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Cryptosporidiosis **- From Epidemiology to Treatment**

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1. Introduction

Cryptosporidiosis is a disease caused by *Cryptosporidium* spp, an obligate intracellular protozoan parasite.

It is a frequent cause of diarrheal disease in humans, and several groups of humans are particularly susceptible to cryptosporidiosis. In developing countries, *Cryptosporidium* infections occur mostly in children younger than 5 years (Newman et al, 1999; Bern et al, 2000; Bhattacharya et al, 1997; Gatei et al, 2006). In immunocompromised persons such as human immunodeficiency virus-positive (HIV) patients, the incidence and severity of cryptosporidiosis increases as the CD4 lymphocyte cell count falls (Navin et al, 1999; Pozio et al, 1997; Sorvillo et al, 1998).

Although cryptosporidiosis was initially described in mice in 1907 (Tyzzer, 1907), human disease was first identified almost three quarters of a century later. Two reports were published in 1976: one case in healthy child and one in an immunosuppressed adult (Meisel et al, 1976; Nime et al, 1976).

The next significant milestone was the emergence of chronic and life-threatening cryptosporidiosis with HIV/AIDS in the early 1980s. The association with AIDS and the appearance of early clinical and epidemiological reports implicating cryptosporidiosis as a frequent cause of acute diarrhea in the general population firmly established that the infection was serious and widespread in humans. The first case of cryptosporidiosis in a homosexual man with AIDS was reported in 1982 (Ma & Soave, 1983) and by mid-1983, some 50 cases had been reported (Ma, 1984). The link with AIDS was so strong that cryptosporidiosis became one of the defining features of the syndrome before the discovery of the causative virus.

Then, other immunocompromised patients and healthy people including veterinary workers and children were also diagnosed with cryptosporidiosis.

Cryptosporidiosis is an opportunistic parasitosis. It is characterised by self-limiting gastroenteritis in otherwise healthy people, while it is more severe in immunocompromised subjects in HIV-infected patients and constitutes a serious threat leading to chronic or fulminant disease, wasting and death (Hunter & Nichols, 2002; Chen et al, 2002).

While improved antiretroviral regimens have significantly reduced the prevalence of AIDS and AIDS-related opportunistic infections, cryptosporidiosis remains among the most common causes of diarrhoea in patients with AIDS (Hunter & Nichols, 2002; Morpeth & Thielman, 2006).

During the three last decades our knowledge about cryptosporidiosis has expanded remarkably.

The focus of this revue is to summarize current knowledge on taxonomy, epidemiology, diagnosis, treatment and prevention of cryptosporidiosis in AIDS patients.

2. Parasite

2.1 Taxonomy

Cryptosporidium species are apicomplexan parasites.

Over 100 years have passed since Ernest Edward Tyzzer first made his observations on the genus *Cryptosporidium*. *Cryptosporidium* was so named because of the absence of sporocysts within the oocysts, a characteristic of other coccidia. The first species described was *C. muris*, from the gastric glands of laboratory mice (Tyzzer, 1907). Tyzzer later published a more complete description of the life cycle and subsequently described a second species, also from laboratory mice. *C. parvum* differed from *C. muris* not only by infecting the small intestine rather than the stomach but also because the oocysts were smaller (Tyzzer, 1910, 1912).

Following the initial discovery of *Cryptosporidium*, over 50 years elapsed during which the parasite was commonly confused with other apicomplexan genera, especially members of the coccidian genus *Sarcocystis*.

After the recognition of true differences between *Cryptosporidium* and *Sarcocystis*, the erroneous concept of strict host specificity was applied to *Cryptosporidium* spp. This led to the creation of multiple new species including *C. agni* in sheep, *C. anserinum* in geese, *C. bovis* in calves, *C. cuniculus* in rabbits, *C. garhmani* in humans, and *C. rhesi* in monkeys (Levine, 1980; Barker & Carbonell, 1974).

Subsequent cross-transmission studies demonstrated that *Cryptosporidium* isolates from different animals can frequently be transmitted from one host species to another, which ended the practice of naming species based on host origin and the synonymization of many of these new *Cryptosporidium* species as *C. parvum*.

In recent years, molecular characterizations of *Cryptosporidium* have helped to clarify the confusion in *Cryptosporidium* taxonomy and validate the existence of multiple species in each vertebrate class.

As a result, several new species of *Cryptosporidium* have also been named, *C. andersoni* from cattle, *C. canis* from dogs, *C. molnari* from fish and *C. hominis* from humans (Xiao et al, 2004; Alvarez-Pellitero & Sitja-Bobadilla, 2002; Lindsay et al, 2000; Morgan-Ryan et al, 2002).

Human disease has been traditionally attributed to *C. parvum* but it was apparent from both the early epidemiological questions raised regarding the zoonotic status and transmission of the organism that variants occurred.

C. parvum, *C. hominis* were two confused species. The first observations of genetic heterogeneity among *C. parvum* (currently *C. parvum* and *C. hominis*) isolated from humans and livestock date back to 1992. Southern blotting of restriction enzyme-digested genomic DNA (Ortega et al, 1991), Western blotting (Nina et al, 1991) and isoenzyme profiles obtained from oocyst lysates (Ogunkolade et al, 1993) provided the first insights into the extent of heterogeneity in this species. Significantly, these studies showed for the first time that humans were infected with two subgroups within *C. parvum*, which were variously named "human" and "cattle", H and C or Type 1 and Type 2, respectively. These observations, subsequently confirmed in many laboratories, were significant in showing that humans are part of two distinct transmission cycles, one comprising ruminants and humans

ant the other exclusively comprising humans. It was a small step to the naming of a new species, *C. hominis*, proposed for *C.parvum* parasites exclusively infecting humans (Spano et al, 1998; Morgan-Ryan et al, 2002).

There are currently 16 recognized species of *Cryptosporidium*, which have been isolated from a large variety of hosts (Table 1), (Xiao et al, 2004) : *C. parvum*, *C. hominis*, *C. felis*, *C. canis*, *C. wrairi*, *C. varanii*, *C. suis*, *C. bovis*, *C. andersoni*, *C. muris*, *C. serpentis*, *C. galli*, *C. meleagridis*, *C. molnari*, *C. scophithalmi* and *C. baileyi*. The four basic requirements for the naming of *Cryptosporidium* species are (Xiao, 2010; Chalmers, 2008):

1. Morphometric study of oocysts and, if possible, sporozoites.
2. Multi-locus genetic characterisation by nucleotide sequence analysis of well studied genes or non-coding regions. The ssu rRNA gene is usually included.
3. Demonstration of natural and, if possible, experimental, host specificity.
4. Compliance with the International Code of Zoonotic Nomenclature.

Eight species are known to be infectious for man: *C. parvum*, *C. hominis*, *C. meleagridis*, *C.*

Species	Major host	Minor host	Location
<i>C. muris</i>	Rodents, bactrian camels	Humans, rock hyrax, mountain goat	Stomach
<i>C. andersoni</i>	Cattle, bactrian camels	Sheep	Abomasums
<i>C. parvum</i>	Cattle, sheep, goats, humans	Deer, mice, pigs	Stomach and intestine
<i>C. hominis</i>	Humans, monkeys	Dugongs, sheep	Small intestine
<i>C. wrairi</i>	Guinea, pigs		Small intestine
<i>C. felis</i>	Cats	Humans, cattle	Small intestine
<i>C. canis</i>	Dogs	Humans	Small intestine
<i>C. meleagridis</i>	Turkeys, humans	Parrots	Intestine
<i>C. baileyi</i>	Chicken, turkeys	Cockatiels, quails, ostriches, ducks	Cloacal, bursa, respiratory tract
<i>C. galli</i>	Finches, chicken, capercalles, grosbeaks		Proventriculus
<i>C. serpentis</i>	Snakes, lizards		Intestinal and cloacal mucosal
<i>C. scophithalmi</i>	Fish		Intestine
<i>C. molnari</i>	Fish		Stomach
<i>C. varanii</i>	Snakes, lizards		Intestinal and cloacal mucosal
<i>C. suis</i>	Pigs	humans	Stomach
<i>C. bovis</i>	Ruminants		Intestine

Table 1. Recorded species of *Cryptosporidium*

felis, *C. canis*, *C. suis*, *C. muris* and *C. andersoni*, although some are reported extremely rarely, particularly the latter three species, and the pathogenicity of some species for man has not been proven (Chalmers, 2008).

C. hominis and *C. parvum* are recognized globally as the most important *Cryptosporidium* species infecting humans (Dunand et al, 1997; Xiao & Ryan, 2004).

Muthusamy et al characterized cryptosporidial infections in 48 human immunodeficiency virus-infected individuals in India by multilocus genotyping. *C. hominis*, *C. parvum*, *C. felis*, *C. muris* and *C. meleagridis* were identified (Muthusamy et al, 2006).

2.2 Life-cycle

Sporulated oocysts, containing 4 sporozoites, are excreted by the infected host through feces and possibly other routes such as respiratory secretions. Following ingestion (and possibly inhalation) by a suitable host, excystation occurs. The sporozoites are released and parasitize epithelial cells of the gastrointestinal tract or other tissues such as the respiratory tract.

Cell invasion by sporozoites is followed by intracellular development to trophozoite.

In these cells, trophozoites undergo asexual multiplication (schizogony or merogony) to form schizonts or meronts.

Asexual replication occurs by re-infection of merozoites, released by type I meronts. Development of type II from type I meronts is the initial step of the asexual reproductive cycle. Merozoites are released from type II meronts and re-infect neighbouring cells where they develop into producing microgamonts (male) and macrogamonts (female) by sexual multiplication (gametogony). Upon fertilization of the macrogamont by the microgamont zygote develop, which undergoes further development into an oocyst.

Two different types of oocysts are produced, the thick-walled, which is commonly excreted from the host, and the thin-walled oocyst, which is primarily involved in autoinfection. Oocysts are infective upon excretion, thus permitting direct and immediate fecal-oral transmission.

3. Epidemiology

3.1 Risk factors

The risk of infection increases in more profoundly immunosuppressed persons, as measured by the CD4 T-lymphocyte counts (Haupt et al, 2005).

The incidence and severity of cryptosporidiosis increases as the CD4 T-lymphocyte cell count falls, especially when it falls to below 200 cells/l (Navin et al, 1999; Pozio et al, 1997; Sorvillo et al, 1999; Sara et al, 2008).

Various social and behavioral factors also increase the risk of infection. For example, in a large multicenter European study, the risk of cryptosporidiosis was significantly lower for intravenous drug users than for homosexual men and for women than for men, suggesting that sexual behaviour may be an important risk factor (Pedersen et al, 1996).

3.2 Modes of transmission

Transmission of the parasite is facilitated by a relatively low infectious dose and by the resistance of the parasite oocyst stage to commonly used disinfection techniques e.g chlorination of drinking water.

The infection is spread in a number of ways: from person to person, from animals, via food, and by water. Cryptosporidiosis is now the most common cause of waterborne disease in the world (Xiao & al, 2004).

Because *Cryptosporidium* spp. infects humans and a wide variety of animals and because of the ubiquitous presence of *Cryptosporidium* oocysts in the environment, humans can acquire *Cryptosporidium* infections through several transmission routes (Clark, 1999; Griffiths, 1998). In pediatric and elderly populations, especially in day care centers and nursing homes, person-to-person transmission probably plays a major role in the spread of *Cryptosporidium* infections (Xiao L et al, 2004; Neill et al, 1996; Tangermann, 1991). In rural areas, zoonotic infections via direct contact with farm animals have been reported many times, but the relative importance of direct zoonotic transmission of cryptosporidiosis is not entirely clear (Miron et al, 1991).

Numerous outbreaks of cryptosporidiosis due to contaminated food or water (drinking or recreational) have been reported in several industrialized nations, and studies have sometimes identified water as a major route of *Cryptosporidium* transmission in areas where the disease is endemic (Xiao et al, 2004; MacKenzie et al, 1991; Weinstein et al, 1993).

Many outbreaks in the United States have occurred in waterparks, community swimming pools, and day care centers.

Large outbreaks due to the contamination of water supplies have been documented in recent years (Richardson et al, 1991; Tzipori & Giovanni, 2008) and in one particular outbreak, contamination of a water-treatment plant in Milwaukee (USA) was estimated to result in infections in 403 000 people (Mac Kenzie et al, 1994). This outbreak was associated with municipal drinking water despite state-of-the art water treatment.

The magnitude of these outbreaks highlighted the significance of drinking contaminated water as a major risk factor for contracting cryptosporidiosis in the USA (Tzipori & Giovanni, 2008).

The sources and human infective potentials of *Cryptosporidium* oocysts in water, however, are largely unclear.

One major problem in understanding the transmission of *Cryptosporidium* infection is the lack of morphologic features that clearly differentiate one *Cryptosporidium* spp from many others (Mac Kenzie et al, 1994). Hence, one cannot be sure which *Cryptosporidium* spp is involved when one examines oocysts in clinical specimens under a microscope. Another major problem is the inability to grow the organisms in large numbers from contaminated sources. Adding to the diagnosis problem and technical difficulties is the confusion in the taxonomy of *Cryptosporidium* spp., which is partially caused by the lack of consistency in the classification of protozoan parasites in general.

C. hominis is believed to be transmitted exclusively between humans, whereas *C. parvum* is transmitted between humans as well as through a zoonotic cycle usually involving ruminants. Although calves are often implicated as the reservoir of *C. parvum*, the importance of animals in transmission of *C. parvum* has been brought into question by studies that found that humans are infected with subtypes that perpetuate almost exclusively among humans (Siobhan & Tzipori, 2008).

The study of *Cryptosporidium* transmission dynamics is made more complex when atypical species are considered. Human infections with *C. meleagridis*, *C. muris*, *C. felis*, *C. canis*, *C. andersoni* and *C. suis*, though uncommon, have been reported (Mor MS & Tzipori, 2008; Xiao & Ryan, 2004).

The natural reservoirs of these species are believed to be poultry, rodents, cats, dogs, cattle, and pigs, respectively; however the broad host ranges are not well characterized. Host factors may also increase the likelihood of infection following exposure to these species, because they are more frequently identified in HIV-positive persons. Two recent studies in East Africa have attempted to correlate species diversity with area of residence. In Malawi, *C. meleagridis* and *C. andersoni* were detected only in children from a rural district, although 70% of *C. parvum* cases were identified in urban areas and *C. hominis* predominated in both settings (Mor & Tzipori, 2008; Mersha & Tiruneh, 1992). In Kenyan children, 4% of cases were due to *C. canis*, *C. felis*, *C. meleagridis* and *C. muris*, and there was no discernible difference by region (Gatei et al, 2006).

4. Clinical features

4.1 Gastrointestinal diseases

Cryptosporidium species infect the microvillus border of the gastrointestinal epithelium of a wide range of vertebrate hosts, including humans. Infected individuals show a wide spectrum of clinical presentations. The pathogenicity of *Cryptosporidium* varies with the species of parasites involved and the type, age and immune status of the hosts.

In immunocompetent subjects, cryptosporidiosis is characterized by watery or mucoid diarrhoea and abdominal pain with spontaneous recovery following several days or weeks of symptoms (Mersha & Tiruneh, 1992).

Immunocompetent hosts control and eliminate the infection, which typically causes acute, self-limited watery diarrhea lasting 5 to 10 days. However, in patients with defects in cellular immune responses (e.g. AIDS), *Cryptosporidium* spp frequently causes persistent or chronic diarrhea which can lead to death and can also involve the hepatobiliary and the respiratory tract. It is an opportunistic infection.

The risk of infection increases in more profoundly immunosuppressed persons, as measured by the CD4-T-lymphocyte counts (Haupt et al, 2005; Morpeth & Thielman, 2006).

Various presentations of cryptosporidiosis in HIV-positive patients were described (Blanshard et al, 1992; Mc Gowan et al, 1993; Manabe et al, 1998).

U.S. workers described four clinical syndromes: chronic diarrhea (affecting 36% of patients), cholera-like disease (33%), transient diarrhea (15%), and relapsing illness (15%) (Blanshard et al, 1992, Manabe et al, 1998). Infected patients had a significantly shorter duration of survival from the time of diagnosis than did *Cryptosporidium*-negative AIDS patients (240 and 666 days, respectively; $P = 0.0004$).

One aspect of chronic cryptosporidiosis in patients with AIDS is the large weight loss that many experience (Blanshard et al, 1992). One study from France reported that the severity of weight loss in such patients is independently associated with levels of nutrient intake ($P < 0.005$) and high stool frequency ($P < 0.01$) but not with nutrient malabsorption (Beaugerie et al, 1998).

As well as developing a more severe form of typical gastrointestinal disease, people with HIV infection can develop atypical disease presentations, affecting body systems not usually affected in immunocompetent individuals. Some of these unusual presentations are discussed below.

4.2 Atypical gastrointestinal disease

Many cases of gastritis were described. One particularly problematic complication of gastric involvement is antral narrowing and gastric outlet obstruction (Iribarren et al, 1997; Moon et

al, 1999). Such gastric outlet obstruction can lead to nausea and vomiting and eventually may cause a severe reduction in nutrient intake.

A further unusual complication of cryptosporidiosis in AIDS patients is pneumatosis cystoides intestinalis (Samson & Brown, 1996; Sidhu et al, 1994). This disease is characterized by the presence of thin-walled, gas-containing cysts in the intestinal wall. Sometimes these cysts can rupture, resulting in a pneumoretroperitoneum and pneumomediastinum.

There is a case report of cryptosporidiosis affecting the oesophagus in a 2-year-old child and resulting in vomiting and dysphagia (Kazlow et al, 1986). Finally, there is also a case report of *Cryptosporidium* infection causing appendicitis (Oberhuber et al, 1991). The diagnosis was confirmed histologically after an appendectomy was performed.

4.3 Biliary tract disease

Cholangitis, and particularly sclerosing cholangitis, is an important complication of AIDS. Although not appearing to adversely affect survival, the disease can be a cause of significant pain (Forbes et al, 1993). In a Spanish study of 43 AIDS patients with chronic diarrhea due to *Cryptosporidium* infection, 8 patients (18.6%) were reported to have *Cryptosporidium* infection of the common bile duct (Lopez-Velez et al, 1995).

4.4 Pancreatitis

A series of 15 autopsies on patients with AIDS and cryptosporidiosis showed that five had evidence of infection of the pancreas (Godwin et al, 1991). Histological changes were generally mild and were limited to hyperplastic squamous metaplasia.

Three people with AIDS presented with acute or chronic pancreatitis related to cryptosporidiosis (Calzetti et al, 1997). All three patients had abdominal pain resistant to analgesics, increased serum amylase levels, and abnormalities at both sonography and computed tomography. Endoscopic retrograde cholangiopancreatography revealed papillary stenosis in all three patients. It is difficult to assess the impact of cryptosporidiosis-related pancreatic disease. Certainly, the first study does not suggest significant morbidity due to *Cryptosporidium* in the pancreas (Hunter & Nichols, 2002).

4.5 Respiratory tract disease

In a study from Spain, 7 of 43 patients (16.3%) with chronic diarrhea due to *Cryptosporidium* had *Cryptosporidium* oocysts detectable in the sputum (Lopez-Velez et al, 1995). Of these seven patients, five had respiratory symptoms and an abnormal chest radiograph; *Mycobacterium tuberculosis* was isolated in two of the five, and *M. avium* was isolated in another two. The remaining two patients had no respiratory symptoms and normal chest radiographs.

Other case series of patients with respiratory cryptosporidiosis were reported (Clavel et al, 1996; Hunter & Nichols, 2002). The majority of whom had another pathogen detected. So, the exact role of *Cryptosporidium* in the respiratory symptoms is not clear.

Dunand et al reported on 5 of their own cases and reviewed 14 other cases of parasitic sinusitis in HIV-positive patients from the literature (Dunand et al, 1997). Symptoms often included fever and chills in addition to local tenderness and discharge. Although the prognosis was frequently poor, this was due to other complications of HIV infection.

5. Diagnosis

For intestinal cryptosporidiosis, a parasitological examination of the stools is not only readily accessible and repeatable, but also non invasive for the patient. Oocysts are eliminated at intermittent intervals so stool tests should be repeated three times at three-day intervals (Weber et al, 1991; John & Petri, 2006).

Because of the small size of the *Cryptosporidium* oocysts, they are difficult to identify in fresh samples without specific coloration.

Oocysts may be examined under phase-contrast microscopy after concentration by different techniques. Oocysts may be concentrated by the modified zinc sulfate centrifugal flotation technique or by Sheather's sugar flotation.

Another concentration technique involves formalin-ethyl acetate sedimentation followed by layering and flotation over hypertonic sodium chloride solution to separate oocysts from stool debris (Weber et al, 1991). Oocysts appear as highly refractile spherical bodies (4 to 6 μm).

Several staining techniques can be used, applied to the swabs realized after concentration.

Modified Ziehl Neelsen stain is the best staining technique. The oocysts appear as rose spherical elements and contain four sporozoites (fig 1). The background is stained blue or green depending on the counter-stain used (Fast Green, malachite green or aniline blue) (Weber et al, 1991; Sunnotel et al, 2006).

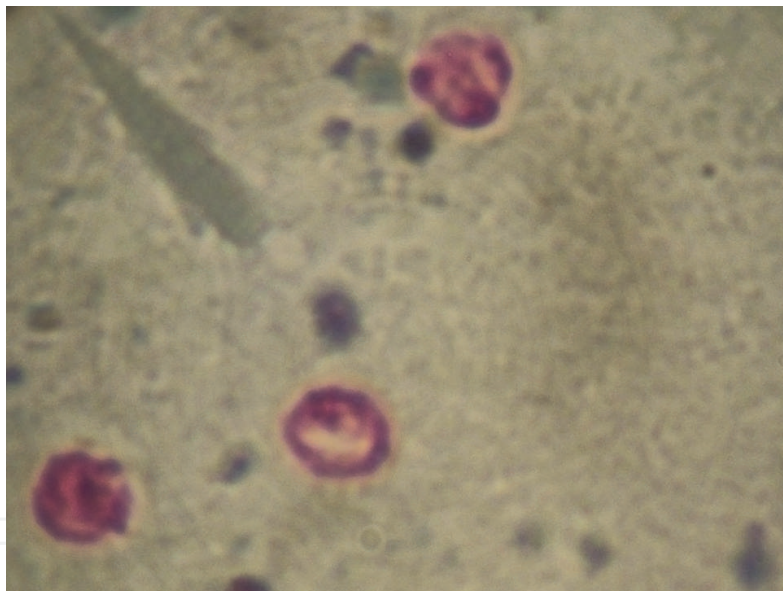


Fig. 1. Oocysts of *Cryptosporidium* sp stained by Modified Ziehl Neelsen stain

Cryptosporidium can also be detected by staining air-dried, methanol-fixed fecal smears with Giemsa's stain.

More recently, detection of oocysts is made by the use of copro-antigen detection kits, such as immunofluorescent antibody stains for microscopy, enzyme linked immunosorbent assays (ELISA) or immunochromatographic tests (Johnston et al, 2003).

Cryptosporidium oocysts also have been detected in fecal specimens by fluorescent stain like auramine-rhodamine.

The analytical sensitivity of these methods is generally in excess of 10^4 oocysts per gram faeces, depending on faecal consistency (Anusz et al, 1990; Weber et al, 1991), although immunofluorescence microscopy offers improved sensitivity (Arrowood, 1997).

Cryptosporidiosis can be diagnosed by identifying organisms (meronts containing merozoites and gamonts containing micro- and macrogametes) in intestinal biopsy material. Organisms stain lightly with hematoxylin and eosin and appear as small round bodies on the mucosal surface of biopsy specimens. With Masson's stain, a small red nucleus and blue cytoplasm can be distinguished in many of the organisms.

Species identification is an important element of outbreak investigations particularly where the source is not clear, and it is important that this is underpinned by routine species identification to establish the background epidemiology (Chalmers, 2008).

Even though oocysts of many *Cryptosporidium* spp are morphologically similar, morphometric measurement of oocysts can play a vital role in the differentiation of some *Cryptosporidium* spp. For example, the established species (interval) in birds and reptiles can easily be differentiated on the basis of the size and shape of oocysts. (Xiao et al, 2004).

However, laboratory techniques are unable to discriminate between the two main species involved in human disease, *C. hominis* and *C. parvum*. Species identification can be achieved with molecular methods which provide a precious tool for detecting *Cryptosporidium* and differentiating species in biological samples of infected patients (Chalmers, 2008).

However, *Cryptosporidium* presents two main problems for the isolation of DNA; the robust nature of the oocysts, requiring a disruption step prior to DNA extraction and the richness of PCR inhibitors in the sample matrix, requiring separation during DNA extraction.

Currently, there is no international consensus of typing methods and many rely on DNA sequence analysis which can be time-consuming and costly (Chalmers, 2008).

In 1991, Mark Laxer was the first to apply PCR to the detection of *Cryptosporidium* oocysts (Laxer et al, 1991).

Among molecular methods, PCR combined with restriction fragment length polymorphism (PCR-RFLP), which was first applied to *Cryptosporidium* typing by Awad-El-Kariem (Awad-El-Kariem et al, 1994) is the most used. PCR-RFLP assay detecting an *RsaI* polymorphism in the *Cryptosporidium* oocyst wall protein (COWP) gene (Spano et al, 1997), and a species-specific assay targeting the small-subunit rRNA gene (Xiao et al, 1999) are the most popular. Papers describing such assays or their application to *Cryptosporidium* typing are too numerous to cite here. Other methods such as random amplification methods (Morgan et al, 1995), sequencing (Lopez-Velez et al, 1995), length polymorphisms of repetitive sequences (Feng et al, 2000) and conformational polymorphism detection methods (Gasser et al, 2001) should also be mentioned in this context. However, the relatively high cost of molecular methods at present has limited their application in developed and developing countries.

The methodologies used in the detection of *Cryptosporidium*-specific antibodies vary widely, which complicates comparison of results. The use of the recombinant CP 41 antigen in a standardized serodiagnostic assay could provide a reliable and cost-effective method for assessing human exposure to *Cryptosporidium* in developing countries (Kjos et al, 2005).

6. Treatment

Despite the importance of cryptosporidiosis in mondial health, there has been any effective therapeutic specifically against *Cryptosporidium* infection, probably because of the unique intracellular extracytoplasmic location of *Cryptosporidium* and the poorly understood host-parasite interface. In addition, difficulties in laboratory propagation, including the absence of an ideal cell culture method, have limited high-throughput drug screening. Hundreds of drugs have been tested in the laboratory, and putative reports suggest that several,

including paromomycin, macrolides (e.g., azithromycin and spiramycin) and albendazole, are partially effective (Mor & Tzipori, 2008; Tzipori, 1998).

Clinical evaluations of these drugs have been disappointing, largely because they failed to clear the parasite from patients with HIV/AIDS.

To date, the broad-spectrum, anti-infective nitazoxanide (NTZ) has shown the most promise against *Cryptosporidium* (Mor & Tzipori, 2008).

It is used in many areas of the world because it appears to be well tolerated, it has a relatively low incidence of adverse effects, and it displays no significant known drug-to-drug interactions (Bobak, 2006). However, it is not effective against cryptosporidiosis in immunocompromised persons.

A meta-analysis of randomized, placebo-controlled trial of NTZ (of which there are only 2) among immunocompromised patients concluded that NTZ was no more effective than placebo in resolving diarrhea and achieving parasitological clearance in HIV-positive persons (Abubakar, 2007).

It has been speculated that HIV-positive persons may benefit from longer-duration regimens or higher doses of NTZ. However, a sustained clinical response was observed in only 59% of patients with HIV/AIDS who received off-label NTZ in a compassionate-use program (Rossignol, 2006).

This study indicate that the drug should be administered 500 mg b.d. until clinical symptoms resolve and oocysts are eliminated from the stool. Doses may be escalated to 1000 mg b.d. to accelerate or improve parasitological response. Fourteen days of treatment are generally sufficient in patients with CD4 counts above 50 cells/mm³ while at least 8 weeks of treatment are likely required in patients with CD4 counts below 50 cells/mm³.

Although refinement of the dosing regimen may improve clinical efficacy of NTZ, a prolonged therapeutic course will be impracticable in developing countries because of the expense and likely patient noncompliance.

ColoPlus is a product which may be an important alternative or additional treatment in HIV-associated diarrhoea. It is a product based on bovine colostrums which is the first milk the suckling calf receives from the cow. It is rich in immunoglobulins, growth factors, antibacterial peptides and nutrients. It supplies the calf with a passive immunity before its own active immunity is established. As well as having a high nutritional value, it is designed for slow passage through the gastrointestinal tract.

Floren et al conducted a study on thirty patients with HIV-associated diarrhoea. The patients were treated with ColoPlus for 4 weeks in an open-labelled non-randomised study, after an observational period of one week. After a post-treatment period of another two weeks, treatment with anti-HIV drugs was started, if deemed appropriate. The effects on the frequency of stool evacuations per day, on body-weight, fatigue, haemoglobin, levels and CD4 + counts before and after treatment with ColoPlus were measured. There was a dramatic decrease in stool evacuations per day, a substantial decrease in body-weight and an increase in CD4 count by 125 % (Floren et al, 2006).

In part because of the failure of other therapeutic approaches, there have been several attempts at passive antibody-based immunotherapy for cryptosporidial infections (Crabb, 1998). These have also had limited success.

One therapeutic intervention that has a dramatic effect on cryptosporidiosis in AIDS patients is antiretroviral therapy leading to recovery of the CD4 count. (Foudraine, 1998; Maggi et al, 2000; Miao et al, 2000; Morpeth & Thielman, 2006). The authors noted that resolution of the diarrhea seemed to be related to an increased CD4 - cell count rather than

to the viral load. These findings give further support to the observation that it is cellular immunity that is of paramount importance in clearing *Cryptosporidium* infection.

7. Prophylaxis

Because of the risk of acquiring a life-threatening disease, people with AIDS should take the following specific measures to help reduce the risk of waterborne cryptosporidiosis: boil drinking water for 1 minute, or filter drinking water with devices that remove particles 1 μm and larger, or use bottled drinking water, especially water obtained from underground sources (eg. springs or wells), which are less likely to be contaminated by *Cryptosporidium* oocysts. However, the boiling of water is the most certain method of killing *Cryptosporidium* oocysts. They should take additional precautions, including avoiding contact with young pets, and avoiding swallowing water while swimming (John & Petri, 2006).

The realization that *Cryptosporidium* oocysts are resistant to many chemical disinfectants (Tzipori & Giovanni, 2008; Rochelle et al, 2005) led to a search for methods that can inactivate oocysts without generating harmful by products. Much attention has focused on UV irradiation and ozone as alternative methods capable of inactivating waterborne oocysts (Tzipori & Giovanni, 2008; Lloyd & Drury, 2002). However, control of surface-water contamination is being emphasized as a first measure to reduce the occurrence of waterborne oocysts. Regulations aimed at reducing the risk of exposure to waterborne oocysts have been put in place; for example, the Long Term 2 Enhanced Surface Water Treatment Rule in the USA and regulations in the UK requiring continuous monitoring for *Cryptosporidium* oocysts in drinking water. A treatment-based standard of one oocyst in 10 l has been adopted (Sidhu et al, 1994).

8. Conclusion

We would conclude that research over the last three decades has dramatically increased our knowledge on cryptosporidiosis, but key questions still remain unclear.

With the new interest in *Cryptosporidium* generated by the emergence of the latter as the cause of human disease, much research is ongoing and will provide continuing information concerning cryptosporidiosis in the future.

Future developments need to include harmonisation of rapid and more cost effective methods.

Effective therapies are likely to become available in the near future. Access to endogenous forms and immortalization of strains in culture or by cryopreservation remain major challenges, which will require new ideas and new approaches.

Identification of *Cryptosporidium* isolates to species level and of subtyping is indispensable for appropriate control measures during outbreaks.

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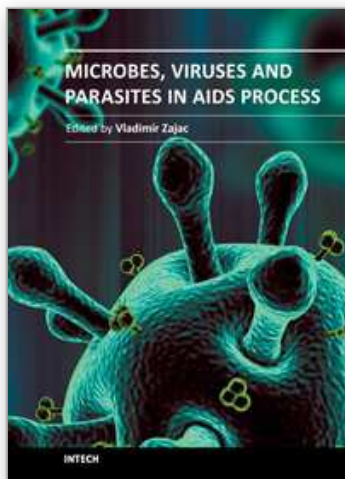
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Microbes, Viruses and Parasites in AIDS Process

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The main goal in compiling this book was to highlight the situation in Africa in terms of AIDS and opportunistic diseases. Several chapters reveal great poverty, an apocalyptic situation in many parts of Africa. Global migration of people resulted in their exposure to pathogens from all over the world. This fact has to be acknowledged and accepted as African reality. New, unconventional hypotheses, not determined by established dogmas, have been incorporated into the book, although they have not yet been sufficiently validated experimentally. It still applies that any dogma in any area of science, and medicine in particular, has and always will hinder progress. According to some biologists, in the future, AIDS is very likely to occur in a number of variations, as a direct result of the ongoing processes in the global human society. Thus, we urgently need a comprehensive solution for AIDS, in order to be ready to fight other, much more dangerous intruders.

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