SMALL INTESTINE PATHOGENS IN AIDS

Conventional and Opportunistic

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Abnormalities of the small bowel associated with opportunistic and conventional pathogens are extremely common in patients infected with HIV. Diarrhea and malabsorption are the most common clinical presentations of small bowel infections; nausea, vomiting, abdominal pain, and weight loss also may be associated with small bowel disorders. Common bacterial, atypical bacterial, viral, protozoal, and fungal infections often are identified in patients infected with HIV, and must be differentiated from other causes of intestinal symptoms, both AIDS-associated and non-specific.[26, 32, 49] Mixed infections are common, and it may be possible to improve symptoms by treating susceptible organisms, even when no treatment is available for other infecting pathogens.[29]

The gastrointestinal tract is particularly vulnerable to opportunistic infection in patients with HIV due to impaired local immune defenses and direct exposure to infectious agents entering the mouth and anus from the external environment. Mucosal mononuclear and CD8 cells are increased, whereas total lymphocytes and the ratio of CD4 to CD8 lymphocytes are decreased.[70] IgA-secreting plasma cells are decreased in the intestinal mucosa, which could further predispose patients to enteric infections.

The relationship between systemic immunodeficiency and intestinal mucosa immune dysfunction remains unclear. Clinical observations indi-

cate that most opportunistic pathogens (e.g., cytomegalovirus [CMV], *Mycobacterium avium* complex [MAC], *Cryptosporidia,* and microsporidia) are detected predominantly in patients with depressed systemic immunity as indicated by a CD4 lymphocyte count less than 50 to 100 cells/mm³.

Diarrhea occurs in over 50% of patients with advanced AIDS at some point during the course of their disease. Of those with diarrhea, 50% to 85% have an identifiable infectious pathogen. Small intestinal rather than large bowel infections should be suspected in patients with large-volume diarrhea associated with weight loss, malabsorption, periumbilical pain, and cramping. Small bowel pathogens in patients with HIV or AIDS may be detected by routine and specialized stool culture, and microscopic and immunodiagnostic examinations. Toxin assay for *Clostridium difficile* should be performed for all patients. If these studies are negative, flexible sigmoidoscopy is indicated when fecal leukocytes or distal colorectal symptoms are present.[79]

Many HIV-related infections of the duodenum elude routine diagnostic stool examination and invasive procedures, such as esophagogastroduodenoscopy with biopsy, may be necessary to obtain a diagnosis by histopathology, examination of aspirated fluid, or culture of tissue. A stepwise algorithm is generally followed, from noninvasive stool studies to endoscopy with biopsy in an attempt to identify treatable conditions while minimizing discomfort and inconvenience to patients and pursuing the most cost-effective investigation. Although enteric bacterial infections require culture for identification, endoscopic mucosal biopsy is a safe and highly useful approach for identification of many viral, protozoal, fungal, treponemal, and helminthic intestinal infections.[45] For patients with abdominal pain, nausea, or vomiting, esophagogastroduodenoscopy may be less useful for arriving at a treatable diagnosis than it is in patients with diarrhea.[8] The range and frequency of pathogens identified varies widely according to endemic agents and available endoscopic and diagnostic facilities. Reported pathogens vary by geographic location with different pathogen prevalences in Atlanta,[79] France,[24] Uganda,[33] San Diego,[16] and London.[12]

Extrinsic causes of diarrhea should always be considered: these may include medications, lactose intolerance, malabsorption (especially of fat), alcohol, caffeine, and megadosing of vitamins (especially vitamin C and preparations using lactose or sorbitol as a filler) can each cause or exacerbate diarrhea. Discontinuing antibiotics or other potential causative agents, if possible, is useful as an initial approach. Furthermore, early nutritional assessment and intervention can prevent the progressive weight loss, malnutrition, and decreased quality of life common to patients with chronic HIV-associated diarrhea. Dietary interventions may obviate the need for extensive invasive tests if they control symptoms.

The diagnostic approach to patients with HIV-associated diarrhea should be tailored to the severity of symptoms and degree of malnutrition, and focused on the interventions most likely to identify a treatable pathogen as follows:

1. Exclude extrinsic contributors
    Antibiotics
    Lactose intolerance

Megadosing of vitamins or herbs, especially vitamin C
Excessive sorbitol, lactose, or caffeine
2. Stool examination
Bacterial culture for *Salmonella, Shigella, Campylobacter*
Stool specimens for ova and parasites, at least three
Special stains (acid-fast bacilli for *Cryptosporidium*) or immuno-
logic tests for protozoa
C. difficile toxin titer
3. Endoscopy with small bowel biopsy (sigmoidoscopy or colonos-
copy first if patient has colitic symptoms or afterward if esopha-
gogastroduodenoscopy is negative)

Understanding the range of potential pathogens and their prevalence at various stages of HIV disease progression is important. Enteric pathogens can be divided into opportunistic (those with a markedly higher incidence in immunocompromised hosts) and other infections with an incidence comparable with normal hosts. *Cryptosporidium* spp, microsporidia spp, *Isospora belli*, CMV, and MAC generally are considered opportunistic infections. *Entamoeba histolytica, Giardia lamblia, Leishmania donovani, Strongyloides stercoralis, Schistosoma* spp, and enteropathic bacteria are agents with pathogenicity for the general population, which also can be identified in patients with AIDS.

PROTOZOAN INFECTIONS

Cryptosporidium

Cryptosporidium parvum is a sporozoan parasite that can infect the gastrointestinal epithelium and other mucosal surfaces, causing a self-limited diarrhea in normal hosts and potentially life-threatening diarrhea in immunocompromised hosts. The organism can be transmitted as a zoonosis (animal to man), person to person, or by contaminated food or water; it is a cause of traveler's diarrhea. The prevalence among patients with AIDS is estimated to be 10% to 15%.[66] Blanshard et al[13] reported the diagnosis of *Cryptosporidium* in 5% of HIV-seropositive individuals and 21% of patients with AIDS.

After ingestion of as few as 10 to 100 oocysts, each oocyst releases four sporozoites that in turn invade the microvillous border of gut epithelial cells (Fig. 1). Once enveloped by the host membrane, a modest inflammatory response and cell injury results. The intracellular sporozoite matures and undergoes asexual reproduction (schizogony) producing merozoites. Merozoites can infect other epithelial cells once released into the intestinal lumen or mature into the sexual form of the parasite. The life cycle may then be repeated with fertilization in the intestinal tract producing walled oocysts that sporulate and release sporozoites, thus causing autoinfection. The small bowel is the most common site of infection, although cryptosporidia have been detected along the gastric, colonic, biliary, nasal, pulmonary, and even ocular epithelial surfaces. Duo-
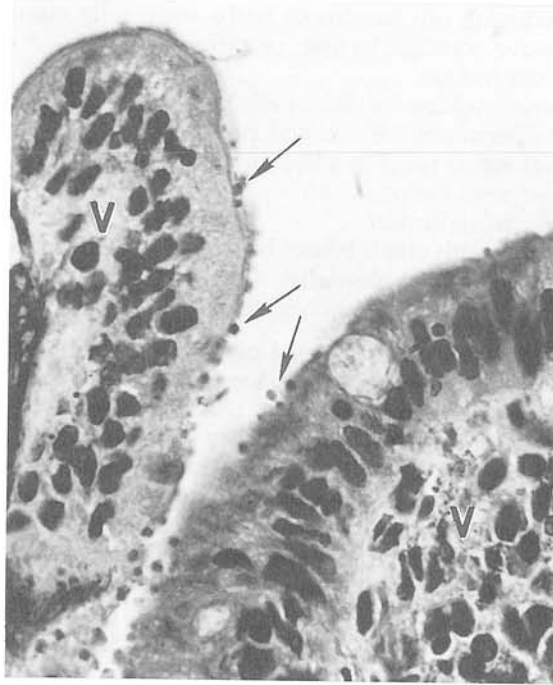
Figure 1. *Cryptosporidium* trophozoites (*arrows*) embedded in microvilli over the surface of villi (V) in an endoscopic biopsy from a patient with chronic diarrhea (original magnification × 64).

denal morphology in AIDS-related intestinal cryptosporidiosis usually is normal,[38] but white plaques in the duodenum, irregular serrated edematous valvulae conniventes, and multiple small well-circumscribed duodenal erosions also have been described.[21a, 64]

The diagnosis of cryptosporidiosis is made by detecting oocysts in stool or tissue biopsy specimens. A modified acid-fast stain of fecal smears is widely used to detect oocysts, which appear as red spherules,[57] although multiple (three or more) stool specimens may be required to make the diagnosis. Hematoxylin-eosin staining of endoscopic intestinal pinch biopsies also can detect *Cryptosporidium*. The small bowel is the most common site of diagnosis, although organisms can be detected on colonic and gastric biopsies as well. Rosenblatt and Sloan[71] found that enzyme-linked immunosorbent assay for the detection of *Cryptosporidium* spp. had a sensitivity, specificity, and positive predictive value of 93%, 99%, and 99%, respectively. This method has not found widespread use, although it might prove to be a more cost-effective method for detecting *Cryptosporidium* than endoscopy.

After an incubation of 1 to 2 weeks, symptoms begin and may wax and wane; spontaneous remissions are common in normal hosts. The

diarrhea is often accompanied by one or more of a variety of symptoms: epigastric or periumbilical pain, weight loss, anorexia, malaise, nausea, vomiting, flatulence, and myalgias. In patients with AIDS, the diarrhea may exceed 15 L of stool per day. A spectrum of disease has been reported in patients infected with HIV. In the 128 patients in the series reported by Blanshard et al,[13] four clinical patterns of disease were identified: (1) transient (29%); (2) chronic (60%); (3) fulminant (8%); and (4) asymptomatic (4%). Although transient disease occurred in patients with a wide range of CD4 lymphocyte counts, fulminant disease (defined as >2 L of stool/d) occurred only in patients with a CD4 count less than $50/mm^3$. Furthermore, those patients with severe diarrhea also had lost more than 7 kg and survived for a median of only 5 weeks. Patients with chronic diarrhea and transient infection survived 20 and 36 weeks, respectively. Flanigan et al[36] confirmed these general findings: in 47 patients with cryptosporidiosis, disease was self-limited in individuals with a CD4 count greater than 180 cells/mm^3, whereas persistent disease was found in 87% of those with a CD4 count less than 140 cells/mm^3.

A variety of therapies have been proposed for cryptosporidial diarrhea; unfortunately, in formal clinical trials most have proved ineffective or too toxic.[69] Of the drugs studied to date, none have proven long-term benefit. Currently, paromomycin, a poorly absorbed aminoglycoside, is the drug of choice for initial therapy, although further placebo-controlled trials are still needed.[14] Azithromycin and clarithromycin, newer macrolide antibiotics, currently are being used based on earlier series that suggested some benefit from spiramycin (a less well-tolerated macrolide); however, controlled studies have not confirmed benefit at currently used dosages. Interestingly, patients with less than 75 CD4 lymphocytes per mm^3, taking either rifabutin or clarithromycin for MAC prophylaxis appear to have been protected from symptomatic cryptosporidial diarrhea, although those taking prophylactic azithromycin were not.[46] Numerous other agents have proved ineffective including a long list of antibiotics and antifungal agents. Treatment of the underlying HIV infection with combined antiretroviral agents including one or more protease inhibitors is often effective in controlling chronic cryptosporidiosis.

Microsporidia

Microsporidia are obligate intracellular spore-forming organisms representing a separate phylum among protozoa. Clinical disease appears to be largely limited to immunocompromised individuals, but it has been reported in immunologically normal patients as well.[1, 78] Microsporidia are unicellular organisms lacking mitochondria and Golgi's apparatus and containing prokaryotic ribosomal RNA. Spores contain extrudable polar tubules that serve as passages for inoculation of the infectious agent (sporoplasm) into host cells.[17]

Two species, *Enterocytozoon bieneusi* and *Encephalitozoon (Septata) intestinalis*, have been identified as enteric pathogens in patients with AIDS.

E. bieneusi infects only small intestinal enterocytes, whereas *E. intestinalis* has been associated with disseminated as well as intestinal infection.[25] *E. bieneusi* has multiple spore organelles in the sporont and a poorly developed endospore layer of the spore wall, features that facilitate identification.[17] Spores within macrophages beneath the intestinal basal lamina characterize infection with *E. intestinalis*. By electron microscopy, *E. intestinalis* spores show double rows of polar tubes, which allow their differentiation from *E. bieneusi* spores, which have single rows of polar tubes.

The diagnosis of microsporidia depends upon identification of the organism in intestinal biopsy specimens (Fig. 2). Initially, transmission electron microscopy was necessary for the diagnosis. Several studies have evaluated the findings on light microscopy and determined that, with
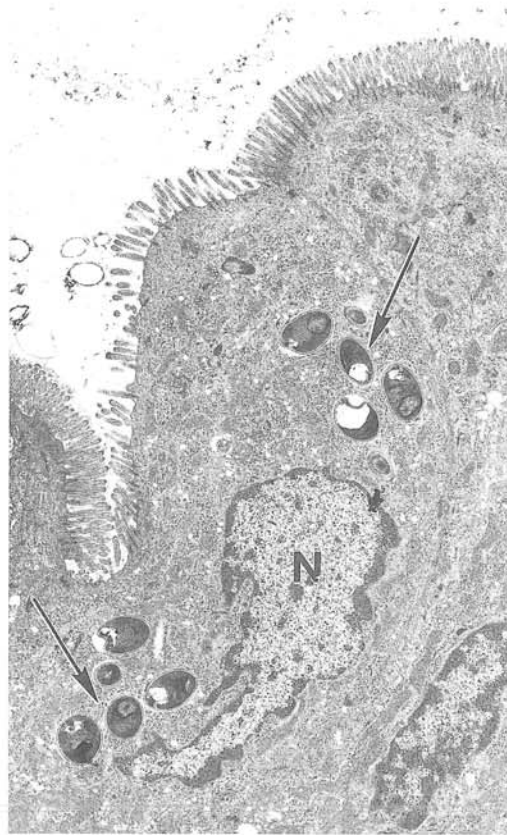
Figure 2. *Enterocytozoon bieneusi* spores (*arrows*), characteristically located in the cytoplasm between an enterocyte nucleus (*N*) and the lumen of a small-bowel biopsy from a man with AIDS and intractable diarrhea (original magnification × 8750). (*From* Current WL, Owen RL: Cryptosporidiosis and microsporidiosis. *In* Farthing MJG, Keusch GT (eds): Enteric Infection—Mechanisms, Manifestations and Management. London, Chapman and Hall Medical, 1988, p 237; with permission.)

sufficient experience, one can identify parasites and spores on standard hematoxylin-eosin stained paraffin sections[35, 39, 53, 62] or by using the Warthin-Starry stain.[35] Electron microscopy remains useful for species identification.

Patients with microsporidiosis present with signs and symptoms similar to those of cryptosporidiosis. Most patients have a CD4 count below 100 cells/mm^3, weight loss, malabsorption, nausea, and vomiting. As with other parasitic small bowel infections, there usually are no colitic symptoms, fevers, or night sweats. *E. intestinalis*, which invades the submucosa, can be associated with intestinal perforation.[75] Microsporidia are detected in 15% to 40% of duodenal biopsies in patients with AIDS-associated chronic diarrhea.[31, 34, 54, 65] The etiologic association of microsporidiosis and diarrhea, however, was questioned by Rabeneck et al,[68] who identified microsporidia in 33% and 25% of biopsy specimens from 55 patients with and 51 patients without diarrhea, respectively. Analysis of 259 HIV-infected patients in Germany showed microsporidia in 19.1% of those with chronic diarrhea but only 1.5% of those without diarrhea.[72] In another prospective study of 97 consecutive patients with HIV in Germany, microsporidia was found in 36% of those with diarrhea but only 4.3% of those without diarrhea.[74]

As with other protozoan parasites, effective therapy for microsporidiosis has been elusive. Metronidazole[3, 28, 31] and albendazole[28, 45] have been reported to improve symptoms, yet not eradicate *E. bieneusi* in patients with HIV. In contrast, albendazole has been shown to eliminate *E. intestinalis* in patients with HIV[74, 75] and also has been effective in eliminating *E. bieneusi* in a patient with chronic diarrhea for 3 months without HIV.[78]

I. belli

I. belli is a protozoan pathogen of the sporozoa class that is endemic in developing countries. This protozoon can cause self-limited diarrhea in normal hosts and chronic diarrhea, which may be clinically indistinguishable from cryptosporidiosis in patients with AIDS. After oocysts are ingested, the organism excysts and invades the small bowel enterocytes, giving rise to symptoms after approximately 1 week. Symptoms are comparable with those produced by other pathogenic enteric protozoa, including profuse watery diarrhea, abdominal pain, cramping, and anorexia.

On stool smears stained with a modified acid-fast stain, *I. belli* oocysts can be distinguished from *Cryptosporidium* oocysts. *I. belli* oocysts are larger (20 to 30 μm by 10 to 19 μm), oval, and contain two sporozoites, compared with *Cryptosporidium* oocysts, which are 4 to 6 μm in diameter, round, and contain four sporozoites. Although *I. belli* is an infrequent cause of AIDS-associated diarrhea in the United States, its prevalence in Haiti has been reported to be 15%.[27] Comin and Santucci[23] documented stages of both asexual (trophozoite, schizont, and merozoite) and sexual (macrogametocyte) phases of the *Isospora* life cycle of the parasite in the intestinal epithelium of an infected patient.

The clinical manifestations of isosporiasis are indistinguishable from other causes of chronic diarrhea in patients with AIDS. Significant weight loss and diffuse, crampy abdominal pain are common.[27] Unlike in other protozoan infections, trimethoprim-sulfamethoxazole leads to a marked clinical response with cessation of diarrhea and clearance of pathogens from stool examination. Recurrent isosporiasis, however, is common, noted within 2 months of therapy in nearly half of patients.[27]

Cyclospora cayetanensis

Since 1983, AIDS patients with diarrhea in Haiti have been found with acid-fast organisms in their stools intermediate in size between *Cryptosporidium* and *I. belli*.[63] Similar organisms were found in travelers around the world and in institutional diarrheal outbreaks among both immunocompetent and immunocompromised patients. After initial uncertainty regarding their appropriate classification, they have been determined to be coccidial parasites with symptoms and transmission patterns similar to microsporidia, *Cryptosporidia,* and *Isospora*.[42] *Cyclospora* species are identified by acid-fast stain of stool showing round acid-fast oocysts 8 to 9 μm in size, which is intermediate between *Cryptosporidium* (5 μm) and *Isospora* (25 $\times$ 15 μm) species. Infection also can be detected by light and electron microscopic identification of *Cyclospora* in endoscopic duodenal biopsies.[76] In Haiti, among 450 HIV patients with diarrhea, 30% had *Cryptosporidium,* 12% had *I. belli,* and 11% had *Cyclospora,* but only 3% had *G. lamblia* and 1% *E. histolytica*.[63] Fortunately, *Cyclospora* have been found to respond to treatment with trimethoprim (160 mg)-sulfamethoxazole (800 mg) four times a day for 10 days, like *Isospora* but unlike microsporidia and *Cryptosporidia*. HIV-infected patients who develop recurrent *Cyclospora* infection and diarrhea respond to retreatment and secondary prophylaxis with a single dose three times a week.[63]

G. lamblia

G. lamblia is a common cause of parasitic diarrhea in the United States, with significant prevalence rates among individuals practicing oral-anal sex. The flagellated protozoan is transmitted in its resting state (i.e., the cyst). Cysts have rigid outer walls protecting the organism from environmental elements and disinfectants. They are transmitted via water or food contaminated by human or animal feces. Following ingestion, excystation, multiplication, and colonization yield an abundance of trophozoites, which cause a spectrum of histopathologic changes ranging from limited cellular infiltrates to severe loss of villous architecture and absorptive surface.

Clinical disease may be self-limited or accompanied by severe diarrhea, bloating, abdominal cramping, and weight loss. The frequency and virulence of infection is not increased in patients with AIDS, and *G. lamblia* accounts for 2% to 5% of identified pathogens.

The diagnosis is based on identification of cysts and trophozoites in the stool. Cyst excretion may be low, accounting for occasional diagnoses made only at the time of endoscopic biopsy.[45] Asymptomatic cyst carriers and symptomatic patients should be treated. Metronidazole is the first-line drug for routine treatment. Furazolidone, paromomycin, and albendazole are alternative therapies.

E. histolytica

E. histolytica is an enteric protozoan that also can cause diarrhea. E. histolytica is ubiquitous in developing countries and represents a significant cause of acute dysentery. In the United States and Europe, up to 20% of homosexual men[2] may harbor E. histolytica, yet strains usually are avirulent and invasive disease is rare. Patients with symptomatic intestinal amebiasis are treated with metronidazole and asymptomatic carriers may be treated with iodoquinol or another luminal agent.

Other protozoal pathogens

In an AIDS patient dying with acute Toxoplasma gondii infection but no brain lesions, toxoplasma tachyzoites were identified within the submucosa of small ulcers in the intestine, the portal of entry.[10] Among travelers to, and AIDS patients living in, endemic areas, visceral leishmaniasis can produce fever, weight loss, and diarrhea.[47, 59] Duodenal mucosa was the most frequently reported site of gastrointestinal involvement in a series of 15 reported and reviewed cases, with the initial diagnosis made by endoscopic biopsy in 10 patients.[55]

Nonpathogenic Protozoa

Endolimax nana, Entamoeba hartmanni, Entamoeba coli, Iodamoeba buetschlii, and Blastocystis hominis generally are considered nonpathogenic even in patients with AIDS. Nonetheless, in the setting of chronic diarrhea, some clinicians treat empirically with metronidazole and assess the clinical response.

NEMATODES

S. stercoralis

S. stercoralis is an intestinal nematode found in tropical and subtropical regions of the world, including the southeastern United States. The intricate life cycle begins with waterborne filariform larvae penetrating skin or mucous membranes to enter the host bloodstream. The larvae

break out of the pulmonary capillaries into the alveolar space, ascend the bronchial tree to the glottis, and are swallowed and carried into the small intestine where they mature into adult stages. The female adult lives within the mucosa, laying eggs that hatch to form new larvae. Intestinal autoinfection results from larvae penetrating the intestinal mucosa and entering the bloodstream. Gram-negative bacteremia may result from bacteria carried into the bloodstream by the penetrating larvae.

Several cases of disseminated strongyloidiasis have been reported in HIV-infected patients in the United States, although in endemic areas there has been no significant increase reported among HIV-infected patients. The disease usually manifests itself clinically as watery, mucoid diarrhea alternating with constipation. Pulmonary manifestations may accompany the disease. Larvae can be detected on stool examination and adults identified on duodenal biopsy. Thiabendazole is the drug of choice; however, dosage and length of treatment are controversial in immunosuppressed patients and disease recurrences have led some to promote chronic suppressive therapy.[43]

VIRAL INFECTIONS

CMV

CMV infection typically occurs late in the course of AIDS, when the CD4 count invariably is below 50 cells per mm^3. The colon is the most common intestinal site of infection, although esophageal, gastric, and small bowel infections occur. CMV infects the vascular endothelial cells, producing vasculitis with bowel wall ischemia. Symptoms of CMV enteritis may be nonspecific, including diarrhea, weight loss, and abdominal pain. Increased stool frequency, hematochezia, dyschezia, and lower quadrant abdominal tenderness are suggestive of colonic infection.

Mucosal hemorrhage, erosions, and ulceration are seen at endoscopy, but CMV enteritis is confirmed by light microscopy examination of the enteric biopsy specimen.[41] Intranuclear inclusions are the pathognomonic feature. Immunostaining, in situ hybridization, and blood culture can confirm the presence of CMV. These methods generally are not clinically significant, however, in the absence of biopsy evidence of CMV vasculitis, the hallmark of clinically relevant disease. In severe infection, intestinal perforation may occur.

Intravenous ganciclovir and foscarnet are used to treat enteric CMV infections. Ganciclovir, an acyclovir derivative, is associated with significant bone marrow toxicity, which can limit its use. Foscarnet, a pyrophosphate analogue, has significant renal toxicity. Either agent generally is given for 2 to 6 weeks, or 1 week beyond a clinical response. Maintenance therapy, similar to that given for CMV retinitis, has been advocated, although no long-term survival benefit has been demonstrated for treatment of enteritis. A randomized open-label comparison of ganciclovir and foscarnet showed good response to either drug but recurrence or

progression occurred after treatment was ended[11]; maintenance was ineffective in preventing progression of disease.

Other viral intestinal infections have been reported in patients with HIV. These viral infections are primarily identified on colonic biopsies. Whether they also infect the small intestine is unclear. Adenovirus can cause a hemorrhagic colitis[7] and rotavirus has been recovered from stool specimens with markedly varying geographic prevalences. In a United States study of enteric infections in homosexual men with HIV, infections with rotaviruses, adenoviruses, and Norwalk agent were infrequent, even in AIDS patients.[50] In Germany, among 256 HIV-infected patients undergoing endoscopy because of diarrhea, adenovirus was found in 6.6% and coronavirus in 1.3%.[73] Herpes simplex virus infection occurs more frequently in the oropharynx, anorectum, and esophagus in HIV-positive subjects than in HIV-negative patients.

HIV Enteropathy

It has been proposed that HIV infection of enterocytes or lamina propria can cause diarrhea due to associated small bowel mucosa abnormalities.[77] A wide range of pathologic intestinal changes have been reported in patients without other indefinable pathogens.[20] Subtotal villus atrophy (decreased villus height), decreased mitoses in crypts, decreased epithelial height, increased intraepithelial lymphocytes and plasma cells, and decreased brush border enzyme activity have been noted on histologic examinations.[4, 77] Whether these changes are direct effects of the HIV virus, indirect effects of changes in intestinal immune system constituents, or manifestations of still unidentified intestinal pathogens is uncertain.

Bacterial Infection

Enteropathogenic bacteria are a significant cause of diarrhea in patients with HIV and frequency of bacterial enteritis is reportedly higher with HIV disease.[12] The most common causes of bacterial enterocolitis include *Salmonella*, *Shigella*, and *Campylobacter*. These bacterial pathogens are associated with bacteremia more frequently in patients with AIDS than in normal hosts.

In a retrospective review of 101 episodes of bacterial diarrhea in HIV-seropositive patients, 56 episodes of *Salmonella*, 37 of *Campylobacter*, and eight of *Shigella* infection were identified.[61] *Shigella* was most likely to occur early in HIV disease, whereas *Campylobacter* or *Salmonella* were more likely to occur in individuals with a previous AIDS diagnosis. Septicemia was most frequently observed in patients with *Salmonella*, again primarily in individuals with an AIDS-defining diagnosis.

Furthermore, infection relapse was common in patients with *Salmonella* and low CD4 lymphocyte counts, initial septicemia, and those not treated with ciprofloxacin.[61] The authors concluded that patients with

salmonellosis, low CD4 lymphocyte count, or a septicemic illness should be considered for life-long secondary prophylaxis with ciprofloxacin because of the high rate of relapse observed.

Escherichia coli also appears to be another cause of bacterial enteritis in patients with AIDS.[12]

Small Bowel Overgrowth

Small bowel bacterial overgrowth results in a clinical syndrome consisting of diarrhea and malabsorption of fat, vitamin B_{12}, and carbohydrates. Although diarrhea and malabsorption frequently are associated in patients with HIV, few studies have searched for and identified abnormally high bacterial counts in these patients.[12] The morphologic changes reported in patients with small bowel overgrowth include villus atrophy and inflammatory infiltrates (similar to the findings in HIV enteropathy). In HIV-seropositive persons, gastric hypoacidity,[9] impaired intestinal immunity,[16a] or impaired intestinal motility may predispose to bacterial overgrowth. Few centers routinely perform small bowel aspirates for quantitative bacterial cultures, so that the true prevalence of this condition remains unknown.

MAC

MAC is present throughout the environment yet rarely was associated with disease in humans prior to the HIV epidemic. Disseminated infection is reported in 15% to 40% of patients with AIDS, characteristically occurring once CD4 counts fall below 100 cells/mm^3. Disseminated disease usually is associated with fever, weight loss, and anemia and is most readily diagnosed by blood culture. Small bowel MAC infection can be detected on endoscopic duodenal biopsies, although in most studies of AIDS-associated diarrhea the prevalence does not approach the 86% to 98% reported for bacteremia.[67] Diagnosis by histologic evaluation of endoscopic biopsies is much more rapid than is diagnosis by culture due to slow growth of *Mycobacteria*. At endoscopy the mucosa can appear edematous and friable with fine frondlike nodules, produced by villi that are swollen by infiltrating macrophages engorged with *Mycobacteria*.[67] Duodenal biopsies reveal macrophages distended with acid-fast organisms below the epithelium. This produces a frosted appearance of the intestinal mucosa with lesions, which are larger, more papular, and yellowish, compared with the whitish plaques occasionally reported in *Cryptosporidia* infection (Color Fig. 3).[19, 21] In the presence of severe malabsorption and weight loss, duodenal MAC infection can mimic Whipple's disease.[40, 67]

It remains unclear what factors contribute to the decreased survival of patients with disseminated MAC. Patient survival reportedly is reduced by 6 months by disseminated MAC infection.[48] What role, if any, small bowel involvement with MAC has in patient survival remains unclear.

Although treatment of disseminated infection appears to improve survival, eradication of the organism generally is unsuccessful. Controlled trials of prophylaxis indicate that rifabutin decreases the frequency of disseminated MAC infection in patents with CD4 counts less than 100.[67]

Mycobacterium tuberculosis

M. tuberculosis infection can involve the gastrointestinal tract in patients with AIDS and most commonly involves the ileocecal region.[5] *M. tuberculosis* infection is not as common as MAC infection.

Mycobacterium genavense

M. genavense, a recently recognized mycobacterium, resembles MAC but has an even greater propensity for the gastrointestinal tract. It also produces a velvety thickened appearance with fine nodularity, but requires longer incubation for cultural identification.[52] Developing DNA amplification techniques may speed diagnosis of cases identified by the presence of acid-fast bacilli in the intestine.[30]

FUNGAL INFECTION

The small intestine of patients with AIDS can be involved in systemic fungal infections including candida,[6] *Histoplasma capsulatum*,[15, 44] *Coccidioides immitis,* and aspergillosis (Color Fig. 4).[18] Gastrointestinal fungal infections usually are incidental to the clinically predominant illness (i.e., pulmonary and hepatic disease). Occasionally, diarrhea or intestinal obstruction predominates because of enterocolitis or fungal mass lesions.[22] Intestinal *Cryptococcus neoformans* infection with enlarged swollen villi was found in a man with AIDS, abdominal pain, and vomiting. Endoscopy showed white plaquelike lesions in the duodenum resembling esophageal candidiasis.[21] Zygomycosis (mucormycosis) of the small and large intestine producing deep submucosal ulcerations from the duodenum to the ileum was found at autopsy in a woman with AIDS and a CD4 count of 70.[60]

INTESTINAL NEOPLASMS

Non-Hodgkin's Lymphoma

The incidence of non-Hodgkin's lymphoma among HIV-infected persons is increasing.[51, 56] Whether lymphoma results from opportunistic infection with Epstein-Barr or other viruses is uncertain. Estimates indicate that 8% to 25% of cases of lymphoma in the United States result from HIV infection.[37] A characteristic feature of HIV-associated lymphomas is

Figure 3. Frosted duodenum in a patient with intestinal *Mycobacterium avium* complex infection. This white, granular endoscopic appearance of the duodenum is a suggestive but nondiagnostic finding.

Figure 4. An ulcerated duodenal mass (*arrows*) confirmed to be *Histoplasma capsulatum* in a patient with AIDS and systemic symptoms of histoplasmosis.
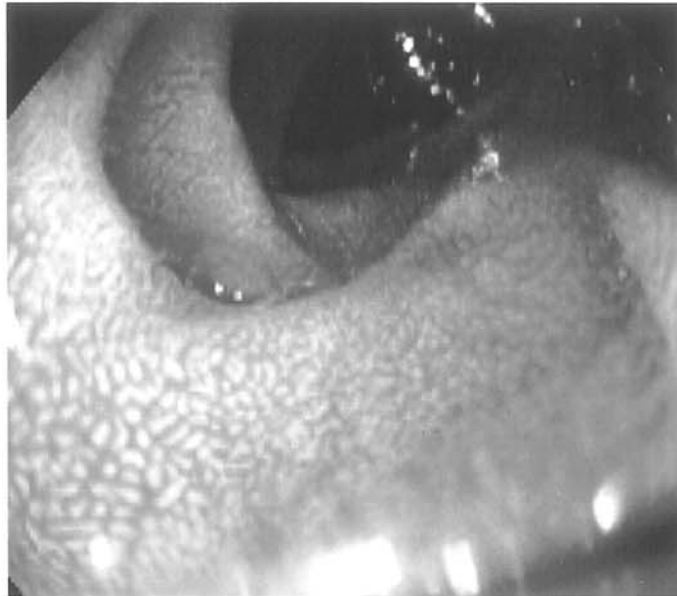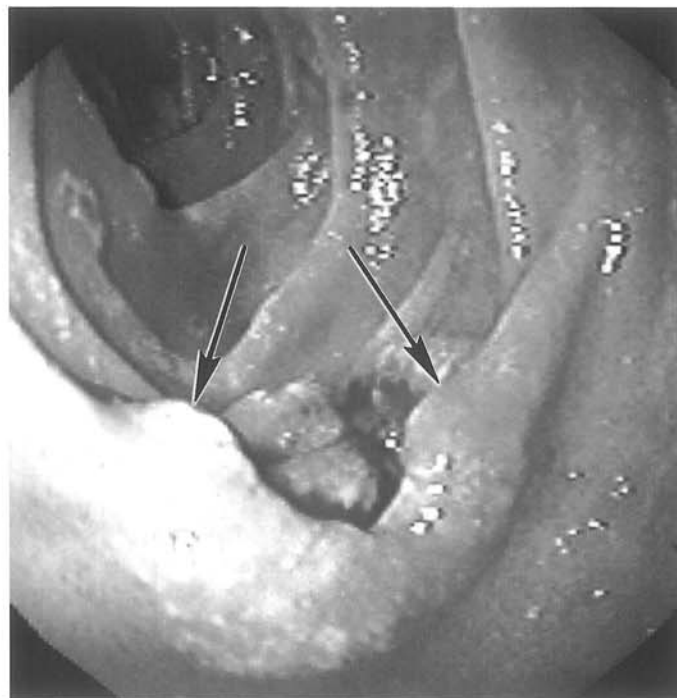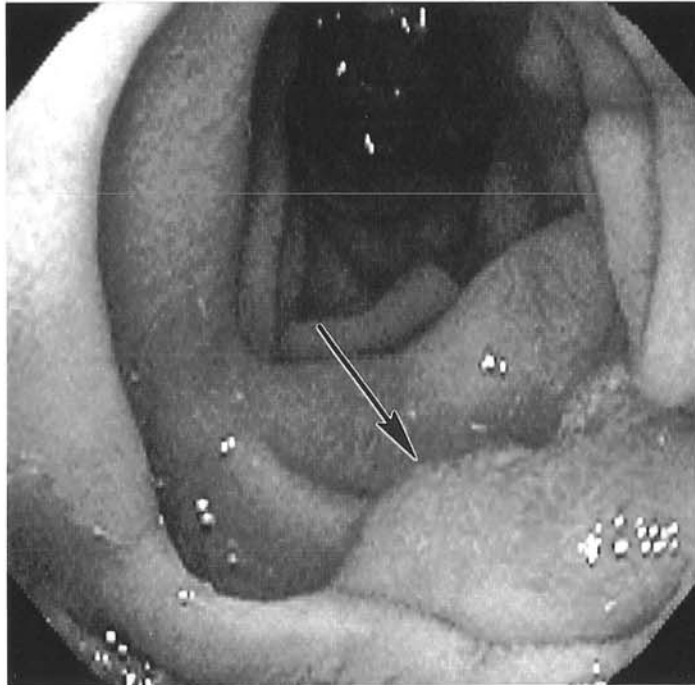
Figure 3.

Figure 4.

Figure 5. Biopsy confirmed Kaposi's sarcoma (*arrow*) in the duodenum of a patient with AIDS.

the high degree of extranodal involvement.[80] Gastrointestinal involvement frequently includes the stomach and small bowel. Small bowel involvement carries a higher incidence of perforation.

Kaposi's Sarcoma

Kaposi's sarcoma is an unusual malignancy that was found early on in the epidemic to be associated with HIV-infection. The higher prevalence among homosexual men suggested a sexually transmitted infectious etiology or cofactor, which has now been identified as human herpesvirus 8.[58] Kaposi's sarcoma often is limited to cutaneous manifestations. Occasionally, typical gastrointestinal lesions (red nodules) generally 5 mm up to 2 to 3 cm in diameter may be noted throughout the intestinal tract (Color Fig. 5). Intestinal lesions generally do not cause specific symptoms, although they can infrequently be associated with intestinal hemorrhage, and large mass lesions can obstruct the intestinal lumen. Chemotherapy, primarily intralesional therapy, has been advocated for cutaneous lesions. In contrast, most intestinal lesions do not require treatment. Some studies

have demonstrated regression of intestinal Kaposi's sarcoma with aggressive antiretroviral therapy.

SUMMARY

The small intestine, coming in direct contact with ingested potential pathogens, depends on active mucosal immunity to withstand invasion and damage. In patients with AIDS and severe impairment of immunoregulatory lymphocytes, proliferation of protozoal, viral, bacterial, and fungal pathogens produces diarrhea and malabsorption. When noninvasive tests of stool and blood fail to identify responsible organisms, endoscopy can reveal mucosal lesions, which are suggestive if not diagnostic. *Cryptosporidium, E. intestinalis,* CMV, MAC, and other infections can be identified by intestinal biopsy quicker and often at lower overall cost than they can by culture.

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