# Treatment Modalities of *Cryptosporidium* Infection

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## Abstract
Immune status of infected patients is an important factor in recovery of cryptosporidiosis, the symptoms and signs usually disappear in less than 2 weeks without treatment in most people who have healthy immune system. Treatment is only by supportive therapy like drinking plenty of fluids and electrolyte replacement with oral rehydration solutions to prevent dehydration, anti-nausea drugs, antiemetic drugs, and analgesic drugs may be required. Although intravenous therapy may be necessary and nutritional support is probably beneficial. On the other hand, immunocompromised patients, whose illness is fulminant and life-threatening, no agent or antidiarrheal compound offers clear benefit, so removal the exogenous causes of immunosuppression is essential for cure. There have been a large number of studies aimed at developing a satisfactory therapy for cryptosporidiosis, particularly in immunosuppressed patients. Due to failure of other therapeutic approaches, there have been several attempts at passive antibody-based immunotherapy for *Cryptosporidium* infections, but these have also had limited success. Only one therapeutic intervention that has a dramatic effect on cryptosporidiosis in AIDS patients is antiretroviral therapy leading to recovery of the CD4 count.
**Keywords:** Treatment Modalities, *Cryptosporidium*, Infection.

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## Introduction:

Twenty-six species and 61 valid genotypes of *Cryptosporidium* spp. have been described from a wide range of vertebrates **(1).** The most common *Cryptosporidium* species were found in human infection are C. parvum, and C.hominis which are responsible for more than 90% of human cases. Several species have been also isolated from immunocompromised individuals such as C. canis, C.felis, C.meleagridis, C.suis, C.muris, and C.andersoni **(2).**

Although most *Cryptosporidium* species were named after the host they infect, but it turned out that they are not strictly host specific. There is many spp. have been reported in human from which, C. hominis and C. parvum. These two species are responsible for the majority of humans'

infections (3). C. hominis (previously known as C. parvum human genotype or genotype 1) was thought to infect only humans, and was found in nature to infect the dugong, a marine mammal. C. parvum (previously known as C. parvum bovine genotype or genotype type 2) is the least host specific species and has been identified in cattle, mice, horses, humans and many other mammalian hosts (4).

## TREATMENT:

Immune status of infected patients is an important factor in recovery of cryptosporidiosis, the symptoms and signs usually disappear in less than 2 weeks without treatment in most people who have healthy immune system. Treatment is only by supportive therapy like drinking plenty of fluids and electrolyte replacement with oral rehydration solutions to prevent dehydration, anti-nausea drugs, antiemetic drugs, and analgesic drugs may be required. Although intravenous therapy may be necessary and nutritional support is probably beneficial (5).

On the other hand, immunocompromised patients, whose illness is fulminant and life-threatening, no agent or antidiarrheal compound offers clear benefit, so removal the exogenous causes of immunosuppression is essential for cure (6).

There have been a large number of studies aimed at developing a satisfactory therapy for cryptosporidiosis, particularly in immunosuppresed patients. Due to failure of other therapeutic approaches, there have been several attempts at passive antibody-based immunotherapy for cryptosporidial infections, but these have also had limited success. Only one therapeutic intervention that has a dramatic effect on cryptosporidiosis in AIDS patients is antiretroviral therapy leading to recovery of the CD4 count. It was noted that resolution of diarrhea seemed to be related to an increased CD4+ cell count rather than to the viral load. The eradication of infection in people on highly active antiretroviral therapy has also been observed (7). These findings support the importance of cellular immunity in clearing *Cryptosporidium* infection, so the improvement in cellular immune function is the main priority for management of cryptosporidiosis in immunocompromised patients.

In AIDS patients, combination of restoring immunity along with antimicrobial treatment of *Cryptosporidium* is necessary. So clinicians should consider symptomatic therapy, optimization of antiretroviral therapy, and the inclusion of nitazoxanide or paromomycin (8).

It has been shown that the use of Anti-Retroviral Therapy (ART) improves the recovery and survival rates in immunocompromised individuals and the use of highly active antiretroviral therapy (HAART) may has an additional benefit, as it appears to directly interfere with the life cycle of the parasite in addition to the immune reconstitution effect. So, resolution of cryptosporidiosis can be maintained with effective HAART (9).

Problems associated with the discovery of new anti-cryptosporidial drugs are the limitations of in vitro culture for *Cryptosporidium*, the inability to genetically manipulate the parasite and the unique metabolic features in this parasite (10).

*Cryptosporidium* has completely lost the plastid derived apicoplast present in most other apicomplexans, and the remnant mitochondrion lacks the citrate cycle and cytochrome based respiratory chain. Therefore, most targets of classic drug are unavailable in *Cryptosporidium* and novel targets need to be identified for drug development **(10).**

Although a number of therapeutic agents have been evaluated for anticryptosporidial activity such as macrolides, aminoglycoside paromomycin, ionophores such as maduramycin, rifaximin, octreotide, and immunotherapy **(11),** they were suboptimal.

**Nitazoxanide:**

Nitazoxanide is the only approved drug by the Food and Drug Administration for the treatment of diarrhea associated with cryptosporidiosis from age of 1 year **(12).**

Nitazoxanide (NTZ) and its two metabolites, tizoxanide (TZ) and tizoxanide-glucuronide (TZglu) were shown to inhibit C. parvum growth at concentrations lower than 10 mg/L. NTZ works by inhibiting pyruvate ferredoxin oxidoreductase enzyme which is an essential enzyme in *Cryptosporidium* anaerobic metabolism. This drug has been shown to be effective in reducing duration and severity of symptoms and decreasing oocyst shedding in immune competent patients **(13).**

It has a wide spectrum activity against intestinal protozoans and this suggests its role in empiric therapy of chronic diarrhea **(14).**

It can't be effective without a good immune response of the host so that it can't be used effectively in immunocompromised individuals. Nitazoxanide remains the most effective therapeutic agent available against cryptosporidiosis in immunocompetent individuals**,** however it only gives a partial efficacy in immunocompromised individuals **(9).**

NTZ was shown to be more effective than paromomycin on biliary cryptosporidiosis in immunosuppressed gerbils **(15).**

The other commonly used drugs against cryptosporidiosis are paromomycin, and azithromycin, which are partially effective and not approved by FDA for the treatment of cryptosporidiosis. These drugs have only partial efficacy in reducing disease severity **(9).**

**Paromomycine:**

paromomycin is an aminoglycoside antibiotic poorly absorbed orally but apparently, it can be absorbed in small quantities across the apical membrane bounding the extracytoplasmic parasite. Its mechanism of action is targeting the ribosome to disrupt protein synthesis. Based on experimental studies and clinical experience, paromomycin has a modest activity against C. parvum. In most studies there was a good clinical and parasitological response. However, after its discontinuation many patients relapsed, moreover several studies concluded that it was only partially effective in immunocompromised patients **(16).**

Several therapies like paramomycin and a combination of paramomycin and azithromycin have been tried in AIDS and transplant patients but the effectiveness of any of these agents is still unclear **(17).**

**Masood et al; (18)** carried out a study to test the therapeutic efficacy of albendazole, metronidazole and paromomycin against *Cryptosporidium.* Albendazole and Metronidazole treatment lead to a significant decrease in oocyst shedding, while Paromomycin showed better results than both of them.

## AZITHROMYCIN:

Azithromycin is an antibiotic interfere with the microbial protein synthesis. It is the most active one of macrolides against cryptosporidiosis in animal models. It was reported that long term and low dose of azithromycin is well tolerated and may induce stable remission of chronic cryptosporidiosis in HIV patients. Good results were reported with azithromycin when given in combination with paromomycin in HIV patients with cryptosporidiosis**., Kadappu et al. (19)** study the efficacy of short-term use of azithromycin in thirteen AIDS patients and there was a good clinical improvement but parasitological benefit was doubtful.

## ANTIBODY THERAPY:

The close relationship between Cryptosporidiosis and host immune status led to investigations of antibody therapy. It has been reported that hyperimmune bovine colostrum may modify the course of *Cryptosporidium* infection in immunocompromised hosts (**,** but the obtained Results are mostly contradictory**.** In a work regarding neutralizing monoclonal antibodies, it was hypothesized that targeting the apical complex and surface antigens CSL, GP25- 200, and P23 could passively immunize against cryptosporidiosis. The results indicated that anti-CSL MAb had highly significant efficacy in reducing, not eliminating, C. parvum infection in adult gamma interferon-depleted SCID mice.

## pyrvinium pamoate:

This anthelminthic drug was the treatment of choice of pinworm infections many years ago. It was found to be effective against *Cryptosporidium* in both cell culture and a neonatal mouse model. It has been used as anthelminthic for at least four decades. It is safe and well tolerated when given in a single dose or over a few days. It remains to be seen if the drug will be able to be given for prolonged durations as usually needed in the treatment of cryptosporidiosis in immunocompromised individuals **(20).**

## NUTRITIONAL REHABILITATION:

Proper rehydration and nutritional support with total parenteral nutrition may be necessary due to massive fluid loss with diarrhea, sometimes in excess of 2 L. glutamine or alanyl glutamine has been used in patients with severe diarrhea to aid in fluid and electrolyte absorption. In animal

models infected with *Cryptosporidium* or Rotavirus, glutamine has been shown to stimulate sodium reabsorption in the small intestine even in the context of bowel villous atrophy **(21).**

It has been reported that supportive management including rehydration therapy, electrolyte replacement and antmotility agents will remain the best treatment strategies until better drugs emerge **(16).**

**ANTIRETROVIRAL THERAPY:**

The best strategy for managing *Cryptosporidium* in HIV-infected patients appears to be immune reconstitution with highly active antiretroviral therapy (HAART) which increase patient's CD4 above risk thresholds **(22).** Some studies using protease inhibitors such as indinavir, saquinavir, and ritonavir claim a drastic reduction of *Cryptosporidium* infection both in vivo and in vitro although there are no reports of the presence of aspartyl proteases in C. parvum **(23).**

*Cryptosporidium* has completely lost the plastid derived apicoplast which present in most of the apicomplexans, and the remnant mitochondrion lacks the citrate cycle and cytochrome based respiratory chain. Therefore, many classic drug targets are unavailable and novel targets need to be identified for new drug development **(10).**

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