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Cryptosporidial infection, with special reference to nosocomial transmission of *Cryptosporidium parvum*: a review

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Cryptosporidium is a coccidian protozoan parasite found in a wide variety of host species including mammals, birds and lower vertebrates (poikilotherms). With the exception of one report of infection in a severely immunocompromised man with a *Cryptosporidium* which was thought to have characteristics suggestive of *C. baileyi* (Ditrich et al. 1991), human infection usually appears to be with *C. parvum*. This species seems to lack both the host and tissue specificity typical of most other coccidia. The developmental site of *C. parvum* is usually in the brush border of enterocytes, particularly of the small bowel, in an intracellular but extracytoplasmic location which appears to be unique. Cryptosporidial infection is usually asymptomatic in small mammals such as rodents but *C. parvum* is the cause of enteritis (scours) in young livestock animals such as calves and lambs. Older animals seem to be refractory to symptomatic infection although intermittent excretion has been demonstrated. Periparturient recrudescence may be important for the parasite in ensuring transmission to young animals which often become rapidly infected after birth despite antibodies in the colostrum. Once active symptomatic infection starts in a group of young animals it spreads rapidly (Blewett 1989a) and diarrhoea may be an important mechanism from the parasite's perspective, in ensuring rapid transmission to new hosts.

Infection in immunocompetent humans

Cryptosporidial infection in immunocompetent humans causes an acute self-limiting gastroenteritis. Symptoms include watery stools typical of an excretory diarrhoea, anorexia, vomiting, weight loss, and a variety of other symptoms (Casemore 1989). In a detailed study of the clinical presentation of 85 cases among the immunocompetant during a waterborne outbreak (Aston et al. 1991), the modal number of symptoms suffered was seven out of a list of 12, the mean duration was thirteen days (range 2-31 days), and 10% required hospital admission. The infection is normally limited by the immune system. Asymptomatic infection appears to be generally uncommon but has been reported in some studies, particularly in developing countries. This probably reflects hyperendemicity with recurrent exposure and re-infection in the immune. In such populations, apparently asymptomatic, chronic or recurrent infection may contribute to enteropathy and malnutrition.

Infection in immunocompromised humans

In those who are severely immunocompromised, especially those with the Acquired Immune Deficiency Syndrome (AIDS), the infection is usually more severe and protracted, and sometimes life-threatening. Diarrhoea may be cholera-like; vomiting is uncommon and tends to occur terminally. The severity of the infection reflects the total level of immunosuppression, although the nature of the immune deficit is also important; the risk of serious infection is greatest in those with CD4 T cell counts of <=200/mm^3 (Anon. 1991, Blanchard et al. 1992, Connolly et al. 1988, Petersen 1992). Intact humoral and cellular responses seem to be essential for limiting the infection. AIDS patients sometimes show fluctuation of oocyst excretion and clinical severity of infection: recrudescence and remission, and apparently asymptomatic infection, have all been described (Casemore 1989) and may reflect fluctuations in levels of immune function. The severe cholera-like illness, sometimes with vomiting, seen in terminal AIDS is distressing and is often refractory to symptomatic or palliative treatment. The lack of tissue specificity of *C. parvum* is of particular importance in AIDS patients in whom the infection may be found extending

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not only throughout the enteric tract, and thence to the associated abdominal organs such as the biliary system, but also to the respiratory tract. Effective specific therapy has not been identified despite trials of numerous compounds although some, eg. paromomycin, dyclazuril, somatostatin, the macrolides, etc., have been shown to ameliorate symptoms in some cases (Anon. 1991, Canning 1992, Dubey et al. 1990, Fichtenbaum et al. 1992, Menichetti et al. 1991, Rehg 1994). The effect in such cases may be an indirect one, rather than from killing of the parasite, as cessation of treatment often results in a return to the previous level of infection. Severe symptoms sometimes result from the effects of multiple infecting agents, including viruses such as CMV, and may thus respond to specific therapy aimed at those agents.

The incidence of cryptosporidiosis in AIDS patients differs in different centres but in some it exceeds 20% and *Cryptosporidium* is often the commonest single cause of gastrointestinal disease in these patients.

In leukaemic patients, cryptosporidial infection can be severe, especially if it coincides with or provokes an aplastic crisis. Under such circumstances, interruption of their anti-leukaemic chemotherapy may be required to permit resolution of the cryptosporidiosis.

Pathogenesis

The mechanism by which the parasite causes symptoms have not been identified but would appear to be multifactorial (Casemore 1989, Zu et al. 1992). The factors involved include malabsorption of water, loss of brush-border enzymes with consequent osmotic effects, and probably also a so far unidentified secretagogue. Vomiting is a common feature of human cryptosporidiosis, especially in children, and the parasite has been identified in vomit where it may have been derived from regurgitated small bowel contents or the cells of the stomach. The mechanism involved is not known and an emetic factor has not been identified. Respiratory tract involvement sometimes occurs, especially in AIDS patients. Oocysts and endogenous stages attached to exfoliated cells have been found by acid-fast and immunofluorescent antibody test (IFAT) staining of sputum and in respiratory tract tissues (Casemore 1989, 1991b; Moore et al. 1991). Respiratory tract infection probably occurs as a result of aspiration during vomiting although the haematogenous route has also been suggested (Gentile et al. 1987). Cough is a not uncommon symptom during cryptosporidiosis in the immunocompetant but direct evidence is lacking for respiratory tract infection in such cases. Aerosol transmission has been suggested as a means of acquiring cryptosporidiosis (Casemore 1989).

Epidemiology

Infection in humans may be zoonotic or acquired by person-to-person transmission and may be direct or acquired indirectly through the environment (Casemore 1991a). The incidence of human infection often shows temporal peaks which have generally been shown to reflect rainfall and farming events and practices such as lambing, calving, and muck-spreading (Casemore 1990, 1992). Human infection is not age-limited and occurs in all age groups; the peak incidence, by age, among the non-immunocompromised is in the one to five year age group with a smaller peak in the 20 to 40 year age group, some of which may be linked to occupational exposure (Casemore 1990). Such exposure has generally been attributed to contact with farm animals, for example among veterinarians.

Nosocomial transmission

There are a number of reports of transmission to health-care staff from immunosuppressed and immunocompetent patients, and between patients. The first report (Baxby et al. 1983) was of a nurse who had been caring for a hospitalised infant with acute cryptosporidiosis. In two nosocomial outbreaks there appeared to have been transmission of *Cryptosporidium* to staff caring for infected immunocompromised patients. In the first of these (Koch et al. 1985) serological studies suggested increased exposure among the staff involved in the care of an AIDS patient with confirmed cryptosporidiosis. However, infection was not demonstrated in staff by the presence of oocysts in stools. In the second episode (Dryjanski et al. 1986) a single nurse had confirmed infection, acquired while nursing a bone-marrow transplant recipient who had developed cryptosporidiosis. The nurse was believed to have had minimal unprotected exposure, thus suggesting that the minimum infective dose was small.

There have been several episodes involving patient-to-patient transmission. In an outbreak in a bone-marrow transplant unit (Martino et al. 1988), five patients developed cryptosporidiosis following admission to the unit of a sixth patient with the infection. Contamination of the ward environment was demonstrated.

In a renal unit, 11 of 14 patients with diarrhoea, and a member of nursing staff and her husband, were found to have cryptosporidiosis; a number of asymptomatic patients also had evidence of infection (Roncoroni et al. 1989). The apparently widespread transmission was thought to have resulted from sharing of toilet facilities.

Three of six leukaemic children with cryptosporidiosis, two of whom died, were thought to have acquired their infection while in hospital (Foot et al. 1990). Two of three severely malnourished children who acquired

cryptosporidiosis while in hospital, died from the effects of the infection (Sarabia-Arce et al. 1990). It was thought that malnourishment might predispose to the infection. Investigation of an outbreak among paediatric patients suggested that poor hand washing practice was an important factor, and naso-gastric feeding tubes were also thought to have been a vehicle of transmission (Navarette et al. 1991).

In an outbreak in a ward of immunocompromised patients in Denmark (Ravn et al. 1991), 18 HIV-positive patients developed cryptosporidiosis, together with a departmental secretary and a visiting relative. There was a high mortality rate among the AIDS patients. The evidence also suggested a low infective dose with transmission by a patient's hands via an ice machine.

Two hospital-associated outbreaks have involved day-care centres for children of staff, located within hospitals. In one of these, (Combee et al. 1986), eight children, and also day-care staff and family members were affected. In the other outbreak (Melo Cristino et al. 1988), 28 children, and one member of the staff, were affected. Such centres may provide a source of infection for hospital staff which may then be transmitted, especially to immunocompromised patients with potentially fatal consequences.

The North Wales outbreak

Five cases of cryptosporidiosis were confirmed among nursing staff, contracted from a terminally ill AIDS patient in a North Wales infectious diseases unit (O'Mahony et al. 1992). This outbreak is described here in some detail and further details of nursing and infection control measures are described elsewhere (Gardner, in preparation). The index case, a 36 year old man, was admitted with full-blown AIDS (CDC stage iv) of seven months duration: he had already been diagnosed elsewhere as suffering from cryptosporidiosis, the source of which was unknown. He also suffered from oral candidiasis, and from facial and anal herpes infections during his time in the unit. His immune status was very low (CD4 T cells <1%); CD4 counts were not done during the final stages of the infection but just prior to admission to this unit were between "undetectable" and 68/mm^3. He was receiving zidovudine, cotrimoxazole, fluconazole, and vitamin supplements. He showed signs of early dementia and, despite control of hydration and electrolyte status, his condition deteriorated within 24 hours. He became semi-conscious, was pyrexial, and had profuse watery diarrhoea and vomiting. After three days he had a remission for about six days when he became mobile and able to use the toilet. He subsequently became restless and confused, and was frequently soiled with faeces. This pattern continued until his death one month later. The diarrhoea and vomiting proved difficult to control, being unresponsive to high dose loperamide or codeine and with only a transient response to cyclimorph. Large numbers of cryptosporidia were persistently present in his stools, and were also found in a vomit sample. There was no apparent evidence of respiratory tract involvement. At one stage he was producing over six litres of watery stool which, coupled with the intractable vomiting and a degree of dementia, led to significant environmental contamination. Autopsy was not performed.

The patient was nursed over the four week period by a team of well motivated, trained nursing staff in a modern, specially designed infectious diseases unit. Eleven days after his admission, one of the nursing staff involved with the care of the patient developed diarrhoea. Because of the patient's cryptosporidial infection an investigation was instigated. Stools from nine of the sixteen nursing staff involved were obtained and examined for cryptosporidia and five were found to be infected with *Cryptosporidium*. Laboratory diagnosis was by phenol-auramine stain, and identity was confirmed by modified Ziehl Neelsen and monoclonal antibody immunofluorescence staining (Casemore 1991b). Although all five had some degree of diarrhoea, the severity, range and duration of symptoms varied widely. Another 11 nurses had various symptoms, including loose stools (as distinct from diarrhoea), abdominal pain or cramps, nausea and or vomiting, and other vague non-specific symptoms such as headache or fever. Of these, four with diarrhoea were screened by single stool examination at varying times after onset, but cryptosporidia were not found. Some of the contacts who did not provide samples had episodes clinically indistinguishable from confirmed cases. Two relatives of the patient and his partner, all of whom had spent time with him in the unit, and with whom he had lived prior to admission, had been symptomatic but were not screened. All affected members of staff were questioned about other possible sources of infection, such as animal contact, with negative results.

Examination of nursing procedures during management of the patient did not reveal any obvious lapses in nursing practises. However, his faecal incontinence and intractable vomiting often necessitated immediate close attention and thus raises the possibility of both faecal-oral and aerosol transmission. In one case, an infected nurse had only minimal contact with the patient but she did, however, have contact during rest breaks with a member of staff subsequently confirmed as having cryptosporidiosis. She may thus have been a secondary contact case.

None of the medical or domestic staff are known to have been infected; none had symptoms but none provided samples. Transmission to other patients in the unit, or to staff family contacts, are not known to have occurred.

Discussion

Cryptosporidium, although often considered to be a zoonotic infection, is readily transmissible from person-to-person, either directly by the faecal oral route or indirectly via food, water or sometimes by fomites, including medical instruments. Oocysts do not survive desiccation, freezing or moderate heat but are surprisingly resistant to many commonly used disinfectants (Blewett 1989b, Casemore et al. 1989, Dubey et al. 1990).

The oocysts are shed in large numbers during acute infection (Goodgame et al. 1993) and are immediately infective; the infective dose is thought to be small (Blewett et al. 1993) and studies in gnotobiotic lambs indicated a minimum infective dose (MID) of one to five oocysts. Continuing studies by the same workers using conventional lambs indicate a similar MID in that model (Wright et al., unpublished observation). The evidence of the outbreaks described here would also support the possibility of a small MID for humans.

Many features of *C. parvum* thus enhance the risk of rapid, direct or indirect, transmission of the infection (Casemore 1990) and are clearly of relevance to these outbreaks. The episodes described above illustrate some of the many ways in which infection can be transmitted within the hospital environment. However, the most likely explanation of what went wrong in the North Wales outbreak was severe environmental contamination. Doubts were also raised about the effectiveness of elbow operated wash hand basin taps used by staff and relatives assisting in his care and these have now been replaced by knee-activated electronic taps.

AIDS patients, especially those with dementia, suffering from a variety of intercurrent infections including cryptosporidiosis, impose severe demands on nursing staff. Aerosols or droplets from vomiting may provide a generally unrecognized route of cryptosporidial infection. The extent and nature of the outbreak described here was documented only because of vigorous infection control investigation of staff, irrespective of symptoms, when one nurse reported ill.

A study of renal transplant and AIDS patients, following a widespread outbreak resulting from water contamination in the UK, suggested that renal patients are no more likely to be infected nor to have more severe infection than normal subjects (Clifford et al. 1990, Richardson et al. 1991). AIDS patients, in contrast however, seemed to be more prone to acquire cryptosporidiosis and to suffer severe and potentially fatal infection. Drinking water is increasingly recognized as a source of cryptosporidial infection, sometimes involving many thousands of cases (Casemore 1991a, Edwards 1993). HIV-positive and other severely immunocompromised subjects should be advised to avoid consumption of unboiled water as a control measure (Casemore 1992, Petersen 1992).

As more hospitals become involved in the care of the increasing numbers of AIDS patients, units need to be particularly vigilant in the management of patients with cryptosporidiosis. Staff involved with the care of such cases should report even minor gastrointestinal symptoms which should then be investigated to minimize risk of spread to other patients or to staff.

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