Diarrhea in the HIV-infected patient

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P PHILLIPS. Diarrhea in the HIV-infected patient. Can J Infect Dis 1994;5(Suppl E):42E-48E. Gastrointestinal manifestations may be encountered throughout the course of HIV disease. The problems range from asymptomatic hairy leukoplakia to overwhelming diarrhea due to opportunistic infections such as cryptosporidiosis. Diarrheal disease is an important contributing factor to wasting in advanced HIV disease. Considerable progress has been made in recent years regarding our understanding of HIV-related diarrhea, including etiological agents, diagnostic methods and treatment.

Key Words: AIDS, Diarrhea, Enteric pathogens, Human immunodeficiency virus

Diarrhée chez le patient infecté par le VIH

RÉSUMÉ : Les manifestations gastro-intestinales peuvent s’observer tout au long de la maladie au VIH. Les problèmes varient d’une leucoplasie à cellules chevelues asymptomatique à une diarrhée considérable due aux infections opportunistes, comme la cryptosporidiose. La maladie diarrhéique est un important facteur contributif dans les états de déperdition observés dans la maladie au vih avancée. Des progrès considérables ont été accomplis au cours des dernières années dans notre compréhension de la diarrhée liée au vih, y compris au chapitre des agents étiologiques, des méthodes diagnostiques et des thérapeutiques.

DISEASES RESULTING IN GASTROINTESTINAL TRACT SYMPTOMS are common and occur in up to 50% of patients with AIDS (1). Diarrhea is the most frequent symptom in such patients; others include oral and esophageal symptoms, nausea, vomiting, abdominal pain, jaundice and wasting. A wide range of intestinal infections may account for diarrheal illness in the HIV-infected patient. These pathogens include bacteria, (Salmonella, Shigella, Campylobacter and Yersinia species and Clostridium difficile), viruses (cytomegalovirus [CMV], adenovirus), mycobacteria (Mycobacterium avium, Mycobacterium tuberculosis), and protozoa (Cryptosporidium species, Giardia lamblia, Entamoeba histolytica, Isospora belli and microsporidia).

Three types of enteric infections include the following (2):

- Noninflammatory processes involving primarily the proximal portion of the small bowel as a result of an enterotoxin (eg, enterotoxigenic Escherichia coli) or infection that interferes with small bowel absorption (eg, cryptosporidium, giardia, rotavirus, Norwalk-like viruses, CMV, M avium and possibly HIV).
- Inflammatory dysentery, which involves the colon as a result of invasive infection, possibly including a cytotoxin (eg, Shigella, Salmonella and Campylobacter species, C difficile or amebiasis). Included in this category of disease are the various causes of sexually transmitted proctitis (eg, herpes simplex virus, gonococcus, chlamydia and Treponema pallidum).
- An enteric fever syndrome, which may occur with bacteremic illness, often associated with constipation early in the course of the disease (eg, Salmonella species, and occasionally campylobacter or yersinia).

Patients presenting with the noninflammatory diarrhea involving predominantly small bowel tend to have soft to watery bowel movements, which may be associated with midabdominal discomfort, in the absence of...
blood or mucus per rectum. In contrast, inflammatory
dysentery involving the colon or rectum usually results
in frequent, smaller volume diarrhea, with or without
lower abdominal pain, tenesmus, rectal urgency and
blood or mucus per rectum. Fecal leukocytes are usu­
ally absent in noninflammatory diarrhea, but are often
present in inflammatory diarrhea involving the colon or
rectum; however, the sensitivity of fecal leukocyte smears
for the diagnosis of inflammatory diarrhea is unclear,
and has not been evaluated in HIV-infected patients.

The commonly identified causes of chronic diarrhea
in AIDS patients include cryptosporidiosis, microsporidiosis,
isosporiasis, or intestinal involvement with
M. avium or cytomegalovirus. No specific etiology is
found in 30 to 50% of cases of HIV-related chronic
diarrhea. By exclusion, these cases have been diag­
nosed as idiopathic HIV enteropathy (3), although the
diagnostic criteria for this entity have been debated (4),
and the etiological significance of other enteric viruses
such as astrovirus and picobirnavirus has not been
determined in HIV-infected patients (5).

CRYPTOSPORIDIOSIS

Cryptosporidiosis is a zoonosis. Both animal to per­
son and person to person transmission have been
documented. Risk factors for cryptosporidiosis include
deficient cellular or humoral immunity, infancy, close
contact with infected individuals, travel to developing
countries, poor sanitary facilities and occupational ex­
posure (animal workers and day care centre employees)
(6). The infection has also been documented to be
waterborne. The two recognized species are Crypto­
sporidium parvum and Cryptosporidium muris.

Infection of the gastrointestinal tract with crypto­
sporidium is one of the most common causes of chronic
diarrhea in AIDS patients (7) and accounts for consider­
able morbidity.

A significantly higher mortality rate has been associ­
ated with AIDS patients who have cryptosporidiosis com­
pared with those who do not, suggesting that the
infection often results in general deterioration (8). The
prevalence of cryptosporidiosis is 3 to 4% for AIDS pa­
tients in the United States compared with prevalence
as high as 50% in Haiti and Africa (7). The disease may
affect both the normal and immunocompromised host
and usually results in self-limited and chronic disease,
respectively.

Clinical presentation includes diarrhea that is often
severe and ranges up to 25 bowel movements per day.
The stools are watery, voluminous (up to 20 L/day) and
not associated with blood or inflammatory cellular
exudate. Frequently there is marked weight loss, and
both lactose intolerance and fat malabsorption have
been documented in association with cryptosporidiosis.
In the normal host the infection is usually self-limited
with symptoms resolving within two weeks, but stools
remain positive for the organism for an additional two
to three weeks (9). Chronic cryptosporidiosis lasting
longer than one month in patients without other causes
of immunodeficiency is an AIDS-defining illness. Among
HIV-infected individuals with cryptosporidiosis, self­
limited disease has been associated with higher CD4 cell
counts (mean 312 cells/mm³) compared with those
cases of persistent infection (mean CD4 counts 57 cells/
mm³) (10). Flanigan et al (10) observed spontaneous
resolution of cryptosporidiosis in all patients (n=8) with
CD4 counts greater than 180 cells/mm³; however, 34 of
39 (87%) cases with CD4 counts less than 180 cells/
mm³ had persistent disease. Symptoms of cryptosporidio­
sis tend to wax and wane even without treatment (11).

Cryptosporidiosis has been shown pathologically to
involve all portions of the gastrointestinal tract from the
pharynx to the rectum including the biliary tree. Most
often the disease is largely confined to the small and
large intestine. Extraintestinal sites of infection have
included the biliary tract, pancreatic duct, liver and
lung (6). The pathology of cryptosporidiosis is similar to
that seen in giardiasis, including small intestinal
changes with epithelial loss, villous atrophy, crypt elon­
gation and often minimal inflammatory infiltrate in the
adjacent lamina propria (6.12).

Diagnosis is most readily made by stool smears which
may be stained using a number of techniques includ­
ing modified acid-fast stain, fluorescent auramine­
rhodamine stain, periodic acid-Schiff and carbol fuchs­
in stains (7). The modified acid-fast stain is generally the
preferred method for diagnosis. Methods for concen trat­
ing stool samples are usually not required for diagnosis
in acute cases. A sodium chloride layering technique
followed by ethyl acetate sedimentation has been shown
to be superior to other concentration methods (13).
Radiographs of the bowel in patients with crypto­
sporidiosis usually show nonspecific findings including
prominent mucosal folds, thickened intestinal wall and
disordered motility. Intestinal biopsy is generally con­
sidered to be less sensitive than stool examinations
because of the patchy nature of the disease and the
absence of gross signs of inflammation to help direct the
diagnosis (15). Intestinal biopsy may reveal the presence
of 4 to 5 μm diameter organisms, which are adherent to
the epithelial surface on the microvilli and which are
contained in a vacuole that is considered intracellular,
but extracytoplasmic to the enterocyte (7).

Management of cryptosporidiosis in AIDS has been
mainly supportive (6.7.9). There are now some poten­
tially beneficial antiparasitic agents, but none proven
effective in randomized, placebo controlled, compara­
tive trials. Oral and sometimes intravenous fluid re­
placement may be required. Antimotility agents are not
always helpful and in some patients may be associated
with increased abdominal cramping (7). Intravenous
hyperalimentation is helpful for stabilizing occasional
patients but may be inappropriate for terminally ill
patients, and is further limited by cost considerations.
<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Preferred treatment</th>
<th>Alternative treatment</th>
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| Cryptosporidiosis | Symptomatic treatment with nutritional supplements, antidiarrheal agent (eg, loperamide, diphenoxylate), ± fluid (IV/po) and electrolyte replacement | Experimental agents: • Paromomycin (EDRP) 500 mg po qid with food 14-24 x 28 days, then 500 mg po bid 1  
• Azithromycin (EDRP) 1200 mg po first day, then 600 mg/day x 27 days, then 300 mg/day Ocreotide (Sandostatin) 50-500 µg sc tid for 5-10 x 1 month 2 | Duration of high dose TMP-SMX therapy is not well defined  
No controlled trials to show efficacy of antimicrobials. Spiramycin ineffective in non-HIV infants 3. Numerous anecdotal but unproven treatments. Nutritional supplements often required for severe cases. ± parenteral hyperalimentation. Spontaneous resolution unlikely if absolute CD4 count < 200/mm³ 4  
Efficacy not clearly established for syndromes other than retinitis. Some evidence for efficacy in colitis 5. Ganciclovir preferred if renal impairment; foscarnet preferred if neutropenia or AZT used concurrently. Need for maintenance therapy remains controversial except for CMV retinitis  
Efficacy not clearly established.  
Modified trichrome stain optimal for detecting microsporidia in stool and duodenal aspirates 6  
Recurrent bacteremia may be suppressed by ciprofloxacin 500 mg po bid or TMP-SMX 1 DS bid indefinitely.  
Unlike normal host, HIV+ patient requires treatment of uncomplicated salmonella enterocolitis to reduce complication rate (eg, bacteremia).  
Long term ciprofloxacin, norfloxacin or TMP-SMX if recurrent shigellosis. C difficile colitis more common in HIV+ patients. Similar efficacy 7 but vancomycin more expensive than metronidazole. For severe infection: vancomycin 250-500 mg po every 6 h. Either drug unreliable iv for C difficile colitis. Try to decrease responsible antibiotic(s). Avoid antimotility agents. Relapse in up to 20%.  
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and potential complications. It is believed that the biliary tree may serve as a reservoir for cryptosporidiosis and thereby contributes to recurrent infections because of difficulty in eradicating the organism from this site. A wide range of specific treatments has been employed for cryptosporidiosis (6,7,9,14) with some reported clinical and microbiological responses. Favorable responses have been observed in association with paromomycin (15), bovine hyperimmune colostrum (16), and letrazuril (17).

An important aspect of management is reducing transmission by good hygiene including hand washing and awareness of the risks of direct fecal-oral exposure (9). Nosocomial spread of this infection has been documented.

**ISOSPORIASIS**

Isosporiasis is an uncommon cause of chronic diarrhea in HIV-infected individuals in North America (less than 0.2%) but has been observed in up to 15% of AIDS patients in Haiti. It is clinically indistinguishable from cryptosporidiosis, typically presenting with chronic, watery diarrhea without blood or mucus, and associated with crampy abdominal pain, nausea and weight loss (18). Stool smears are usually negative for fecal leukocytes, and the diagnosis is established by stool smears (modified acid-fast stain or iodine preparation) demonstrating the 25 to 30 μm diameter oocysts, which are larger than the 5 μm cryptosporidial cysts. Other means of establishing the diagnosis include duodenal aspirate or biopsy in which organisms are demonstrated within the cytoplasm of villous epithelium. In contrast to cryptosporidiosis, most patients respond promptly to treatment (Table 1), but relapse occurs in approximately 50% without secondary prophylaxis (18).

**MICROSPORIDIOSIS**

Microsporidiosis is an intestinal protozoal infection caused by *Enterocytozoon bieneusi*. It has been found to be an important cause of chronic diarrhea in HIV-infected patients when routine stool microbiology has been negative (12). Microsporidia are spore-forming, obligate, intracellular protozoan parasites, and the organism resides in the cytoplasm of the intestinal epithelial lining cells. The clinical presentation is indistinguishable from that of cryptosporidiosis, with watery, nonbloody diarrhea associated with progressive weight loss and usually no fever. Previously the diagnosis was usually only established by duodenal or jejunal biopsy with the parasite identified on hematoxylin and eosin or Giemsa stain. Electron microscopy has been used to confirm the diagnosis, although in a recent study, light microscopy appeared to be of similar sensitivity (19). Recently, a practical method using a modified trichrome stain was reported for the identification of the spores of *E. bieneusi* in fecal samples (20). Optimal treatment for intestinal microsporidiosis has not been established, but responses have been reported with metronidazole as well as albendazole (Table 1) (21,22). However, patients with microsporidia infection may not have diarrhea. This observation prompted Rabeneck et al (23) to question the role of microsporidia in the pathogenesis of HIV-related chronic diarrhea.

**CYTOMEGALOVIRUS COLITIS**

CMV disease may occur at any site of the gastrointestinal tract in HIV-infected patients, but most often affects the colon. esophagus, stomach or hepatobiliary system. CMV colitis occurs in approximately 5 to 10% of AIDS patients, and is usually associated with chronic diarrhea, abdominal pain, anorexia, weight loss and fever (24). Diarrhea is usually nonbloody, although complications may include gastrointestinal hemorrhage or perforation. Diagnosis is most reliably established by the presence of CMV inclusions on intestinal biopsy specimens, and is supported by the presence of CMV antigen or positive biopsy viral culture for CMV. The absence of other intestinal pathogens is also helpful in establishing the relationship of gastrointestinal complaints to positive findings for CMV. The efficacy of antiviral therapy for CMV disease has not been documented as clearly for colitis as it has for retinitis. A recent placebo controlled trial showed that ganciclovir treated patients had improvement in mucusal abnormalities seen on colonoscopy and some protection against development of new extraintestinal CMV disease, compared with placebo. However, clinical endpoints (eg, diarrhea, body weight, etc) did not differ between the groups (25). Diarrhea response may have been confounded by the use of antidiarrhea agents in both arms of the study. The need for long term maintenance therapy with ganciclovir or foscarnet has not been established, but should at least be offered to those individuals experiencing frequent relapses, which appear to respond to treatment.

**MYCOBACTERIUM AVIUM**

*M. avium* infection occurs in 30 to 50% of AIDS patients, usually beginning with a localized gastrointestinal infection (duodenum, small or large bowel) and frequently followed by dissemination. Macrophages are infected and pathological involvement mainly involves the reticuloendothelial system, including lymph nodes, liver, spleen, bone marrow and gastrointestinal tract (26). The clinical presentation of disseminated *M. avium* infection often includes fevers, night sweats, weight loss and progressive anemia. The presence of abdominal pain and diarrhea without evidence for other enteric pathogens suggests specific gastrointestinal tract involvement, which is often associated with mesenteric lymphadenopathy. Intestinal involvement may result in a malabsorption syndrome, similar clinically and pathologically to Whipple's disease except for the presence of macrophages laden with acid-fast bacilli.
Management of diarrhea in the immunocompromised (1) * HIV-infected patient

- History (2) and physical examination (3)
- Fluid and electrolyte management if fluid volume depleted (4)
- Diarrhea severity
  - Severe or with blood
    - Stool culture x 1
    - Stool ova and parasites x 3, including acid-fast stain (5) and modified trichrome stain
    - ± Clostridium difficile culture and toxin assay (6)
    - ± blood cultures if fever (7)
  - Mild-moderate
    - Stool culture x 1 (12)
    - ± C difficile (6)
    - ± blood cultures if fever (7)

Diagnosis

- Antidiarrheal agent (8)
  - Persistent diarrhea
    - Stool ova and parasites (5) x 3, including acid-fast and modified trichrome stain
      - No diagnosis
        - Specific treatment
        - Diarrhea improved (<500 mL/day)
          - Continue symptomatic treatment
        - Diarrhea profuse (>500 mL/day) and poorly tolerated
          - Consider octreotide (11)

*Please see Footnotes to Figure 1 on following page*
(27). Endoscopic biopsy and mycobacterial culture are most reliable for establishing the diagnosis. The role of stool smears for acid-fast bacilli in the diagnosis of either intestinal or disseminated infection is unclear because of variable sensitivity, and the possibility of mycobacterial colonization and symptoms related to other etiologies.

**BACTERIAL ENTERIC PATHOGENS**

Bacterial enteric pathogens should be considered in patients with inflammatory diarrhea; however, approximately half of salmonellosis cases present with fever in the absence of colitis. Salmonellosis (28) and possibly shigellosis (29) are more likely to be associated with bacteremia in the HIV-infected patient than the general population. Unlike the immunocompetent host, all HIV patients with uncomplicated salmonella gastroenteritis require antimicrobial therapy. Recurrent enteric infections require long term suppressive therapy (Table 1). C. difficile colitis, which appears to be more common in HIV patients, should be considered in those receiving antimicrobial agents for prophylaxis or treatment of various opportunistic infections.

**AIDS ENTEROPATHY**

Idiopathic AIDS-associated enteropathy has been defined as chronic diarrhea (longer than one month) associated with negative investigations for enteric pathogens, with or without the demonstration of villous atrophy. The negative studies should include stool microbiology, endoscopy and biopsies, as outlined in Figure 1. Possible etiologies for AIDS-associated enteropathy include: previously unrecognized or seldom isolated enteric pathogens (5); low grade bacterial overgrowth possibly due to impaired development of gut B lymphocytes (related to CD4 lymphocyte depletion) and immunoglobulin A production (1); or HIV (30).

**MANAGEMENT**

Management of HIV-related diarrhea is summarized in the algorithm (Figure 1). Treatment of specific, selected enteric pathogens is summarized in Table 1 (31).

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**FOOTNOTES TO FIGURE 1**

1. *Opportunistic infections* involving the gastrointestinal tract, such as *Mycobacterium avium* or cytomegalovirus (CMV) usually occur in patients with absolute CD4 counts less than 100/mm³.

2. Inquire regarding:
   - use of diarrhea-inducing drugs and caffeinated beverages;
   - recent antibiotic use (*Clostridium difficile*);
   - sexual orientation (homosexual men at risk for proctitis due to herpes simplex virus, gonococcus, chlamydia and syphilis);
   - ingestion of inadequately cooked seafood (eg, vibrio, Norwalk-like viruses);
   - travel to tropical areas (eg, enterotoxigenic *Escherichia coli*, giardia, *Entamoeba histolytica*, strongyloides, Norwalk-like viruses or rotavirus and invasive bacterial infections);
   - bloody diarrhea (eg, *E coli*, amebiasis, campylobacter, CMV, shigella).

3. *Physical examination* should include assessment of intravascular volume, including supine/standing blood pressure and pulse, and jugular venous pressure.

4. Initial management for *fluid volume-depleted patients* should be oral or intravenous fluids and electrolytes. A simple oral rehydration solution consists of: one level teaspoon of table salt, plus four heaping teaspoons of sugar, added to 1 L of water (*J Trop Med Hyg* 1981;84:73). Give volume equivalent to 5 to 7% of body weight for mild-moderate dehydration.

5. *Stool acid-fast staining* is needed for identification of *cryptosporidium* and *isospora belli*. However, stool smear for acid-fast bacilli not routinely recommended because of variable results of sensitivity and specificity for true mycobacterial infection versus colonization. Positive stool smear may be more likely than mycobacterial stool culture to reflect invasive infection rather than colonization.

6. If *recent antibiotic use*, then also include *C difficile* culture and toxin assay.

7. **Routine blood cultures** should be obtained in patients with fever and diarrhea to exclude bacteremia due to salmonella, shigella and campylobacter. Salmonellosis is 20 times more common in AIDS patients and five times more likely to be associated with bacteremia than in the general population (*J Infect Dis* 1987;156:998).

8. *Mycobacterial blood cultures* are indicated if persistent or recurrent fever develops in association with CD4 lymphopenia.

9. *Antidiarrheal agent* of choice is loperamide (Imodium), which is not associated with narcotic dependency, but this may occur with diphenoxylate (Lomotil) (*Gastroenterology* 1980;79:1272). Diarrhea and abdominal cramps respond earlier with loperamide than bismuth subsalicylate (*JAMA* 1986;255:757). Antimotility agents should usually be avoided in patients with fever or bloody stools, because they may worsen dysentery due to shigella (*JAMA* 1973;226:1525) or *C difficile* (*JAMA* 1976;235:1454).

   Loperamide dosing: 4 mg initially, then 2 mg after each unformed stool (maximum 16 mg/day). When daily dose established, it may be given as one to four divided doses/day.

10. *Sigmoidoscopy specimens* should include wet mount (*E histolytica*). Biopsies are obtained for pathology, viral (CMV, adenovirus, herpes simplex virus) and mycobacterial culture. Barium enema and colonoscopy are seldom useful for the investigation of chronic diarrhea in HIV-infected patients (AIDS 1990;4:687).

11. *Upper gastrointestinal endoscopy* for duodenal fluid specimens should be sent promptly for parasitology (wet.
mount, acid-fast and modified trichrome stains), and biopsies for hematoxylin and eosin, acid-fast, ± Giemsa stains looking primarily for protozoa (microsporidia, isospora, giardia), mycobacteria and CMV. Electron microscopy may be helpful for diagnosis of microsporidiosis but is expensive and usually not necessary (Ninth International Conference on AIDS, 1993, Abst WS-820-2). A specimen may be prepared for electron microscopy but not examined unless other specimens are nondiagnostic.

11. Octreotide (Sandostatin) is a synthetic analogue of somatostatin, and in doses of 50 to 500 μg subcutaneously tid may provide benefit in severe refractory AIDS-associated watery diarrhea, particularly when no pathogens have been identified (Ann Intern Med 1991;115:705).

12. Initial investigation of mild to moderate AIDS-related diarrhea should be limited to a stool culture (Ann Intern Med 1990;112:942). More extensive investigations, which are both expensive and may be associated with patient discomfort, should be reserved for those with a negative stool culture and persistent diarrhea despite symptomatic antidiarrheal treatment.

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