Cryptosporidiosis

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Cryptosporidium is a protozoan parasite that has emerged as an important cause of diarrhoeal illness worldwide, particularly in young children and immunocompromised patients. In the UK Cryptosporidium is the commonest protozoal cause of acute gastroenteritis, with 3000–6000 laboratory-confirmed cases annually, although this is almost certainly an underestimation of the disease burden. Two species, Cryptosporidium hominis and Cryptosporidium parvum, account for most of these laboratory-confirmed cases. Species distinction between C. hominis and C. parvum is quite recent and for several years both parasites were referred to as C. parvum (sometimes genotypes 1 and 2). Large waterborne outbreaks highlight the parasite’s clinical and economic importance.

The clinical problems associated with Cryptosporidium are increasingly becoming recognised internationally, and the parasite was included in the World Health Organization’s Neglected Diseases Initiative 2004. These neglected diseases are defined as those that “exhibit a considerable and increasing global burden, and impair the ability of those infected to achieve their full potential, both developmentally and socio-economically.”

In this review, we assess the epidemiology, clinical presentation, diagnosis, and management of cryptosporidiosis.

SUMMARY POINTS

Cryptosporidium is a common cause of diarrhoea worldwide, and is the commonest protozoal cause of acute gastroenteritis in the UK

In immunocompetent patients the illness is self-limiting but generally lasts one to two weeks and sometimes longer

Laboratory diagnosis is required for confirmation

Sources of infection include animals, as well as people, and the parasite is resistant to normal water disinfection

In those with T-cell deficiencies the disease is chronic and protracted and may be severe, with complications including sclerosing cholangitis and rarely, biliary cirrhosis and pancreatitis

Specialist tests may be required

Treatment options are limited. In the US nitazoxanide is licensed, and available by regular prescription, for disease in the immunocompetent, in whom it reduces the severity of symptoms, which may be prolonged. Nitazoxanide is available in the UK on a named-patient basis

In England the Chief Medical Officer advises that patients whose T-cell function is compromised should boil all drinking water to reduce the risk of infection

Box 1 | Risk factors for acquisition of Cryptosporidium

Drinking contaminated water
Travel to less industrialised countries
Use of swimming pools and water based recreation
Contact with animals in farms or petting zoos, especially young ruminants
Contact with animal dung, for example, during outdoor recreation
Contact with another person with diarrhoea, especially a child
Attendance at child care settings
Changing nappies or toileting young children (even those with no diarrhoea)

Sources and selection criteria

We searched MEDLINE for authoritative articles and studies and by consulting the archived resources of the UK Cryptosporidium Reference Unit, Swansea, of which one of the authors (RMC) is the head. The Cochrane database contains a systematic review of treatment in the immunocompromised.

Who gets cryptosporidiosis?

Anyone can be infected and become ill with Cryptosporidium. Cryptosporidiosis is commoner in young children, particularly in those under age 5 years, but the disease can also affect healthy people of any age. However, most clinical problems are encountered in patients who are profoundly immunocompromised. Asymptomatic carriage of the organism is possible: a recent study of young children in day care nurseries found that three of 230 (1.3%, upper 95% CI 3.8%) were carrying the parasite without any symptoms. Risk factors for the acquisition of Cryptosporidium identified from outbreaks and sporadic cases are listed in box 1.

How is cryptosporidiosis acquired?

Transmission is usually via the faeco-oral route. As well as person-to-person transmission of both C. parvum and C. hominis, particularly within households and nurseries, C. parvum can also be acquired as a zoonosis, for example, during children’s farm visits or exposure to animal dung during outdoor recreation. Oocysts, which are the transmissible form that contains infectious sporozoites, can survive for prolonged periods in damp soil and ingestion of very low numbers can cause disease.

The largest outbreaks of cryptosporidiosis are associated with contamination of drinking water by
sewage effluent or manure. Ordinary water disinfection processes do not kill Cryptosporidium, and filtering is required to remove the parasite. Improved quality of drinking water, particularly with the installation of filtration at previously unfiltered supplies, has reduced disease burden. Nonetheless, there can still be a background risk in some mains water and many private water supplies.

Outbreaks of the disease associated with swimming pools are well recognised because oocysts are relatively resistant to chlorination, and pool water filtration is often inadequate. Patients with diarrhoeal illness should be advised not to go swimming, and in particular, patients with a confirmed diagnosis of cryptosporidiosis should be discouraged from using pools for two weeks after diarrhoea has stopped because oocysts can still be shed during this time. Advice for patients diagnosed with cryptosporidiosis is outlined in box 2.

Food borne infection is probably less common but can be caused by contaminated fruit or vegetables, food washed in contaminated water, or inadequate pasteurisation of milk.

What are the clinical features of cryptosporidiosis?
Cryptosporidiosis presents as a gastroenteritis-like syndrome. Symptoms indicate its pathogenesis with disease predominantly affecting the small bowel, with malabsorption, and some elements of inflammation. A 3-12 day dose dependent incubation period precedes watery diarrhoea accompanied by abdominal cramps (in 96% of patients who present for consultation), vomiting (65%), mild fever (59%), and loss of appetite. Symptoms can be prolonged, with a mean duration of 12.7 days, and can persist for up to a month. The relapse of symptoms, indicating persistent infection, occurs in over a third of cases, but after clearance of the parasite the epithelium recovers. In one study, 61 of 427 (14%) sporadic cases were hospitalised. The differential diagnosis is usually of other causes of infectious gastroenteritis.

In the developing world, cryptosporidiosis is associated with substantial morbidity, and with children who are malnourished, including those with apparently asymptomatic infection who may exhibit poor growth.

Immunocompromised patients commonly experience chronic or intractable disease. Those patients most at risk are those with T-cell immune deficiency, including those with haematological malignancies (particularly children), patients with HIV infection with CD4 counts lower than 200 (and in particular those with counts below 50), and patients with primary T-cell deficiencies such as severe combined immunodeficiency and CD40 ligand deficiency (hyper IgM syndrome). In these immunocompromised patients the entire gastrointestinal tract can be affected, including the pancreatic duct and gall bladder. Complications include pancreato-biliary infection, which can lead to pancreatitis, sclerosing cholangitis, and rarely, subsequent biliary cirrhosis. Tracheo-bronchial involvement, though uncommon, can occur and sinusitis has been described. Rarely, in advanced HIV, cryptosporidiosis is associated with pneumatosis cystoides intestinalis, in which cysts containing gas occur in the gut wall, and can rupture, leading to pneumoretroperitoneum and pneumomediastinum.

There is also concern about cryptosporidiosis in bone marrow and solid-organ transplant patients. A review of the evidence regarding Cryptosporidium infection in immunocompromised patients found that the severe disease reported in those who had undergone

**Box 2 | Advice for patients diagnosed with cryptosporidiosis**

- Expect the diarrhoea to last longer than with some other causes of infectious gastroenteritis, and be prepared for the possibility that symptoms may relapse before the infection is completely cleared
- Observe stringent personal hygiene because the organism is highly infectious from person to person; wash hands carefully and do not share towels
- Avoid using swimming pools for two weeks after the diarrhoea has stopped
- Children should not attend nursery settings until 48 hours after diarrhoea has stopped
- Food handlers and those caring for vulnerable adults (such as patients in hospital and older people) should not attend work until 48 hours after diarrhoea has stopped

**Fig 1 | Cryptosporidium parvum: modified Ziehl-Neelson staining with x100 objective. Courtesy of G Robinson, UK Cryptosporidium Reference Unit, Swansea**

**Fig 2 | Cryptosporidium parvum: auramine phenol staining with x50 objective. Courtesy of G Robinson, UK Cryptosporidium Reference Unit, Swansea**
A PARENT’S PERSPECTIVE

Our son Sam got Cryptosporidium after visiting the sheep shed during lambing when he was of pre-school age, in a pushchair, but did not actively go into the pens. He got very ill, had a tummy ache, and lost weight. It was a very worrying time as the diagnosis took several weeks and the illness carried on and on.

A PATIENT’S PERSPECTIVE

The first inkling that something was wrong was when I woke in the night with intense cramping stomach pains. They came in waves over a couple of hours before the vomiting started. By morning I had vomited so much that it felt as though there was nothing left inside me, but I continued to retch on an empty stomach. Around mid-morning the diarrhoea started. It was like nothing I had ever experienced before: the cramps would build and then the most awful, profuse, offensive, and watery diarrhoea would follow. It left me physically weak. I couldn’t leave the bathroom, and certainly couldn’t look after my children, not that I’d have wanted to in case they got it.

I could not face eating, but made myself sip water; however this often caused further episodes of vomiting and diarrhoea. I continued night and day like this for three days before finally I could venture out of the bedroom to take drinks and clear soup without immediately being ill again. It was a full ten days before I felt like I had enough energy to start eating normally or functioning.

About two weeks after this I woke again in the night with stomach cramps, no way near as severe as the first attack, but it filled me with dread as to what was going to follow. The diarrhoea only lasted 24 hours this time, there was no vomiting, and then all my symptoms resolved.

I have not had cryptosporidiosis since, but it is an episode of illness I will never forget, and a disease I have the greatest respect for.

Bone-marrow transplant typically depended on the underlying diagnosis for which the transplant was performed. Cryptosporidiosis in solid organ recipients and in patients with non-haematological malignancies has been described, but does not seem to be as problematic as it is in the highest risk groups.

What are the long term effects of infection?

Little is known about the long term effects of Cryptosporidium infection. A case-control study found that infection with C. hominis (but not C. parvum) was associated with joint pain, eye pain, headaches, and fatigue during the two months after infection. Seronegative reactive arthritis has been reported in adults and children, including one report of Reiter’s syndrome. It has been suggested that Cryptosporidium infection may cause relapse of inflammatory bowel disease. There are anecdotal reports of an association between Cryptosporidium and irritable bowel disease but this link, if it exists, is very unclear and requires further study.

How is infection with Cryptosporidium diagnosed?

Cryptosporidium causes a spectrum of disease from asymptomatic, through mild, to severe. Incidence of the disease is almost certainly underestimated because a confirmed diagnosis can only be made after a stool sample is sent to the local microbiology laboratory. Although UK guidance states that all stool samples from community cases of diarrhoea should be tested for Cryptosporidium, laboratories have varying criteria for selecting stools for testing. Examination for Cryptosporidium may not necessarily be included in a request for “ova cysts and parasites” (as the methods of examination for the two tests differ). The usual methods of detecting Cryptosporidium oocysts in the stool are by acid-fast or auramine-phenol staining and microscopy, which often show the organisms in great numbers (figs 1 and 2), or by antigen detection. Clinicians are advised to become familiar with local laboratory practice, and to specify Cryptosporidium on the request form to ensure appropriate testing is carried out.

More sensitive, specialist tests available in reference facilities include PCR, and for maximum sensitivity in exceptional circumstances, immunomagnetic separation with immunofluorescence microscopy, which can detect as few as two organisms per gram of stool.

In patients with profound T-cell immune deficiency, examination of small bowel or gastric biopsies can reveal the parasite or histopathological changes where the stool sample is negative. Other samples occasionally examined include bile, in cases of cholangitis, and sputum/blood alcohol level where pulmonary cryptosporidiosis is suspected. Possible specimen types are listed in the table.

How is cryptosporidiosis managed?

Immunocompetent patients

In immunocompetent patients, the disease, though unpleasant and debilitating, is self-limiting. Rehydration salts may be required. Patients and carers should be informed that symptoms may persist for longer than with other common causes of acute gastro-

## Types of specimens that can be examined for Cryptosporidium

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Appropriate Patient Group</th>
<th>Test and Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool (most commonly examined specimen)</td>
<td>Any patient with community acquired or unexplained diarrhoea</td>
<td>Routine diagnostic tests available locally or specialist tests if negative and Cryptosporidium still suspected</td>
</tr>
<tr>
<td>Jejunal +/- gastric biopsy</td>
<td>Persistent idiopathic gastrointestinal symptoms in high risk groups</td>
<td>Specialist tests</td>
</tr>
<tr>
<td>Bile from endoscopic retrograde cholangiopancreatography</td>
<td>If symptoms of cholangitis in high risk groups</td>
<td>Specialist tests</td>
</tr>
<tr>
<td>Sputum/ bronchoalveolar lavage</td>
<td>High risk patients with profound immunosuppression and unexplained respiratory symptoms</td>
<td>Specialist tests</td>
</tr>
<tr>
<td>Antral washout</td>
<td>High risk patients with profound immunosuppression and unexplained sinusitis</td>
<td>Specialist tests</td>
</tr>
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teritis, making the diagnosis helpful to the clinician. Cryptosporidiosis is highly infectious person-to-person, as large numbers of oocysts are excreted and the infectious dose is low (possibly in single figures\(^{33-35}\)), so scrupulous personal hygiene is required. As with other causes of infectious gastroenteritis, UK guidance issued by a working group of the former Public Health Laboratory Advisory Committee on Gastrointestinal Infections\(^3\) states that affected children should not attend day care centres until 48 hours after diarrhoea has stopped, and that food handlers and carers of highly susceptible patients should be excluded from work for the same period. Regulations for notifying infections vary among jurisdictions. In the UK, cryptosporidiosis is notifiable only where believed to be food borne or water borne. Elsewhere, for example, in the United States, it is a nationally notifiable disease.

**Immunocompromised patients**

In the high risk groups outlined earlier, infection can be severe and difficult to manage. Because treatment modalities are limited, prevention and risk reduction are the most important interventions. The Department of Health in England advises, on the basis of the Bouchier report\(^{24}\), that those with compromised T-cell function should boil all drinking water (including bottled water) to reduce the risk of infection.\(^{25}\) Whether this permanent, blanket advice is still necessary and should be applied across the UK is currently under review.

The aim of treatment is symptomatic improvement, with complete clearance of the parasite being unlikely unless the underlying immune deficiency can be corrected.

**Immune reconstitution**

In patients with HIV, highly active antiretroviral therapy (HAART) is the treatment of choice. As well as improving the CD4 cell level and restoring a degree of immunity, protease inhibitors have reduced *Cryptosporidium* host cell invasion and parasite development in vitro, an effect enhanced with paromomycin.\(^{65}\) In other patients, improving immunity can also lead to improvement—for example, in a renal transplant patient, accidental reduction in immunosuppression was associated with parasite clearance and resolution of sclerosing cholangitis.\(^{66}\)

**Specific therapy**

Nitazoxanide (Alinia, Romark Laboratories) is approved by the United States Food and Drug Administration for use in immunocompetent patients older than 1 year and is available there by regular prescription. In the UK, nitazoxanide is not licensed but is available on a named patient basis. In a randomised placebo controlled trial of Zambian children with cryptosporidiosis, 100 mg nitazoxanide twice daily\(^{26}\) resulted in statistically significant improvement in diarrhoea and parasite clearance amongst those who were HIV negative. In an HIV positive group, there was no benefit after the primary treatment course, but after a second course of therapy diarrhoea (but not parasite carriage) had resolved in most. A double blind placebo controlled study in Mexican HIV positive patients\(^{27}\) used higher doses of nitazoxanide (500 or 1000 mg twice daily), and reported that parasite clearance was significantly better than placebo. Oocyst shedding and diarrhoea resolved in patients with CD4 greater than 50 but not in those with a lower CD4 count. Overall the data support the efficacy of nitazoxanide in immunocompetent patients, with some less conclusive evidence of benefit in immunosuppressed patients, although not, unfortunately, in the subgroup with the most advanced HIV disease. Nitazoxanide is well tolerated with a good safety profile.

All drugs that are currently available in the UK are of unproven benefit and unlicensed for the indication of cryptosporidiosis. Published trials are small and evidence is anecdotal and conflicting. Drugs that have been used to treat *Cryptosporidium* infection include the aminoglycoside paromomycin, and macrolides such as spiramycin, azithromycin, and clarithromycin, which all have anti-parasitic activity. A randomised double blind trial of paromomycin in 10 patients with AIDS and cryptosporidiosis found clinical and parasitological response reaching statistical significance.\(^{28}\) Another small open uncontrolled prospective study of paromomycin in HIV positive patients with cryptosporidiosis found that most responded clinically but that continuous maintenance therapy was required to prevent relapse.\(^{29}\) The largest prospective, double blind, placebo controlled trial included 35 adults who were HIV positive.\(^{30}\) Paromomycin was not more effective than placebo but the study lacked power to conclusively refute its usefulness. There are anecdotal reports of both responses\(^{37-39}\) and failures\(^{40-42}\) with azithromycin. Cases reports\(^{41-42}\) and one uncontrolled series of patients with AIDS\(^{43}\) describe success with azithromycin and paromomycin combination treatments.

**What else is known about the epidemiology of cryptosporidiosis?**

Of the two species accounting for most disease in humans, *C hominis* seems to be largely host adapted to humans while *C parvum* can result in infection in both humans and animals. Less commonly, other species such as *C meleagridis*, *C canis*, and *C felis*, and unusual genotypes have also been reported in patients with diarrhoea but their acquisition is not fully understood.\(^{31}\) Interestingly, a recent study of young children in day care centres found that unusual genotypes were found proportionately much more frequently in asymptomatic carriers than in patients with symptomatic disease, raising the possibility that some genotypes may be commoner than previously thought and possibly have lower pathogenicity.\(^{32}\)

In the UK, *C parvum* infections peak in spring and *C hominis* peaks in late summer and autumn. There has been a reduction in the number of cases in the first half of the year, but the number of cases in the second...
QUESTIONS FOR ONGOING AND FUTURE RESEARCH
What is the true incidence of cryptosporidiosis in the community?
Are there long term health effects of infection with Cryptosporidium, and if so what are they?
What are the risk factors for cryptosporidiosis in the second half of the year?
We are currently gathering evidence to discover whether we should be screening for Cryptosporidium carriage in high-risk patients such as those with primary immune deficiencies.

TIPS FOR NON-SPECIALISTS
Consider cryptosporidiosis in any case of acute gastroenteritis, particularly in young children and especially if the symptoms are prolonged.
A request for “ova cysts and parasites” testing may not routinely include microscopy for Cryptosporidium so specify on the request form if you suspect the diagnosis.
In immunocompetent patients no specific treatment is required.
If your patient with cryptosporidiosis is severely immunocompromised seek specialist advice.

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals
Health Protection Agency (www.hpa.org.uk/infections/topics_az/crypto/menu.htm)—Epidemiological data, general information and guidelines
Drinking Water Inspectorate (www.dwi.gov.uk/consumer/consumer/crypto.html)—Webpage about cryptosporidiosis in water supplies
Chartered Institute of Environmental Health (www.cieh.org/policy/cryptosporidium.html)—Comprehensive listings of UK guidance and links to other relevant sites

Resources for patients
Association of Medical Microbiologists (www.amm.co.uk/files/factsabout/fa_crypto.html)—Fact sheet for patients
Institute of Child Health/Great Ormond Street (www.ich.ucl.ac.uk/factsheets/families/F000291)—Factsheet: Reducing Exposure to Cryptosporidial Infection—Advice for Families with an Immuno-compromised Child

part of the year remains high, with the risk factors not clearly identified.

Risk factors for acquisition of C. hominis and C. parvum also differ. Infections associated with foreign travel, in children under one year and in adults, particularly girls and women aged 15 to 44 years, tend to be caused by C. hominis. C. hominis is also associated with changing children’s nappies (whether or not the child was symptomatic) or swimming in a toddler pool, while C. parvum is associated with farm animal contact.

Thus, although routine diagnosis outside a reference laboratory is to genus level only, typing to species level yields useful epidemiological information that may shed light on likely sources and routes of transmission.

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25 CMO Update 23. Cryptosporidium in water: advice to the immunocompromised. A communication to all doctors from the Chief Medical Officer (August 1999).