected villi and an intense lymphocytic infiltration in the lamina propria and overlying epithelium (Fig. 8.8.6.5), features which are common to all coccidian infections of the small intestine. Treatment Co-trimoxazole (960 mg two times daily for 1 week) has proved effective in eliminating the parasite in immunocompetent patients and has been shown successfully to control relapses in those with AIDS by the administration of 960 mg three times a week, indefinitely. Ciprofloxacin (500 mg two times daily for 1 week) is recommended for patients who react badly to sulphonamides. (a) (b) 10 μ m Fig. 8.8.6.2 Extracellular stages in a typical life cycle of a *Cyclospora*:

ss(a) unsporulated oocyst in the intestinal lumen; (b) sporulated and ruptured oocyst in faeces. L, lumen; Sp, sporozoite; Sr, sporocystic residuum. Bar, 10 μ m (all figures). From Lainson R (2004). The genus *Cyclospora* (Apicomplexa: Eimeriidae), with a description of *Cyclospora schneideri* n.sp. in the snake *Anilius scytale scytale* (Aniliidae) from Amazonian Brazil—a review. Mem Inst Oswaldo Cruz, 100, 103–110, with permission. (a) (b) (c) Fig. 8.8.6.3 Developing oocysts of *C. cayetanensis* as seen by Nomarski interference-contrast microscopy: (a) unsporulated oocyst; (b) formation of the two sporoblasts; (c) formation of the two sporocysts. Bar, 5 μ m. From Ortega YR, Gilman RH, Sterling CR (1994). A new coccidian parasite (Apicomplexa: Eimeriidae) from humans. J Parasitol,

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1435 (a) (b) 10 μ m (c) (d) Fig. 8.8.6.4 Faecal stages of the five intestinal coccidia that infect humans: (a) oocyst of *Cryptosporidium parvum*, (b) oocyst of *Cyclospora cayetanensis*, (c) sporocyst of *Sarcocystis hominis* or *S. suis* (the two are morphologically indistinguishable), and (d) oocyst of *Cystoisospora belli*. Bar, 10 μ m. (c) (a) (d) (b) Fig. 8.8.6.5 Comparison of normal human jejunal villi (a, c) and villi infected with *C. cayetanensis* (b, d): low-power appearance (a, b) and high-power appearance (c, d). Note the blunting and widening of the villi, with inflammatory lymphocytic infiltrate in the lamina propria and infiltration of overlying epithelium. From Ortega YR, et al. (1997). Pathologic and clinical findings in patients with cyclosporiasis and a description of intracellular parasite life-cycle stages. *J Infect Dis*, 176, 1584–9, with permission. 8.8.6 *Cyclospora* and cyclosporiasis

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