Invited Review

Gastrointestinal Manifestations of AIDS

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ABSTRACT: Although gastrointestinal complications have decreased dramatically in patients with acquired immunodeficiency syndrome (AIDS) who received highly active antiretroviral therapy, these disorders still occur in those who do not seek healthcare, those with resistant virus, and those in developing countries where these drugs are not available. Opportunistic infections are the most frequent causes of gastrointestinal disease in patients with AIDS. A practical approach based on the character of the complaints and location of symptoms will help direct the most appropriate evaluation. In most patients, a diagnosis should be sought because effective antimicrobial therapy is available for most infections in these patients. When possible, improvement in immune function forms an integral part of the treatment regimen.

Human immunodeficiency virus (HIV) infection remains an important cause of mortality worldwide. Although the incidence of infection in developed countries has stabilized or decreased, recent projections suggest rapid growth of HIV incidence in China, the Soviet Union and Eastern Europe, and India; countries in sub-Saharan Africa will continue to have high rates of HIV infection. Gastrointestinal complications associated with the acquired immunodeficiency syndrome (AIDS) are important because of their frequency, morbidity, and impact on healthcare use. Over the last decade, remarkable reductions in the incidence of opportunistic infections (OIs), due primarily to potent antiretroviral therapy (termed highly active antiretroviral therapy, or HAART), have led to prolonged survival of AIDS patients.[1,2] In addition, the use of prophylactic therapy to prevent immunodeficiency-related infectious complications, such as *Pneumocystis carinii* pneumonia (PCP), has played a beneficial role.[3,4]

Since the initial descriptions of AIDS, weight loss has been recognized as a cardinal manifestation and often leads to an evaluation for a gastrointestinal cause. The HIV wasting syndrome—an AIDS-defining illness—is defined as involuntary weight loss >10% of baseline body weight plus either chronic diarrhea (at least 2 loose stools per day for 30 days) or chronic weakness and documented fever (for at least 30 days and either intermittent or constant) in the absence of a concurrent illness or condition other than HIV infection that explains these findings.[5] In developing countries, the symptom complex of weight loss, fever, or chronic diarrhea, termed "slim disease,"[6] remains common. Although the frequency of the wasting syndrome has markedly fallen but not disappeared in developed countries in the era of HAART, weight loss and protein calorie malnutrition remain important worldwide problems.

Given the wide spectrum of potential etiologies of gastrointestinal disease, both opportunistic and nonopportunistic, several important principles of management should be followed[7–9] (Table 1). This review will take an organ-based approach to examine causes, manifestations, evaluation, and therapy of gastrointestinal disorders in AIDS patients. Where appropriate, nutritional implications of these disorders will be highlighted.

Oropharyngeal Diseases

Disease of the oropharynx may be the initial manifestation of HIV infection; oropharyngeal candidiasis (thrush) remains a common presentation.[10] Symptoms of oropharyngeal disease vary from asymptomatic to taste disturbances or pain, depending on the underlying disease process. Oropharyngeal disease often results in decreased oral intake because of dysgeusia or pain. Oropharyngeal or hypopharyngeal pain is usually a manifestation of ulceration. Although a variety of disorders may cause oropharyngeal ulcers, aphthous ulcers are the most common cause of single or multiple well-circumscribed ulcers; the pathogenesis of these lesions remains undefined. Other causes of oropharyngeal ulcers include cytomegalovirus (CMV), herpes simplex virus (HSV), and other rare infections. Neo-

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Table 1
General principles for the management of gastrointestinal and hepatobiliary complaints in patients with AIDS

1. In patients with AIDS, multiple coexistent diseases are frequent.
2. OIs occur when immunodeficiency is severe. Therefore, the CD4 lymphocyte count will stratify the likelihood of an opportunistic or nonopportunistic cause for gastrointestinal complaints.[5]
3. OIs are often systemic. Identification of a pathogen outside of the gut (eg, blood) may establish a presumptive cause of gastrointestinal disease.
4. Geographic differences exist in the frequency of OIs. For example, tuberculosis is especially common in developing countries as an AIDS-defining illness.[6,7]
5. The most specific means of establishing an etiologic diagnosis is demonstration of a pathogen in tissue.
6. Identification of a specific cause for all gastrointestinal symptoms is not always possible because some problems still elude a specific etiologic diagnosis.
7. Without HAART, antimicrobial therapy for opportunistic infections rarely results in "cure" because of persistent immunodeficiency.

AIDS, acquired immunodeficiency syndrome; OI, opportunistic infection; HAART, highly active antiretroviral therapy.

plasms that involve the oropharynx include lymphoma, which usually presents as an ulcerative mass lesion, and Kaposi's sarcoma (KS) which has a characteristic appearance as purple plaques or nodules. Oral hairy leukoplakia, caused by an Epstein-Barr virus infection, has a well-recognized appearance as white plaque coating the lateral aspects of the tongue. Given the prevalence of aphthous ulcers, however, biopsy of all oropharyngeal ulcers is not required. Empiric therapy based on the appearance of the lesion is an appropriate first-line strategy; when neoplasms are suspected, biopsy is appropriate. Therapy for most oropharyngeal diseases parallels esophageal disease (see below). Like most opportunistic diseases in AIDS, despite effective therapy, recurrence is common.

Esophageal Diseases

Disorders of the esophagus are frequent in patients with AIDS, found in up to 40% of patients at some point during the course of disease. By far, the most common etiology is *Candida*, seen in 40% to 70% of patients.[11] Next in importance are viral diseases. In contrast to non HIV-infected immunocompromised patients, CMV is a much more frequent esophageal pathogen than HSV.[12] An important cause of esophageal disease whose pathogenesis remains poorly understood is the idiopathic esophageal ulcer (IEU). Multiple coexistent esophageal disorders may be identified in 10% of symptomatic patients.[12,13] Gastroesophageal reflux disease occurs at any stage of immunodeficiency and pill-induced esophagitis and neoplasms (KS, lymphoma, carcinoma) remain infrequent.

Esophageal disease is manifested by symptoms of dysphagia (difficulty in the transit of a food bolus, usually described as "food sticking") or odynophagia (painful swallowing). Symptoms limited to the hypopharynx implicate hypopharyngeal rather than esophageal disease. In HIV-infected patients, odynophagia, especially in the absence of dysphagia, is highly suggestive of esophageal ulceration, usually because of an opportunistic cause, whereas dysphagia is more commonly seen with *Candida* esophagitis or a benign or malignant stricture. Spontaneous substernal chest pain or back pain may be reported with severe ulcerative esophagitis. Heartburn suggests gastroesophageal reflux disease rather than an OI. The chronicity of these esophageal diseases often significantly affects nutritional intake, and weight loss may be profound. Furthermore, odynophagia not only hampers the ability to take pills but also makes nutritional supplementation difficult.

Examination of the oropharynx may provide a clue to the cause of esophageal complaints. Most patients (~66%) with *Candida* esophagitis have concomitant thrush; oropharyngeal ulcerations are frequently associated with HSV esophagitis but are rarely present with CMV esophagitis and IEU.[14]

Given the prevalence of *Candida* esophagitis, at most centers, empiric antifungal therapy is commonly prescribed to the HIV-infected patient with new-onset esophageal symptoms. The clinical response to *Candida* esophagitis is typically rapid, with most patients improving within days; thus, if no symptomatic response is seen within 1 week of initiating empiric therapy, especially in the patient with severe symptoms, additional diagnostic testing, preferably endoscopy, is required rather than initiating further empiric trials such as antacid or antiviral therapy.[15] Radiographic studies of the esophagus may suggest a specific cause but are rarely diagnostic. On barium radiographs, *Candida* esophagitis is manifested by 1 or multiple plaque-like lesions which, when severe, may mimic ulcerations. One or multiple well-circumscribed, large (>2 cm) deep ulcers are typical for CMV or IEU, whereas HSV presents radiographically as 1 or multiple shallow ulcers or a diffuse esophagitis.

Endoscopy is the definitive diagnostic test for esophageal disease in AIDS patients. At the time of endoscopic evaluation, the appearance of some lesions, such as *Candida,* may be diagnostic, and ulcerative lesions may be biopsied. CMV esophagitis (ulcers) and IEU have similar clinical, radiographic, and endoscopic features.[16] HSV esophagitis usually results in multiple shallow ulcers or a diffuse esophagitis, whereas deep well-circumscribed lesions are typically caused by CMV or IEU. CMV or CMV/HSV coinfection may result in a patchy superficial esophagitis. Multiple biopsies should be obtained of all ulcerative lesions to increase diagnostic yield. Immunohistochemical stains for viral pathogens will improve the diagnostic yield and specificity.

Additional histologic examination for fungi or mycobacteria may be necessary, depending on the clinical, endoscopic, and histologic findings.[17] Cytologic brushings are more sensitive than biopsy to diagnose *Candida* but are not helpful for the diagnosis of ulcerative lesions (particularly CMV), and viral culture of biopsy material is less sensitive and specific than histologic evaluation to detect viral pathogens. If an ulcer is seen endoscopically and histologically, infections are excluded by extensive histologic studies, and pill-induced esophagitis and reflux disease are not suggested by the clinical presentation or endoscopic findings, then the ulcer can be considered an IEU and treated accordingly (see below).

Therapy for esophageal diseases is highly effective. *Candida* esophagitis can be cured in 80% or more patients with systemic antifungal agents. Fluconazole is currently the drug of choice because of its excellent absorption, minimal drug interactions and side effects, and superior efficacy.[18] Although slightly less effective, itraconazole may be an alternative to fluconazole, whereas ketoconazole is inferior to these 2 agents. Also, ketoconazole has several important drug interactions, and both ketoconazole and itraconazole have reduced bioavailability in an alkaline pH. Seven to 14 days of antifungal therapy is adequate in most patients. Close follow-up is important because the relapse rate of *Candida* esophagitis is high; prophylaxis may be required if relapses are frequent. The long-term use of azole therapy and severe immunodeficiency are associated with the development of azole resistance.[19] Voriconazole or caspofungin may be used when resistance is clinically present, thus avoiding the use of toxic agents such as amphotericin B.[20] CMV esophagitis responds in ~80% of patients to either ganciclovir, foscarnet, or cidofovir, often achieving clinical and endoscopic remission. The main side effect of ganciclovir is myelosuppression, whereas foscarnet and cidofovir are nephrotoxic and foscarnet causes electrolyte (hypocalcemia, hypophosphatemia) disturbances. Renal insufficiency may be prevented by vigorous saline hydration before and during therapy and by dose adjustments according to creatinine clearance. Valganciclovir, an oral form of ganciclovir with excellent systemic absorption, has shown efficacy for retinitis,[21] but large trials for gastrointestinal disease are lacking. Without HAART, the relapse rate following therapy is about 50%; CMV retinitis should be excluded at the time of diagnosis as long-term therapy will be required in these patients. We do not routinely give maintenance treatment to maintain remission for isolated gastrointestinal disease but institute HAART. Both corticosteroids and thalidomide are effective therapy for IEU.[22]

Gastric Diseases

Disorders of the stomach are relatively uncommon in HIV-infected patients. Some studies suggest that HIV-infected patients are less likely to have *Helicobacter pylori* infection, which may explain the low incidence of ulcer disease observed in these young patients.[23] In addition, hypochlorhydria has been found in approximately 10% to 25% of patients with AIDS, and this finding has implications for drug absorption (eg, ketoconazole).[24] The most frequent OI involving the stomach in AIDS is CMV, which appears endoscopically as a patchy gastritis or 1 or multiple ulcers. Infrequent gastric infections include cryptosporidia, cryptococcus, and other parasitic disorders such as toxoplasma and pneumocystis. KS frequently involves the stomach, and although usually asymptomatic, obstruction (pyloric disease), bleeding, or abdominal pain may be reported. In contrast, gastric lymphoma is almost always symptomatic and manifested by epigastric pain; fever and peripheral adenopathy are uncommon associated findings.

Evaluation for gastric disease may be accomplished by a variety of methods. Upper-GI series may identify inflammatory changes, ulcerations, or mass lesions. Computed tomography (CT) may reveal thickening of the gastric wall or mass lesions. Additional findings by CT may include hepatic, pancreatic, or splenic diseases and adenopathy that suggests a widely disseminated process (eg, *Mycobacterium avium* complex [MAC] or lymphoma). Nevertheless, given the broad differential diagnosis for patients with severe immunodeficiency, the identification of gastric disease by noninvasive studies usually still requires endoscopy and mucosal biopsy for a definitive diagnosis.

Small Bowel Disease

Infections of the small intestine are very common but not unexpected in HIV-infected patients in part because of the altered gut immune function. Reduction in lamina propria CD4 lymphocytes parallels changes in the systemic circulation. This reduction in small bowel CD4 lymphocytes may account for alterations in small intestinal morphology and function (see below). In addition, decreased intestinal production of IgA may further predispose to these infections. These abnormalities have recently been summarized.[25]

Diseases of the small bowel in AIDS, generally caused by OIs, represent a major cause of morbidity and potential mortality. Worldwide, *Cryptosporidium parvum*, a coccidian parasite, is the most common infection involving the small bowel found in up to 20% of AIDS patients with diarrhea.[26] Although this infection is a self-limited illness in normal hosts, in HIV-infected patients, the incidence and severity of disease parallel the degree of immunodeficiency. Patients with a CD4 count >200/mm^3 may have spontaneous remission, whereas the disease is chronic, can be life threatening, and is associated with poor survival when the CD4 count is <50/mm^3.[27] The diarrhea is characteristically secre-

tory and, when severe, results in dehydration and electrolyte disturbances (hypokalemia). Weight loss is almost uniform because of malabsorption or reduced caloric intake from associated nausea and vomiting. Intestinal malabsorption plays an important contributing role in AIDS patients with small bowel infection such as cryptosporidia. In these patients, the degree of fat malabsorption may be striking (ie, >20 g/day); however, steatorrhea may be observed in the absence of an identifiable infection. Likewise, gastrointestinal evaluation in asymptomatic AIDS patients without an identifiable small bowel infection has documented functional and morphologic abnormalities such as reductions in D-xylose absorption.[25] In the appropriate clinical setting, pancreatic malabsorption should also be considered.

Periumbilical crampy abdominal pain and gas are frequent complaints of patients with intestinal infections. The diagnosis can be established by modified acid fast staining of fresh stool, although the sensitivity may be as low as 50%. Use of direct fluorescent antibody technique improves the sensitivity over standard stool staining alone. Because intestinal shedding may be sporadic, evaluation of multiple stools may be necessary to establish the diagnosis. If stool testing is negative and the disease is suspected clinically, upper endoscopy and small bowel biopsy will establish the diagnosis. Colonic biopsies may be positive; ileal biopsies obtained at the time of colonoscopy appear to have a high diagnostic yield.[28] Numerous therapies have been used, most without success. Paromomycin, a nonabsorbable aminoglycoside, results in a clinical response in approximately 50% of patients.[26] However, eradication is rarely achieved, and unfortunately, those patients with the most severe infection tend to have the poorest response. Azithromycin has shown some efficacy,[29] whereas nitazoxanide holds promise.[30]

Microsporidia have emerged as one of the most common gastrointestinal infections in AIDS. Worldwide, in HIV-infected patients with diarrhea, microsporidia has been identified in 10% to 20%. A prospective study from New York identified small bowel microsporidiosis in 39% of HIV-infected patients undergoing small bowel biopsy for diarrhea.[31] Gastrointestinal disease is caused by 2 species, *Enterocytozoon bienusi* and *Encephalitozoon intestinalis*. Infection occurs when immunodeficiency is severe, with most patients having a CD4 count $<100/mm^3$. Diarrhea is the most common presenting symptom. These parasites may be found in asymptomatic patients, and the clinical illness tends to be much less severe than with cryptosporidia; as such, dehydration and electrolyte disturbances are rare. Weight loss, if present, is usually mild, although D-xylose and fat malabsorption are often present. Nausea and vomiting are uncommon. On small bowel biopsy, the organism appears as small round structures in the supranuclear portion of the enterocyte cytoplasm. Colonic involvement has not been described. These small intracellular parasites may be difficult to recognize on hematoxylin and eosin staining, thus necessitating additional staining methods; electron microscopy has been considered the gold standard for diagnosis and will make a species-specific diagnosis. Stool studies are now available that should reduce the need for diagnostic small bowel biopsy. Therapeutic options are limited. Despite initial reports, metronidazole is ineffective. *E. intestinalis* responds to albendazole, with some patients achieving clinical and microbiological cure, whereas *E. bienusi* has a poor response rate to this agent.[32]

Other small bowel parasitic diseases in AIDS include *Isopora* and *Cyclospora*.[33] *Isospora* is a common diarrheal pathogen in developing countries. *Cyclospora* has a number of microbiologic and clinical similarities with cryptosporidia; trimethoprim-sulfamethoxazole is effective therapy for both of these pathogens. There is no difference in the incidence or clinical expression of *Giardia* in HIV-infected patients as compared with normal hosts. Likewise, amebic disease is neither more prevalent clinically nor associated with more severe disease in HIV-infected patients than uninfected individuals.[34]

Mycobacteria are important intestinal pathogens and include MAC (previously termed *M. avium* intracellulare) and *M. tuberculosis*. MAC is the most common mycobacterium complicating AIDS and may be increasing in incidence in areas where widespread use of PCP prophylaxis is used.[4] Although diarrhea and abdominal pain may be observed in disseminated MAC, fever and wasting tend to dominate the clinical presentation. Diarrhea is usually mild or moderate in severity but may be associated with significant weight loss when small bowel disease is severe. Anemia and elevation of the serum alkaline phosphatase are common laboratory findings. MAC is seen almost uniformly when the CD4 count is $<100/mm^3$; the median CD4 count in most series is $<50/mm^3$. Stool culture positivity for MAC may not be predictive of gastrointestinal disease, although it is associated with a high incidence of subsequent disseminated disease.[35] Stool staining is less sensitive than culture for diagnosis. MAC may be considered the likely cause of diarrhea when blood cultures are positive in the appropriate clinical setting; however, small bowel biopsy is the definitive diagnostic test. When the disease is highly suspected, empiric therapy is often provided pending blood culture results. Multidrug regimens are clinically effective because of the high *in vitro* efficacy of clarithromycin, azithromycin, and ethambutol.[36] Nevertheless, therapy is not considered curative and must be given indefinitely. Tuberculosis, a disease primarily of developing countries, may involve any portion of the gastrointestinal tract. In contrast to MAC, tuberculosis occurs at any stage of immunodeficiency and is cured by a 9- to 12-month

multidrug therapy, provided resistance is not present.[37]

Clinically significant viral diseases of the small bowel are uncommon.[36] CMV small bowel disease presents with abdominal pain or bleeding because of mucosal ulceration, rather than diarrhea. Therapy for small intestinal CMV disease is similar to the esophagus and colon. The role of other viruses such as adenovirus and coronavirus are not well defined.[38] The importance of HIV-1 in causing intestinal disease remains controversial.

Neoplasms, including KS and lymphoma, may involve the small bowel, resulting in abdominal pain, intussusception, or bleeding. The diagnosis of intestinal neoplasms may be suspected by the presence of cutaneous or other extraintestinal neoplastic disease (eg, KS), or by the appearance of the lesion(s) on small bowel series or CT scanning.

HIV Enteropathy

The term *HIV enteropathy* has been applied to the patient with diarrhea in whom no cause can be found despite extensive evaluation. A variety of both functional and pathologic abnormalities of the small intestine have been identified in HIV-infected patients, many of which are independent of OIs.[39,40] These changes can occur in both early- and late-stage disease. Chronic inflammation of both the large and small bowel is common in HIV-infected patients. Small bowel atrophy resembling celiac disease has also been observed. Functional abnormalities of the small intestine described in these patients include reduced enzyme levels (lactase), malabsorption of both sugars (D-xylose) and vitamins (B_{12}), and increased small bowel permeability. The cause of these abnormalities has not been clearly delineated but does not appear to be the direct result of HIV infection of the enterocyte.[25] Loss of CD4 lymphocytes in the lamina propria paralleling the systemic circulation has been considered the likely cause of the mucosal changes because these cells seem to have a trophic effect on the intestinal mucosa.[25]

Colonic Disease

In contrast to the small intestine, bacteria and CMV are the most important colonic pathogens in AIDS. The spectrum of bacterial pathogens is similar to the normal host and includes *Campylobacter* sp., *Shigella* sp., and *Salmonella* sp.[41,42] *C. difficile* colitis is one of the most common pathogens in these patients because of the frequency of hospitalization and use of antibiotics, both of which are risk factors for this infection coupled with the increasing use of HAART therapy.[43] Bacterial colitis typically presents acutely with fever, abdominal pain, and watery or bloody diarrhea. Fecal leukocytes are often present. In contrast to the normal host, bacteremia is common, and thus in the ill patient with associated fever, blood cultures should be obtained in addition to stool cultures. The clinical presentation, response to therapy, and relapse rate of *C. difficile* colitis is no different in HIV-infected patients compared with other patients.[44]

CMV colitis is one of the most common causes of chronic diarrhea in late-stage HIV disease with most patients having a CD4 count $<100/mm^3$.[45] Like esophageal disease, coexistent retinitis may be present in 10% to 20% of patients. Although the presentation is variable, watery diarrhea is the most common presenting symptom. Abdominal pain, seen in 50% or more patients, may be severe and can be independent of diarrhea. When the distal colon is involved, symptoms of proctitis (urgency, frequent low volumes stools) are prominent. Fever is inconsistent, whereas weight loss is almost universal. Infrequent manifestations include gastrointestinal bleeding or perforation. CMV colitis should be suspected in any HIV-infected patient with severe immunodeficiency, abdominal pain, chronic diarrhea, weight loss, and repeatedly negative stool tests.[46]

The endoscopic appearance of CMV colitis includes isolated ulcerations or an endoscopic appearance resembling ulcerative colitis.[45] In some patients, the disease may be limited to the right colon, necessitating colonoscopy for diagnosis.[46,47] In patients with severe pain, CT is often performed initially and may suggest the diagnosis when the colon is markedly thickened, although this finding is not specific. The diagnosis is best established by identification of diagnostic viral cytopathic effect in colonic biopsies. Ganciclovir or foscarnet usually results in a clinical and endoscopic response,[45] although a longer course of therapy (4–6 weeks) than for esophageal disease may be required. As noted above, trials of valganciclovir for therapy of gastrointestinal disease are lacking.

A number of other OIs have been reported to involve the colon in AIDS patients, including histoplasmosis, *Rochilema*, and *Pneumocystis* toxoplasma. KS and non-Hodgkin's lymphoma may also involve the colon. As with the rest of the gastrointestinal tract, colonic KS is usually asymptomatic, whereas colonic lymphoma usually presents with abdominal pain.

Barium enema examination may document colitis, ulcers, or mass lesions, but endoscopic examination with biopsies will be required. In addition, barium studies should not be used in the evaluation of diarrhea as barium interferes with stool testing and endoscopy. However, these opportunistic disorders are best established by mucosal biopsy because the clinical presentation and radiographic findings are nonspecific.

Approach to Diarrhea

Given the many etiologic agents causing diarrhea coupled with involvement of either the small or large

bowel, a systematic approach for diagnosis is essential (Table 2).[48] Symptoms of small bowel disease include periumbilical crampy abdominal pain, flatulence, borborygmi, large stool volume particularly when fasting, and nausea/vomiting. Lower abdominal pain and symptoms of proctitis point to inflammatory disease of the distal colon. Fever suggests an infectious cause of diarrhea, and when present, blood cultures should be obtained to exclude bacterial colitis (acute diarrhea) or disseminated MAC. The presence of fecal leukocytes points to a colitis and warrants evaluation for bacterial causes including *C. difficile* and CMV colitis. If *C. difficile* toxin and routine bacterial cultures of the stool are negative in the patient with proctitis symptoms, evaluation of the distal colon with sigmoidoscopy is appropriate in the setting of severe immunodeficiency.[46,49] If multiple stool tests are negative and fecal leukocytes are absent, evaluation of the distal colon to exclude CMV should also be performed. Weight loss and severe immunodeficiency in a patient with chronic diarrhea are most likely caused by an OI. Upper endoscopy and small bowel biopsy will improve the diagnostic yield over stool tests alone for the diagnosis of microsporidia and cryptosporidia.[49] Colonoscopy and ileoscopy with biopsy are often adequate.[28] Nevertheless, the use of small bowel biopsy should be individualized because therapies for these parasitic diseases are neither uniformly effective nor widely available. A recommended approach for the evaluation of chronic diarrhea is provided in Figure 1. Acute diarrhea should be managed similarly to any other patient.

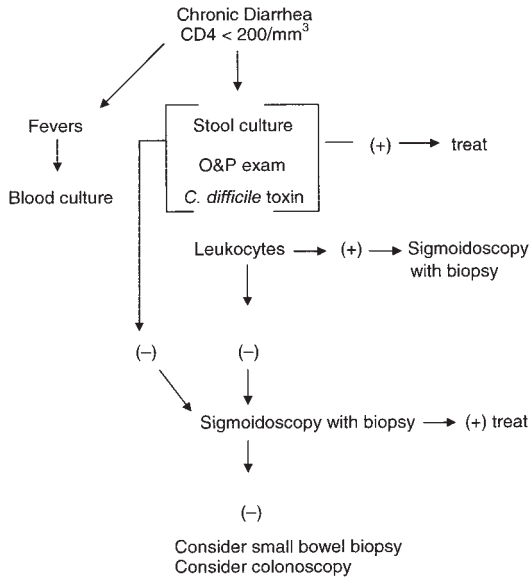

Figure 1. Suggested approach to the evaluation of chronic diarrhea in AIDS. O, ova; P, parasite.

Anorectal Disease

Since "safe sex" practices have been widely publicized in the homosexual community, acute anorectal disorders have decreased in frequency. Disorders related to unprotected anal intercourse include acute gonorrheal, syphilitic, and chlamydial proctitis. Human papilloma virus infection has been implicated as the main factor associated with the high incidence of anal carcinoma in homosexual men. Traumatic disease of the anorectum including fissures deserves consideration in the appropriate clinical setting. Non-Hodgkin's lymphoma may also involve the anorectum.

As with all anorectal diseases, anorectal pain, dyschezia, bleeding, urgency, and proctitis symptoms are the usual manifestations. Symptoms of proctitis (urgency, tenesmus, frequent low-volume stools) suggest distal colonic inflammation, usually from an infectious cause. Dyschezia is usually a manifestation of ulceration of the anal canal (fissure, infection). Careful inspection of the anorectum should be performed, noting the presence of ulceration, fistula, hemorrhoids, or mass lesions. Digital examination should document sphincter tone or mass lesions. Viral culture of perianal ulcer is the best method for the diagnosis of HSV. Evaluation of the anorectum can be performed with anoscopy and proctoscopy or sigmoidoscopy. If severe anorectal pain limits a thorough evaluation, evaluation under general anesthesia or sedation will be required. Biopsy of all mucosal abnormalities is emphasized.

Table 2
General principles for the evaluation of diarrhea in patients with AIDS

1. The likelihood of a colonic versus a small bowel cause of diarrhea should be determined by history and physical examination.
2. The differential diagnosis should be based on the CD4 lymphocyte count. When the CD4 count is $<200/mm^3$, opportunistic processes are most likely.
3. Stool tests are often diagnostic and initially should be performed. Multiple stool tests increases the diagnostic yield.[42]
4. Geography influences the prevalence of many gastrointestinal infections.[6,7,41]

Hepatobiliary Disease

Diseases of the liver are particularly common and not unanticipated in HIV-infected patients because the risk factors for acquiring HIV infection and the hepatotropic viruses are similar. In addition, infections and neoplasms frequently involve the liver during the process of lymphohematogenous dissemination. Furthermore, these patients receive a variety of medications, many of which have well-established hepatotoxicity. Over the last decade, aggressive evaluation of liver disease has been tempered by the fact that liver test abnormalities are so common that routine evaluation in all patients is both unnecessary and unwarranted and that OIs

frequently involve the liver secondarily, and thus detection of OIs outside the liver may yield a presumptive diagnosis of hepatic disease.

Histopathologic abnormalities of the liver in patients with AIDS are almost uniform. The most common finding by liver biopsy or at autopsy is steatosis. Fatty liver is believed to result from malnutrition and drugs, most commonly antiretroviral agents. Granulomas are particularly common and may be caused by infections (mycobacteria, fungi), drugs, or may be nonspecific. Changes of viral hepatitis are common, although at least for patients with hepatitis B virus (HBV) infection, tend to be less severe than in immunocompetent hosts. A variety of nonspecific abnormalities have also been found, including bile stasis, Kupfer cell hyperplasia, and hemosiderosis. Peliosis hepatis, previously considered a nonspecific finding, is now recognized to have an infectious etiology in many patients.

Diseases of the Biliary Tree

Biliary disease mimicking sclerosing cholangitis was described early in the AIDS epidemic. In the initial reports, patients presented with fever and right upper quadrant pain and were found to have sclerosing cholangitis by cholangiography; this disease has now been termed AIDS cholangiopathy. In most patients, these biliary duct abnormalities have an infectious cause. The most common identifiable infectious cause of biliary tract disease is cryptosporidia, followed by CMV and microsporidia, both *E. bienusi* and *E. intestinalis*. Other unusual causes of biliary tract disease reported in these patients include primary bile duct lymphoma, tuberculosis, MAC, and bile duct compression by lymph nodes.

The cholangiographic findings of this syndrome are variable. The most common pattern is papillary stenosis associated with intrahepatic sclerosing cholangitis, seen in approximately 50% of patients.[50] However, papillary stenosis alone or intrahepatic sclerosing cholangitis alone may occur. Distal bile duct disease may be infectious in etiology, neoplastic because of pancreatic disease, or caused by stones.

The clinical presentation of AIDS cholangiopathy is stereotypical. Right upper quadrant abdominal pain is common and is usually caused by biliary obstruction caused by papillary stenosis. Fever may occur and represent an underlying infection or, less commonly, secondary bacterial cholangitis. Given that parasites are the most common etiology and that these pathogens also have a predilection to infect the small bowel, diarrhea is a frequent associated feature. Liver test abnormalities are almost uniform, and in most series, the alkaline phosphatase is markedly elevated with mean value of 700 IU; jaundice is rare. Because OIs are the most common cause, the CD4 lymphocyte count is usually low ($<100/mm^3$).

The diagnosis is often suspected clinically. Abdominal ultrasound is the best initial test as identification of bile duct dilation is the *sine qua non* of the diagnosis. Thickening of the bile duct representing cholangitis is also frequent. A CT scan may show intrahepatic and extrahepatic biliary dilation and enhancement of the bile duct wall. Ultrasound has a sensitivity of approximately 70%. The definitive diagnostic test is ERCP. Biopsies of the bile duct and biliary cytology should be performed at ERCP to identify a potential infectious cause. Small bowel biopsies should also be performed at the time of ERCP to detect pathogens, especially in the patient with diarrhea.

Therapy for AIDS cholangiopathy is primarily endoscopic.[50] There is no evidence that treatment of the identified pathogens affects the course of the disease. Thus, medical therapy directed toward the OI(s) is most useful to treat the associated bowel disease and diarrhea (see small bowel section). For patients with papillary stenosis, endoscopic sphincterotomy is appropriate and usually results in resolution of abdominal pain. However, if there is associated intrahepatic sclerosing cholangitis, the alkaline phosphatase will continue to increase over time. This syndrome is rarely fatal and, whereas the prognosis is poor,[50] the outcome is primarily related to the degree of immunodeficiency and use of HAART.[51]

Unique gallbladder diseases have also been described in these patients.[52] Acalculous cholecystitis is usually infectious in nature and has been documented from *Isospora belli*, CMV, cryptosporidia, microsporidia, and (rarely) fungal disease. There may be associated involvement of the intrahepatic biliary tree. Symptomatic cholecystolithiasis may occur and should be treated as in any other patient. Although associated with morbidity particularly in the immunosuppressed patient, surgical therapy of gallbladder disease is curative. A laparoscopic approach to cholecystectomy should be attempted where possible to decrease morbidity.

Conclusions

Gastrointestinal complications remain important in HIV-infected patients. Gastrointestinal evaluation, often with endoscopy, will establish a diagnosis in most patients and will direct therapy. A variety of medications are available to treat OIs and neoplasms, and therefore a comprehensive yet pragmatic approach should be undertaken. A cornerstone of therapy today is HAART, which will boost immune function and, depending on the underlying causes, may result in a clinical remission of disease.

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