Prevalence of Intestinal Pathogens in HIV Patients with Diarrhea: Implications for Treatment

B.S. Ramakrishna

Department of Gastrointestinal Sciences, Christian Medical College Hospital, Vellore

Abstract: Patients infected with the human immunodeficiency virus (HIV) commonly experience diarrhea at some time during their illness. A variety of enteric pathogens are identified in 50-80% of these patients, depending on the intensity of the diagnostic work-up that is done. In addition to the common enteric pathogens, several unusual enteric pathogens are recognized to cause diarrhea especially in HIV patients. These include protozoan parasites such as Cryptosporidia, Isospora bellii, Cyclospora cayatenensis and Microsporidium species, bacteria such as enteropathogenic Escherichia coli and Mycobacterium avium-intracellulare, fungi including Candida albicans and Histoplasma capsulatum, and viruses such as astroviruses and caliciviruses. Diagnosis of these infections sometimes involves special procedures not readily available everywhere, and empiric therapy based on knowledge of the likely pathogens has been advocated for developing countries. This article reviews the currently available data on geographic variation of enteric pathogens in HIV patients with diarrhea and outlines a rational strategy for empiric therapy of these patients. (Indian J Pediatr 1999; 66: 85-91)

Key words: Diarrhea; Enteric pathogens; Human immunodeficiency virus.

Diarrhea is a very common complication of infection with the human immunodeficiency virus (HIV) and often leads to wasting and malnutrition. Most HIV-infected children experience diarrhea at some time during the course of their disease. In developing countries, up to 80% of children and 90% of adults with HIV infection develop diarrhea. Diarrhea can occur both in early and in advanced HIV disease. When diarrhea persists for more than one month, and is associated with weight loss of at least 10%, it becomes an acquired immunodeficiency syndrome (AIDS)-defining condition. Chronic diarrhea is an independent marker of poor prognosis in patients with AIDS.

When a comprehensive diagnostic evaluation is used, a probable pathogen can be identified in between 50-80% of patients with diarrhea. Diarrhea in HIV patients is most often due to an infectious pathogen, which may be parasitic, bacterial, viral or fungal in nature. The list of pathogens being recognized as responsible keeps increasing with time, as new and emerging pathogens are identified. Rarer causes of diarrhea include Kaposi’s sarcoma of the gastrointestinal tract and lymphoma. In approximately 20% of patients, no clear cause is identified for the diarrhea. In these patients, diarrhea may be due to as yet unrecognized pathogens, direct effects of the HIV virus on the
gastrointestinal tract, autonomic denervation, or altered mucosal immune regulation with production of cytokines. There is a paucity of published data on the profile of enteric infection in HIV-infected children with diarrhea. In one study carried out in children, the profile of enteric pathogens was the same in HIV positive diarrheal children as in HIV-negative diarrheal children.

Gastrointestinal pathogens are also frequently isolated from patients with HIV infection without diarrhea, causing doubt as to the significance of isolation of pathogens in patients with diarrhea. It is likely that either the pathogen load or unidentified alterations in the host response may be responsible for diarrhea in symptomatic patients. In developed countries, when a HIV patient presents with diarrhea, the approach is primarily to search for an infecting opportunistic pathogen. Treatment is then aimed at eradicating this pathogen. Such an approach can be expensive for developing countries, where laboratories may not be adequately equipped either to safely handle stool specimens from HIV patients or to carry out the special procedures for identification of a pathogen. For these reasons, an empiric approach to therapy has been advocated in these countries. Such an approach requires knowledge of the pathogens likely to be found in HIV patients in developing countries, and the treatment regimens that are likely to be effective against them. This article briefly describes unusual enteric pathogens that may cause diarrhea in HIV patients, their therapy, and a summary of the prevalence of various enteric pathogens found regionally in different parts of the world. Necessarily, this is summarized mostly from work in HIV-infected adults. Finally, a strategy is outlined for therapy of these patients based on the above knowledge.

**UNUSUAL PATHOGENS RESPONSIBLE FOR DIARRHEA IN HIV PATIENTS**

*Cryptosporidium parvum* is a coccidian protozoan parasite that inhabits primarily the microvillus membrane brush border of intestinal epithelial cells. Infection is common in children in developing countries, causing doubt as to the significance of isolation of pathogens in patients with diarrhea. It is likely that either the pathogen load or unidentified alterations in the host response may be responsible for diarrhea in symptomatic patients. In developed countries, when a HIV patient presents with diarrhea, the approach is primarily to search for an infecting opportunistic pathogen. Treatment is then aimed at eradicating this pathogen. Such an approach can be expensive for developing countries, where laboratories may not be adequately equipped either to safely handle stool specimens from HIV patients or to carry out the special procedures for identification of a pathogen. For these reasons, an empiric approach to therapy has been advocated in these countries. Such an approach requires knowledge of the pathogens likely to be found in HIV patients in developing countries, and the treatment regimens that are likely to be effective against them. This article briefly describes unusual enteric pathogens that may cause diarrhea in HIV patients, their therapy, and a summary of the prevalence of various enteric pathogens found regionally in different parts of the world. Necessarily, this is summarized mostly from work in HIV-infected adults. Finally, a strategy is outlined for therapy of these patients based on the above knowledge.

**UNUSUAL PATHOGENS RESPONSIBLE FOR DIARRHEA IN HIV PATIENTS**

*Cryptosporidium parvum* is a coccidian protozoan parasite that inhabits primarily the microvillus membrane brush border of intestinal epithelial cells. Infection is common in children in developing countries, causing doubt as to the significance of isolation of pathogens in patients with diarrhea. It is likely that either the pathogen load or unidentified alterations in the host response may be responsible for diarrhea in symptomatic patients. In developed countries, when a HIV patient presents with diarrhea, the approach is primarily to search for an infecting opportunistic pathogen. Treatment is then aimed at eradicating this pathogen. Such an approach can be expensive for developing countries, where laboratories may not be adequately equipped either to safely handle stool specimens from HIV patients or to carry out the special procedures for identification of a pathogen. For these reasons, an empiric approach to therapy has been advocated in these countries. Such an approach requires knowledge of the pathogens likely to be found in HIV patients in developing countries, and the treatment regimens that are likely to be effective against them. This article briefly describes unusual enteric pathogens that may cause diarrhea in HIV patients, their therapy, and a summary of the prevalence of various enteric pathogens found regionally in different parts of the world. Necessarily, this is summarized mostly from work in HIV-infected adults. Finally, a strategy is outlined for therapy of these patients based on the above knowledge.

**UNUSUAL PATHOGENS RESPONSIBLE FOR DIARRHEA IN HIV PATIENTS**

*Cryptosporidium parvum* is a coccidian protozoan parasite that inhabits primarily the microvillus membrane brush border of intestinal epithelial cells. Infection is common in children in developing countries, causing doubt as to the significance of isolation of pathogens in patients with diarrhea. It is likely that either the pathogen load or unidentified alterations in the host response may be responsible for diarrhea in symptomatic patients. In developed countries, when a HIV patient presents with diarrhea, the approach is primarily to search for an infecting opportunistic pathogen. Treatment is then aimed at eradicating this pathogen. Such an approach can be expensive for developing countries, where laboratories may not be adequately equipped either to safely handle stool specimens from HIV patients or to carry out the special procedures for identification of a pathogen. For these reasons, an empiric approach to therapy has been advocated in these countries. Such an approach requires knowledge of the pathogens likely to be found in HIV patients in developing countries, and the treatment regimens that are likely to be effective against them. This article briefly describes unusual enteric pathogens that may cause diarrhea in HIV patients, their therapy, and a summary of the prevalence of various enteric pathogens found regionally in different parts of the world. Necessarily, this is summarized mostly from work in HIV-infected adults. Finally, a strategy is outlined for therapy of these patients based on the above knowledge.
after adding Uvirex 2B or Calcifluor white M2R. Treatment with albendazole (400 mg BD for 2-4 weeks) is curative for *S. intestinalis* and may reduce diarrhea in patients with *E. bieneusi* infection. Other drugs that are less effective include pyrimethamine and co-trimoxazole.

*Isospora belli* is a coccidian protozoan parasite responsible for diarrhea. While uncommon in developed countries, in developing countries it may account for up to 20% of diarrhea in HIV patients. It invades enterocytes, resulting in severe prolonged diarrhea. *I. belli* may be detected both in stool and in small bowel biopsies. Stool examination is often negative since low numbers are excreted in the stool, and small bowel biopsy is the preferred method of diagnosis. *I. belli* is sensitive to many anti-bacterials including pyrimethamine and co-trimoxazole, but may recur in 50% of patients when treatment is withdrawn. In such patients, long-term suppressive therapy has been recommended.

*Cyclospora cayatanensis* is another coccidian parasite that causes chronic intermittent diarrhea in HIV patients. The severity of diarrhea may be related to the stage of HIV infection. Diagnosis is made by stool microscopy using modified acid-fast stains (in which *Cyclospora* appear as acid-fast oocysts intermediate in size between *Cryptosporidium* and *Isospora*), or by inducing auto-fluorescence. Treatment with co-trimoxazole (160mg/800mg QID for 10 days) is usually effective. There is a high rate of recurrence and long-term prophylaxis may therefore be necessary.

*Pneumocystis carinii* has recently been reported to occur in the intestinal mucosa of HIV-infected children with diarrhoea, in whom other enteric pathogens were not detected. This raises the possibility that this parasite may also cause diarrhea in HIV patients.

*Mycobacterium avium-intracellulare* is responsible for diarrhea in 5-10% of Western subjects with HIV with severe immunosuppression. It appears to be less common in developing countries. Diagnosis is made by small bowel biopsy. Quadruple therapy with combination chosen from clarithromycin, ciprofloxacin, amikacin, rifampin, rifabutin, clofazimine and azithromycin is used for greater than 12 weeks. Lifelong suppressive therapy may be needed to prevent relapse.

*Enteropathogenic Escherichia coli* have not been extensively investigated as a cause of diarrhea in HIV-infected patients. In one study involving 53 HIV-positive Zairean infants, protozoal parasites were identified only in 6% and conventional bacterial enteropathogens in 8% whereas various enteropathogenic *Escherichia coli* could be isolated from 82% of the infants during episodes of diarrhoea.

*Cytomegalovirus* enteritis and colitis is also found occasionally in HIV patients as a cause of diarrhea. Treatment with ganciclovir or foscarnet is both expensive and toxic, and the quality of life may not be enhanced with treatment. Diagnosis is usually made by colonic or rectal biopsy, and by serology.

*Adenoviruses* can cause diarrhea in HIV-infected patients and is diagnosed by colonic biopsy, electron microscopy, ELISA or stool culture.

*Histoplasma capsulatum* is another rare cause of diarrhea in HIV patients, and may occur in the setting of multi-organ involvement. Colonic histoplasmosis is associated with acute diarrhea, bleeding, weight loss and fever. Diagnosis is by colonic biopsy. Systemic therapy with amphotericin B,
fluconazole or itroconazole is recommended.

**PREVALENCE OF PATHOGENS IN HIV PATIENTS WITH DIARRHEA**

There are marked geographic differences in the prevalence of individual enteric pathogens in patients with HIV infection and diarrhea. These differences are accentuated by the practice of giving prophylaxis against specific infections of HIV patients in developed countries. Thus, a low prevalence of *Isospora belli* infection in Western patients with AIDS is attributable to the cotrimoxazole prophylaxis given to these patients, aimed primarily at *Pneumocystis carinii* pneumonia. Table 1 shows the worldwide isolation rates for various pathogens from HIV patients with diarrhea and compares them with figures from a study in South India (Mukhopadhya *et al*, under review for publication). Infections with coccidian protozoan parasites (*Isospora, Cryptosporidium, Microsporidia* and *Cyclospora*) were found to be common in Indian patients with HIV infection and diarrhea. *Isospora belli*, in particular, was common in HIV patients with diarrhea, and was seldom found in HIV patients who did not have diarrhea.

**MANAGEMENT**

In practice, when treating patients with HIV infection and diarrhea, it is advantageous to consider them as two groups, those with diarrhea of less than two weeks duration and those with chronic diarrhea of duration longer than two weeks. In the first group, treatment should include attention to hydration using oral rehydration therapy. Luminal agents including kaolin-pectin may be used as also anti-motility agents such as loperamide and lomotil. In our experience, almost two-thirds of these patients demonstrate spontaneous cessation of diarrhea with symptomatic treatment alone, regardless of the presence of an infectious agent. Follow-up indicates that few of these patients have a recurrence of diarrhea in the short term.

Oral rehydration therapy is also indicated in patients with chronic diarrhea if

**TABLE 1. Isolation Rates of Enteric Pathogens From HIV Patients with Diarrhea**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Worldwid</td>
</tr>
<tr>
<td>Cryptosporidia</td>
<td>6.5 - 27.3</td>
</tr>
<tr>
<td>Microsporidja</td>
<td>2.0 - 39.0</td>
</tr>
<tr>
<td>Cyclospora cayatensis</td>
<td>0 - 5</td>
</tr>
<tr>
<td>Isospora belli</td>
<td>0.2 - 28.0</td>
</tr>
<tr>
<td>Giardia intestinalis</td>
<td>1.0 - 11.6</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>0 - 5.2</td>
</tr>
<tr>
<td>Strongyloides stercoralis</td>
<td>0 - 5.0</td>
</tr>
<tr>
<td>Bacterial enteropathogens</td>
<td>0 - 18.0</td>
</tr>
<tr>
<td><em>Salmonella, Shigella, Campylobacter, C. difficile, Aeromonas, Vibrio</em></td>
<td></td>
</tr>
<tr>
<td>Enterogetic forms of <em>Escherichia coli</em></td>
<td>0 - 82</td>
</tr>
<tr>
<td>Mycobacterium avium - intracellulare</td>
<td>2.3 - 25.0</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>7.5 - 28.6</td>
</tr>
</tbody>
</table>

Note: The prevalence rates quoted here are synthesized from references 6, 7, 8, 9, 11, 13, 14 and 15 and the cross references therein. Figures between various studies are not strictly comparable due to differences in study methodology. Prevalence figures for the South Indian study (Mukhopadhya *et al*, submitted for publication) were derived using a stepwise approach to diagnosis.
they are dehydrated. Anti-motility agents are useful in these patients to relieve symptoms. In addition, fiber supplements, resistant starch and cholestyramine may be used in these patients to reduce fecal fluid excretion and to relieve frequency of stool. These measures result in cessation or reduction of diarrhea in about a fourth of such patients. Ideally, all patients should have stool examination, on at least three occasions, along with stool culture. If an offending pathogen is identified, then it should be treated appropriately. If no offending pathogen is detected, these patients will need to undergo biopsy of the small or large bowel. Approximately 50% of treated patients will be expected to respond to specific measures. Patients who had a coccidian parasitic infection, and responded to therapy, will probably need long-term maintenance therapy in order to prevent recurrences (which occur in 50%). In the absence of a clinical response to treatment, infection with another organism must be suspected. Multiple enteric infections are common, occurring in 15-20% of patients with HIV infection.

Empiric therapy, without investigation of the possible cause of diarrhea, has been advocated in developing countries due to constraints of technology and resources. In Zambian patients with HIV infection and diarrhea, the common enteric pathogens were Microsporida species (Enterocytozoon bieneusi and Septata intestinalis), Isospora belli and Cryptosporidium parvum (each in approximately 25%), while Stronglyloides stercoralis and Giardia intestinalis were present in 5% and 1%, respectively. A study was therefore carried out using high-dose albendazole monotherapy (800 mg b.i.d.) given empirically for two weeks to patients with diarrhea of longer than two weeks duration. Albendazole was chosen because it is effective against Microsporida, S. stercoralis and G. intestinalis, although whether it acts against I. belli is unknown. This therapy resulted in remission of diarrhea in 26% of patients, although it also reduced diarrhea in other individuals.

Empiric therapy (for patients who do not respond to symptomatic therapy) may be used on a more rational basis by considering various organisms that cause diarrhea in HIV patients in a specific geographic locale. Bacterial pathogens are common when diarrhea is of less than two weeks' duration. Bacterial pathogens should also be suspected in the HIV patient with diarrhea and high fever. Empiric therapy with ciprofloxacin is probably useful in this situation since it is active against Shigella, Salmonella and Campylobacter, the three common organisms isolated. In the case of both Shigella and Campylobacter, treatment for ten days is adequate. However, there is a high recurrence rate with Salmonella, and treatment may have to be continued for up to four weeks. Prolonged treatment may also be necessary for patients with pathogenic E. coli causing diarrhea. Patients who present with blood and mucus diarrhea suggestive of an invasive colitis, will need therapy against amebiasis as well as for bacterial causes of colitis. If diarrhea fails to subside, the possibility of other causes like cytomegalovirus or herpes simplex or adenovirus infection will need to be considered. In the patient with diarrhea that does not subside with initial therapy, and in those with diarrhea of greater than two weeks' duration, therapy may be commenced with either metronidazole or with co-trimoxazole. In our experience, the prevalence of G. intestinalis infection is similar in HIV patients with and
without diarrhea. Furthermore, the prevalence of *G. intestinalis* or *E. histolytica* infection is not high in HIV patients with diarrhea. These suggest that empiric treatment with metronidazole is unlikely to be helpful in the majority. However, metronidazole therapy has the advantages of short duration, and that *E. bieneusi* may partially respond to the drug. Co-trimoxazole (adult dose 160 mg TMP/800 mg SMX four times a day) is active against *I. belli* and *C. cayat-anensis*, which are major pathogens in HIV patients with diarrhea. A response to co-trimoxazole will warrant long-term maintenance therapy (160 mg TMP/800 mg SMX once a day) to prevent recurrences of diarrhea. The third drug which may be used empirically in these patients is albendazole (adult dose 400 mg twice daily) for 2-4 weeks. This dose may be inadequate for *G. intestinalis* and for *S. stercoralis*. Particularly if the latter is suspected, a higher dose will be necessary.

Patients who do not respond to empiric therapy must be re-evaluated. Multiple infections are common in HIV patients with diarrhea. Hence, re-evaluation should begin with stool examination and culture, and should proceed to small bowel or colonic biopsy depending on the clinical presentation. Further therapy will depend on the pathogen identified. Nonspecific therapy should be used to improve the patient's quality of life. In addition to fiber supplements, kaolin-pectin and cholestyramine can be used for changing the fecal consistency and frequency. Anti-diarrheal agents including loperamide and diphenoxylate-atropine can be used. If these are not useful, opiates including codeine, methadone or tincture of opium can be used to reduce diarrhea. Octreotide (a somatostatin analog) has also been used for therapy of refractory chronic diarrhea in HIV patients, but may induce significant side effects, besides being very expensive.

In summary, a multitude of intestinal pathogens may induce diarrhea in patients with HIV infection. In some patients, diarrhea may be due to the virus itself, since no pathogen may be identified despite a stringent work-up. Specific therapy may cause remission of diarrhea in approximately half of the patients. Supportive and symptomatic measures are necessary in the remainder. Attention to nutrition will also be necessary in the patient with HIV infection and chronic diarrhea.

**REFERENCES**

4. Centers for Disease Control. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *MMWR* 1987; 36 (suppl IS) : IS.


IDENTIFYING PREDICTORS OF FUTURE ALLERGIC SENSITIZATION IN CHILDREN

Accurately predicting children at risk for future allergic sensitization can be helpful in selecting those who might benefit from preventative measures. In a study a total of 1314 children were followed from birth until the age of 3 years. This included 499 (38%) children considered to be at high risk on the basis of having at least two atopic first-degree relatives and/or an elevated cord blood IgE level. Family history was obtained and blood samples collected from cord and at follow up visits at 1, 2 and 3 years of age for determination of total serum IgE and specific IgE antibodies to common food and inhalant allergens.

Prevalence of IgE Abs to at least one of the tested allergens was 16.4%, 26.1%, and 26.7% at ages 1, 2 and 3 years, respectively. Sensitivity to foods was most common with prevalence rates of 14.1%, 17.9%, and 18.1%, respectively. Sensitization to inhalant allergens increased such that by age 3 years it was 10.3% to outdoor allergens, compared with 8.6% to indoor allergens. Predictors for inhalant allergen sensitization were a positive family history and sensitization to hen's egg at the age of 12 months. Elevated cord blood IgE was not associated with inhalant allergens sensitization at age 3 years. Egg specific IgE > 2kU/L in combination with a positive family history of atopy was a highly specific (specificity, 99%) and predictive (positive predictive value, 78%) marker for sensitization to inhalant allergens at age 3 years. It was concluded that hen's egg-specific IgE at 12 months age is a valuable marker for subsequent sensitization to allergens causing asthma and allergic rhinitis. Of note is that most children with egg sensitivity do not have clinical egg allergy thus warranting a skin or radioallergosorbent test to identify at-risk children.

Abstracted from: J Allergy Clin Immunol. 1997; 99: 613-617