Review

AIDS-Related diarrhea – pathogenesis, evaluation and treatment

A.K. Zacharof

SUMMARY

As the AIDS epidemic continues to spread and involve all segments of society, more and more internists and gastroenterologists are called upon to evaluate and treat patients with disabling diarrhea, the most common clinical manifestation of AIDS. It is often asked: Does it make sense to initiate an extensive workup if no specific etiologic agent is identified in many patients? Should we look for organisms when there is no specific therapy for many of them? We will try to answer both questions and outline a rational approach to the patient with AIDS-related diarrhea, on the basis of "small-bowel" versus "large-bowel" diarrhea and severity of symptoms. Isolation of one or more organisms is common if a proper search is conducted, and specific as well as symptomatic therapy can have a significant impact on the patient's quality of life.

INTRODUCTION

Disabling diarrhea will develop in nearly 60% to 80% in patients infected with the human immunodeficiency virus (HIV) sometime during their illness. Diarrhea is an even more common manifestation of HIV disease in third-world countries. The cause of AIDS-relate diarrhea is complex and probably multifactorial, with both common and atypical pathogens noted among patients with diarrhea. Infectious agents, including bacteria, parasites, mycobacteria, and viruses, are frequently isolated in the stools or on mucosal biopsies from patients with AIDS-related diarrhea (Table 1). More recently detailed research described even more atypical viruses in diarrheal

2nd Department of Internal Medicine, Hellenic Red Cross Hospital, Athens, Hellas

Author for correspondence:

A.K. Zacharof, 56, Vas. Constantinou, 152 32 Athens, Greece, e-mail: azach@ath.forthnet.gr

stools from patients infected with HIV. These agents, including adenoviruses, astroviruses, caliciviridae, and picobirnaviruses, were more frequently isolated from stools of patients with AIDS who had diarrhea compared with stools of patients with AIDS who did not have diarrhea. "AIDS enteropathy" was first described by Kotler and associates in 1984 in patients with no identifiable pathogen but with blunt mucosal biopsy, diarrhea, and malnutrition. The pathophysiology of AIDS enteropathy is complex and include infection of enterochromaffin cells and releasing vasoactive intestinal polypeptide. The true prevalence of idiopathic AIDS enteropathy clearly depends on the aggressiveness of the evaluation for diarrhea, with as many as 50% of patients with diarrhea labelled as having idiopathic AIDS enteropathy if the evaluation consists only of stool analyses. However, among patients given a "thorough" evaluation, including endoscopic and colonoscopic biopsies, only 15% to 20% are found to have no identifiable pathogen.

ETIOLOGY OF AIDS-RELATED DIARRHEA

Initial evaluation of patients: Although many enteric pathogens have been identified in stools or mucosa from patients with chronic HIV-related diarrhea, the major pathogens identified today are cryptosporidia, isospora, cyclospora, mycobacterium avium complex (MAC), microsporidia, and cytomegalovirus. As mentioned previously, the accurate identification of one or more pathogens depends on the thoroughness of the enteric evaluation in patients with HIV-related diarrhea. Thus stool analyses should be the initial step in evaluating these patients. Multiple stool samples for routine enteric pathogen cultures should be collected and stool analyses for ova and parasites should be performed in patients with disabling diarrhea. Clostridium difficile toxin assays in the stool should likewise be performed in patients who underwent antibiotic therapy within the 2 months before the onset of diarrhea. It is helpful to have

Table 1. Etiology of diarrhea in patients with AIDS: Infectious agents

Bacteria

Salmonella

Shigella

Campylobacter species

Clostridium difficile

Parasites

Cryptosporidium parvum

Isospora belli

Enterocytozoon bieneusi

Septata intestinalis

Entamoeba histolytica

Giardia lamblia

Microsporidia

Strongyloides

Cyclospora spp

Mycobacteria

Mycobacterium avium intracellulare

Mycobacterium tuberculosis

Viruses

Cytomegalovirus

Herpes

Adenovirus

Astrovirus

Caliciviridae

HIV (AIDS enteropathy)

faecal fats tested via sudan stain because stools that are positive for faecal fat indicate small bowel malabsorption. The presence of faecal leukocytes, however, is more indicative of a distal colonic rather than a small bowel inflammatory process. In addition, some estimate of 24-hour stool count and weight should be made at the outset of the evaluation so the true severity of the illness can be gauged and used as a mark against which therapies are measured.

"Minimal" versus "full" evaluation

Although one or more pathogens will be isolated by careful stool analyses in 50% to 60% of patients, no identifiable pathogen will be isolated in the stool of 30% to 40% of patients. The clinician is therefore faced with the task of deciding the next appropriate step in the evaluation. The entire cost-effectiveness of a "full" evaluation of chronic diarrhea in patients with AIDS has been questioned. Johanson and Sonnenberg used a medical decision analysis with three strategies: "full evaluation," "lim-

ited evaluation" and "minimal evaluation." Their "full" evaluation (including stool cultures, analyses for ova and parasites, stains for pathogens, blood cultures, and endoscopy/colonoscopy) was more costly than "minimal" evaluation (stool cultures alone), yet yielded similar remission rates for diarrhea.

Notwithstanding this "decision analysis," which has not been clinically evaluated, how should the clinician proceed with the evaluation of patients with "stool-negative" diarrhea.

Flexible sigmoidoscopy performed by the experienced physician is a reasonable undertaking in patients with either "small-bowel" or "large-bowel" diarrhea who have negative results of stool analyses. In a retrospective review of 204 patients with AIDS who had chronic diarrhea and for whom results of stool studies were negative, one or more pathogens were detected in 25% of the patients by flexible sigmoidoscopy using a routine sigmoidoscopic biopsy submitted for histopathology and viral cultures. However, for patients who are severely debilitated by diarrhea, upper endoscopy or colonoscopy may be more appropriate than sigmoidoscopy.

Differentiation between small-bowel and large-bowel diarrhea, which can often be done on a clinical basis, is helpful in deciding the next diagnostic strategy. "Small-bowel" diarrhea is characterized by weight loss, paraumbilical pain, and large volume diarrhea (more than one per day) with associated dehydration, the absence of tenesmus -painful defecation- and absence of white cells or gross blood in the stools. Patients with classic "small-bowel" diarrhea may in fact be appropriate candidates for an endoscopic small-bowel biopsy. Patients with "large-bowel" diarrhea, on the other hand, may be excellent candidates for a colonoscopic evaluation and biopsy. Large-bowel diarrhea is not associated with malabsorption and is usually accompanied by lower quadrant or suprapubic abdominal pain. Colonic diarrhea is less voluminous than that in patients with small-bowel diarrhea, and therefore colonic diarrhea is rarely associated with dehydration. Because the distal bowel is often involved in colonic diarrhea, tenesmus and painful defecation are often encountered. The stools of patients with colonic diarrhea frequently contain white cells and visible blood.

MAJOR PATHOGENS OF AIDS-RELATED DIARRHEA

Clearly the most common cause of chronic debilitating diarrhea among patients with AIDS is Cryptosporid-

ium parvum. Patients with cryptosporidiosis have profuse watery diarrhea, weight loss, paraumbilical abdominal pain, nausea, and vomiting. The diagnosis of cryptosporidiosis is usually easily made with use of an acid-fast stain of concentrated stool. The literature does not document how many patients with cryptosporidiosis are shown to have negative results by stool analysis alone but yet are found to have organisms on enteric biopsy. Nonetheless, mucosal biopsies for cryptosporidium are not usually indicated when stool samples are positive. Cryptosporidium is confined to the brush border of enterocyte and is not tissue invasive. Therapy for cryptosporidiosis has been extremely problematic; the largest experience has been with paromomycin. 40% to 90% of patients will respond to an initial course of paromomycin, 1.5 to 2.0 gr per day. Relapses are common; however patients may respond to additional treatment courses. Other treatments under investigation include spiramycin, azithromycin, clarithromycin, roxithromycin, letrazuril, and bovine immune concentrate.

Microsporidiosis was identified in the last 5 years as a major cause of chronic diarrhea among patients with HIV disease. Microsporidiosis is responsible for 15% to 20% of all chronic diarrheal illnesses in patients with AIDS. Clinically, patients with microsporidiosis have profuse watery diarrhea, weight loss, and abdominal pain, but no fever or loss of appetite. The diagnosis of microsporidiosis has traditionally been made by enteric biopsies, whether studied by electron microscopy or light microscopy. Promising new studies indicate that chromotrope-based techniques and "Fungi-fluor" stains may be promising means of making the diagnosis of microsporidiosis on the basis of stool studies alone. However, no specific treatment is available, and in general patients with microsporidiosis are treated with empiric antidiarrheal agents and nutritional support. Albendazole is a promising drug for treatment of microsporidiosis; however, it has not been subjected to randomized, placebo-controlled trials.

Cytomegalovirus is an extremely common agent among patients with HIV disease and may be responsible for 10% to 20% of debilitating chronic diarrheal illness. Enteric cytomegalovirus is extremely variable in its clinical presentation, with some patients manifesting only cytomegalovirus esophageal ulcerations, whereas in others debilitating large- and/or small-bowel diarrhea develops. Abdominal pain is a common component of cytomegalovirus disease in the gut, and not infrequently patients have significant bleeding or even an "acute" abdomen. Cytomegalovirus has also been associated with bile duct obstruction and intrahepatic sclerosing cholangiitis (so-called AIDS cholangiopathy). The diagnosis of cytomegalovirus enteritis usually requires an endoscopic biopsy demonstrating classic cytomegalovirus inclusions on hematoxylin and eosin stains of mucosal biopsy specimens. Immunohistochemical stains and viral culture techniques have not enhanced the overall ability to diagnose cytomegalovirus enteritis when compared with hematoxylin and eosin stains alone. Limited studies support treatment of cytomegalovirus enteritis by either intravenous ganciclovir (5 mg/kg twice a day) or foscarnet (200 gm/kg per day). It is presently unsettled whether all patients should receive indefinite maintenance therapy after successful treatment of acute cytomegalovirus enteritis. Cytomegalovirus enteritis may recur after treatment, and the recurrence may take place in the retina, leading in short order to total blindness.

MAC involves the entire reticulo-endothelial system. In the gut, MAC is associated with diarrhea, weight loss, fever, and generalized abdominal pain, particularly right upper quadrant pain related to hepatic infiltration. Profound anorexia is also noted in these patients. The diagnosis of MAC can be suggested by blood or faecal cultures, while endoscopic biopsies of thickened folds easily demonstrate foamy macrophages in the lamina propria, containing numerous acid-fast-positive organisms. The treatment of MAC in the gut usually involves combination chemotherapy (particularly ethambutol and clarithromycin), although chemotherapeutic regimens are generally poorly tolerated by many patients and are not uniformly beneficial.

TREATMENT OF HIV-RELATED DIARRHEA

The overall management strategy for patients with HIV-related diarrhea should include general measures such as maintaining adequate hydration and good nutrition. Patients should be encouraged to take adequate sugar and electrolyte-rich fluids and, if necessary, an elemental diet or nutrient formula containing medium-chain triglycerides. Patients must also be cautioned against the use of food that contains lactose and sorbitol products. Multiple non-specific medications are helpful in controlling diarrhea, particularly loperamide, diphenoxylate with atropine, codeine phosphate, and seldom paregoric. Multiple non-standard novel therapies have also been recommended, including non-steroidal antiinflammatory agents, parenteral hyperalimentation, and the use of such somatostatin analogs as octreotide.

In large open-label trials completed recently octre-

otide (up to 500 mg subcutaneously every 8 hours) led to a significant decrease in stool volume and stool frequency. In the studied patients the overall response rate was only 41%, but most responders had no pathogen identified after an exhaustive analysis of stools and mucosal biopsies. Steatorrhea was worsened in these patients treated with octreotide. More recently, in a double-blind placebo-controlled trial, we could not demonstrate an impact of octreotide administered up to a maximum of 300 mg every 8 hours. During the open-label phase, however, when the drug dose was raised to 500 mg every 8 hours, a 40% reduction in daily stool weight was noted by the eighth week of octreotide therapy.

CONCLUSIONS

Diarrhea in patients with AIDS is extremely problematic for both patient and clinician. Multiple pathogens, both typical and atypical, may cause debilitating illnesses that have a substantial impact on quality of life. A clinical evaluation, proportionate in aggressiveness to the degree of debility, is the most reasonable way to approach patients with this condition. In most instances, isolation of one or more pathogens is likely with a combination of invasive and non-invasive studies. Whereas some pathogens are treatable with specific therapies, many more organisms have no proven treatments. Patient care should focus, in all instances, on improving quality of life.

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