AIDS

AND THE GASTROINTESTINAL TRACT

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INTRODUCTION

In 1981, following reports from a number of clinicians, the Centers for Disease Control (CDC) identified an outbreak of a new syndrome in homosexual men (1). This syndrome consisted of pneumocystis pneumonia and an aggressive form of Kaposi's sarcoma associated with acquired immunodeficiency. This syndrome became known as the acquired immunodeficiency syndrome (AIDS) and the spectrum of the syndrome has broadened to include a wide array of opportunistic infections and tumors. During the past seven years the number of cases of aids has continued to increase nearly exponentially and through December 1987 approximately 48,000 cases of AIDS had been reported to the CDC. It is now known that AIDS is caused by the human immunodeficiency virus (HIV-I), a retrovirus that is tropic for T-lymphocytes. This virus attacks and depletes the $CD4^+$ ($T4^+$) subpopulation of T-lymphocytes that function as helper/inducer lymphocytes. Because of the central role of T-helper cells in the regulation of the immune system, infection with HIV indirectly impairs a broad array of immune reactions. Immunologic abnormalities that have been documented in patients with AIDS include lymphopenia, a decrease in the number of T-helper cells with reversal of the T-helper to T-suppressor ratio, abnormalities in delayed-type hypersensitivity responses, activation of B-cells with polyclonal gammopathy, decreased proliferative responses in vitro to mitogens (2), allogeneic lymphocytes (2,3) and soluble antigens (4), impaired lymphokine production (5) and diminished (6) cytotoxic T-cell and natural-killer cell activity. These abnormalities in immune function predispose the patient to the development of several opportunistic infections and lead to conditions conducive to the development of secondary malignancies. Almost any organ system of the body may be affected by these opportunistic infections and neoplasms. The gastrointestinal tract, however, is a major target organ and gastrointestinal involvement leads to serious morbidity in the majority of patients with AIDS (7-11). Diarrhea and weight loss are the most common manifestations. In this country diarrhea is present in about 60% of AIDS patients and weight loss in greater than 90%. Odynophagia, primarily due to candida esophagitis is also common and occurs in about 40% of patients with AIDS. In Africa and the tropics, virtually 100% of AIDS patients have intractable diarrhea and weight loss. Although there is presently no cure for AIDS, specific therapy is available for many of the infections that are encountered in AIDS patients.

THE INTESTINAL IMMUNE SYSTEM

The intestinal mucosa, whose absorptive surface area approximates that of a football field, is constantly exposed to a wide variety of potentially pathogenic organisms. A number of nonspecific host defense factors such gastric acid, bile, mucus, digestive enzymes and intestinal motility are important in rendering these ingested organisms nonviable or in allowing them to pass through the GI tract without deleterious effects. The effect of AIDS on these nonspecific factors has not been studied in detail. Nonetheless, defective gastric acid secretion and diminished gut motility appear to be quite common in patients with AIDS.

The intestine is also a major immunologic organ and the intestinal immune system plays a critical role in host defense against the multitude of potential and real pathogens to which the gut is exposed. The intestinal immune system is generally divided into afferent and efferent limbs (12-14). Within the afferent limb are the Peyer's patches which are specialized aggregates of B-cells, T-

cells and macrophages located in the mucosa and submucosa of the intestine (Fig. 1). The Peyer's patches are covered by a specialized epithelium (M-cells) which is capable of sampling antigens from the intestinal lumen. Antigenic material in the gut is derived from several sources including bacteria, viruses, parasites, food products, drugs and other chemicals. This antigenic material is bound and internalized by M-cells and subsequently transported to underlying macrophages. Macrophages process the antigenic material and present it to T-helper cells, causing them to proliferate. Within the Peyer's patches are other T-helper cells that are capable of inducing immature IgM surface-bearing B-cells to switch isotype to IgA. The switched B-cells proliferate and differentiate in response to a variety of growth and differentiation factors secreted by other T-cells. The antigen activated B-cells then migrate to nearby mesenteric lymph nodes and subsequently enter the general circulation via the thoracic duct before homing to various mucosal surfaces throughout the body, including the lamina propria of the gut, where they take up residence as terminally differentiated IgA secreting plasma cells. This entire migration is thought to take 4 to 6 days. Although not as well understood, it is thought that antigen-activated T-cells generated in Peyer's patches follow a similar migration pathway.

MIGRATION PATHWAY OF PEYER'S PATCH CELLS

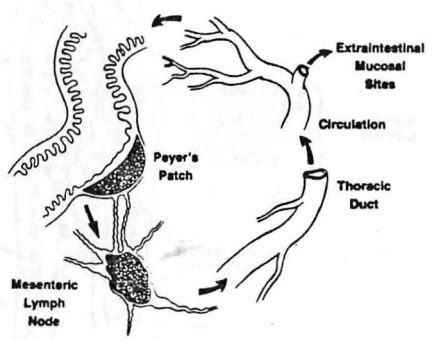


Fig. 1 (from reference 13)

The efferent limb of the intestinal immune system consists of the immune cells located in the epithelial and lamina propria compartments of the intestinal villi. As illustrated in Fig. 2 the intraepithelial lymphocyte compartment consists of lymphocytes interdigitated between enterocytes with approximately 1 lymphocyte for every 6 to 10 enterocytes. The intraepithelial lymphocytes are largely cytotoxic T-cells and natural killer cells by surface markers. Furthermore, these cells have been shown to be capable of cytotoxic function, particularly against cells infected with enteroviruses. Thus, the intraepithelial lymphocytes appear to present a frontline barrier, capable of immediately responding throughout the entire area of the intestine.

The lamina propria contains several different cell types, most of which are terminally differentiated effector cells. Among these effector cells are the IgA plasma cells that originated in nearby Peyer's patches and preferentially returned to the lamina propria of the intestine. IgA secretion in response to exogenous antigens is a central function of the mucosal immune system. IgA secretion adds specificity and memory to the various nonspecific host factors such as gastric acid, mucin and intestinal motility. It protects by excluding and/or neutralizing antigens, toxins and organisms present in the lumen of the gut. It is doubtful that IgA antibody is induced to every single antigen found in the gut because the number of antigens is simply too enormous. The factors that determine which antigens elicit a response and why are not understood, however.

Little is known regarding the function of the intestinal immune system in patients with AIDS. Several groups, however, have performed in situ immunohistological studies of the gut in an attempt to characterize the distribution of T-cell subpopulations within the intestinal mucosa (15-17). Typical results are shown in Fig. 3 (15). In these studies endoscopic mucosal biopsies were obtained from the proximal jejunum using a hydraulic biopsy apparatus. Patient groups included a heterosexual control group, a homosexual control group, patients with lymphadenopathy syndrome and patients with full-blown AIDS. None of the patients had diarrhea or any other gastrointestinal symptoms at the time they were studied. Phenotypic analysis of mucosal lymphocyte populations in patients with AIDS or LAS using Leu-3 (equivalent to OKT4; identifies helper/inducer T-cells) and Leu-2 (equivalent to OKT8; identifies suppressor/cytotoxic T-cells) monoclonal antibodies showed reversal of the helper/suppressor ratio similar to that seen in peripheral blood lymphocytes. Mucosal helper/suppressor ratios were normal in healthy homosexual men although these same individuals had reversed helper/suppressor ratios among circulating T-cells. As in peripheral blood lymphocytes, the decrease in the mucosal helper/suppressor T-cell ratio was due primarily to depletion of the mucosal helper T-cells. Interpretation of these results must be tempered by the realization that the usefulness of cell surface markers for defining T-cell subpopulations has major limitations in man. It is clear that a good deal of functional heterogeneity exists within subsets such that some $CD4^+$ ($OKT4^+$, "helper/inducer") cells actually suppress immunoglobulin synthesis and some $CD8^+$ ($OKT8^+$, "suppressor/cytotoxic") cells derepress immunoglobulin synthesis. Nevertheless, these

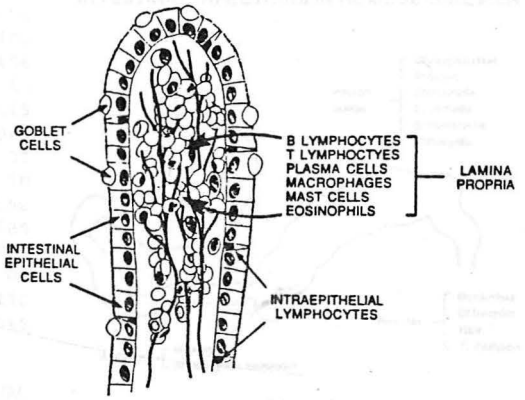


Fig. 2 (from reference 14)

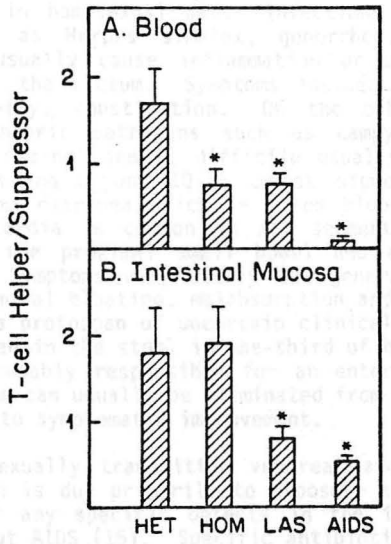


Fig. 3 (from reference 15)

studies suggest that the abnormalities among T-cell subsets in the blood of AIDS patients are paralleled by similar abnormalities in the intestinal mucosa. In addition to these abnormalities in T-cell subsets within the mucosa, some investigators have found a significant depletion of lamina propria IgA plasma cells in patients with AIDS (18). These findings suggest that abnormalities in the intestinal immune system may contribute to the development of intestinal and systemic opportunistic infections and neoplasms in patients with AIDS.

INTESTINAL INFECTIONS IN HOMOSEXUAL MEN

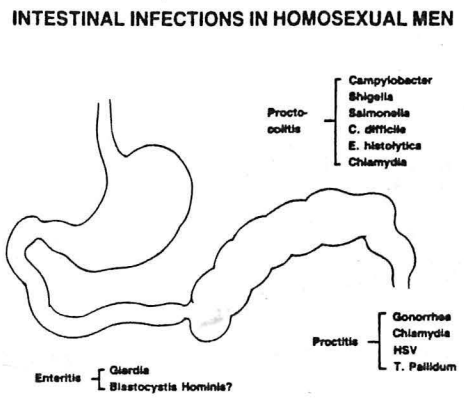


Fig. 4

Homosexually active men are prone to a wide variety of infections that affect the gastrointestinal tract (19). As illustrated in Fig. 4, a large number of enteric pathogens as well as the traditional venereal pathogens may be responsible for intestinal symptoms in homosexual men. Infections with the traditional venereal pathogens such as Herpes simplex, gonorrhea, non-LGV strains of chlamydia and syphilis usually cause inflammation or ulceration limited to the lower 10 to 15 cm of the rectum. Symptoms include anorectal pain, rectal discharge and, frequently, constipation. On the other hand, infections with the more typical enteric pathogens such as campylobacter, shigella, salmonella, chlamydia (LGV stains) and C. difficile usually cause a proctocolitis with inflammation extending beyond 10-15 cm at sigmoidoscopy. Symptoms include frequent small volume diarrhea which is often bloody, lower abdominal cramping and tenesmus. Giardia is common in all segments of the population. This organism inhabits the proximal small bowel and causes an enteritis; sigmoidoscopy is normal. Symptoms vary widely but generally some degree of crampy abdominal pain, abdominal bloating, malabsorption and diarrhea is present. Blastocystis hominis is a protozoan of uncertain clinical significance. In one series it was identified in the stool in one-third of homosexual men. A heavy parasitic burden is probably responsible for an enteritis-like illness in some patients. The organism can usually be eliminated from the stool with Flagyl and this frequently leads to symptomatic improvement.

The high prevalence of these sexually transmitted venereal and enteric pathogens in the homosexual population is due primarily to exposure and sexual practices. There is no evidence for any specific defects in the intestinal immune system in homosexual men without AIDS (15). Specific antibiotic therapy is available for each of these infections as outlined in Table 1. Ciprofloxacin, a recently marketed fluoroquinolone, is highly active against all important bacterial causes of enterocolitis except C. difficile. Although there is not a great deal of clinical experience with ciprofloxacin in terms of side effects and the development of resistance, this antibiotic could become the drug of choice for many of these bacterial enteric pathogens.

TREATMENT REGIMENS FOR ENTERIC INFECTIONS COMMONLY SEEN IN HOMOSEXUAL MEN

Organism	Antibiotic(s)	Alternative(s)
Bacteria		
Campylobacter sp.	Erythromycin 250 mg 4 times daily for 5 days	Tetracycline, 250 mg 4 times daily for 5 days ciprofloxacin, 500 mg BID
Chlamydia trachomatis	Tetracycline, 500 mg 4 times daily for 7 days (Non LGV) or 21 days (LGV)	Erythromycin, 500 mg 4 times daily for 7 days (Non LGV) or 21 days (LGV)
Clostridium difficile	Vancomycin 125 mg 4 times daily	Metronidazole, 250 mg 4 times daily
Neisseria gonorrhea	Aqueous procaine penicillin G, 4,000,000 units IM (once) plus probenicid, 1 gm (once)	Spectinomycin, 2 gm IM
Salmonella sp.	Antibiotics only for severe or bacteremic cases	TMP/SMX; ampicillin, 1 gm 4 times daily; chloramphenicol 500 mg IV 4 times daily; ciprofloxacin, 500 mg BID
Shigella sp.	TMP/SMX	Ampicillin, 1 gm IV 4 times daily; Ciprofloxacin, 500 mg BID
Vibrio sp.	Doxycycline, 100 mg 2 times daily	Tetracycline, 500 mg 4 times daily; ciprofloxacin, 500 mg BID
Parasites		
Entamoeba histolytica	Metronidazole, 750 mg 3 times daily plus iodoquinol, 650 mg 3 times daily for 21 days	Tetracycline, 500 mg 4 times daily plus emetine hydrochloride, 1 mg/kg/ day IM for 5 days
Giardia lamblia	Metronidazole, 250 mg 3 times daily	Quinacrine hydrochloride, 100 mg 3 times daily
Blastocystis hominis	Metronidazole, 1-2 g/d	
Virus		
Herpes simplex	Acyclovir, 5 mg/kg IV 3 times daily or 1 tab PO 5 times daily	

Table 1

OPPORTUNISTIC INFECTIONS OF THE INTESTINE IN AIDS

In patients with AIDS, the spectrum of infections affecting the gastrointestinal tract becomes even more complex. In addition to infections of the gut caused by known enteric and venereal pathogens as discussed above, patients with AIDS are prone to truly opportunistic infections with organisms of very low virulence to the normal host (Fig. 5). Most prominent among these infections are candida, cryptosporidium, cytomegolovirus and atypical mycobacterium.

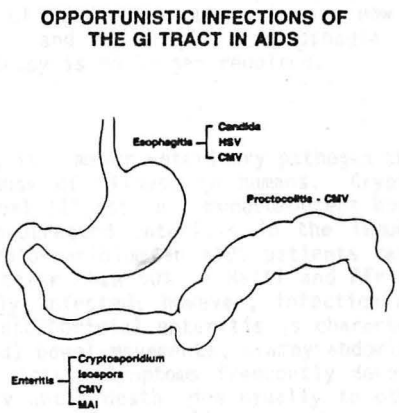


Fig. 5

Candida

Candida albicans is a frequent opportunistic infection in immunocompromised patients and oral candidiasis is almost universal in AIDS patients. Oral candidiasis, though not diagnostic of AIDS, has been shown to be a harbinger for the subsequent development of AIDS in patients at high risk. In one prospective study of high-risk patients with unexplained oral candidiasis, Kline et al. found that 59% of the these patients acquired a major opportunistic infection or secondary cancer at a median interval of 3 months (20). A fairly close association exists between oral and esophageal candidiasis in patients with AIDS. Most patients with oral candidiasis will also have esophageal candidiasis although many will be asymptomatic. On the other hand, the majority of patients with esophageal candidiasis will also have oral involvement. Dysphagia, odynophagia and retrosternal burning are the most common symptoms of esophageal candidiasis. Double contrast barium studies of the esophagus show mucosal edema in mild cases progressing to plaque formation and ultimately diffuse ulceration. Unfortunately, the radiographic appearance is not specific and can be mimicked by other lesions such as Herpes simplex, CMV or acid reflux esophagitis. Candidal esophagitis can be confirmed by endoscopy which typically shows white exudate overlying linear ulceration throughout the esophagus. Diagnosis is usually made on the basis of typical appearance and the presence of mycelia on brush cytology. Invasive mycelia may not always be seen on mucosal biopsies apparently due to sampling error. Candidal enteritis is rare in patients with AIDS with only 1 case being reported (22). This patient presented with watery diarrhea and oral and anal involvement with candidiasis. Bowel perforation and peritonitis subsequently developed and on autopsy extensive ulceration of the ileum, apparently due to candida, and multiple sites of perforation were noted.

Candidal esophagitis should be treated with Ketoconazole (200 mg BID). Symptoms usually respond satisfactorily although evidence for candidal esophagitis frequently persists at endoscopy even after 2 to 6 months of therapy. Short courses of amphotericin B at doses of 100 to 300 mg IV are recommended for refractory cases. Candidal esophagitis may fail to respond to ketoconazole for several reasons. Ketoconazole-resistant strains of Candida albicans have been reported (22). In addition, absorption of ketoconazole is

limited in the absence of gastric acid and many patients with AIDS are hypochlorhydric or are taking H_2-blockers. In terms of fulfilling the CDC criteria for AIDS, a presumptive diagnosis of candidal esophagitis can now be made in patients with oral candidiasis and dysphagia, odynophagia or retrosternal burning; documentation by endoscopy is no longer required.

Cryptosporidium

Cryptosporidium, a coccidial protozoan, is a major veterinary pathogen that only recently has been recognized as a cause of illness in humans. Cryptosporidium causes a mild self-limited diarrheal illness in immunocompetent hosts whereas it is associated with a severe, protracted enteritis in the immunocompromised (24). Prevalence rates for cryptosporidium in AIDS patients range from 1 to 20% in developed countries to greater than 50% in Haiti and Africa. The small intestine is usually most heavily infected; however, infection may extend from the pharynx to the rectum. Cryptosporidial enteritis is characterized by frequent and voluminous (1 to 17 l/d) bowel movements, crampy abdominal pain, nausea, vomiting and profound weight loss. Symptoms frequently develop insidiously and usually increase in severity until death, due usually to other opportunistic infections or secondary neoplasms. The organism does not appear to be invasive; consequently, blood and leukocytes are rarely seen in the stool. Intermediate forms of the parasite (2 to 6 μm in diameter) can be demonstrated on light and electron microscopy to be closely related to the surface of the intestinal mucosa and in some cases appear to be surrounded by an extension of enterocyte membrane. There is a varying degree of blunting and atrophy of the villi with hypertrophy of the crypts and a modest mononuclear infiltrate in the lamina propria. The pathogenesis of the severe diarrhea and weight loss in cryptosporidial enteritis is not completely understood. Severe malabsorption of lactose, d-xylose and triglyceride has been well documented in several patients (25,26) and probably contributes to the severe weight loss in these patients. In addition, malabsorption of carbohydrate may contribute to the watery diarrhea via osmotic mechanisms. For example, it can be estimated that if 10% of the average carbohydrate content of the American diet reached the colon (as sucrose or lactose), a load of 100 mOsm (capable of retaining ~ 300 ml of water) would be produced. Bacterial fermentation of these sugars to short chain fatty acids would stimulate an additional several-fold increase in stool water it the fatty acids were not absorbed by the colon. That this mechanism contributes to the diarrhea in patients with cryptosporidial enteritis is supported by the fact that these patients frequently have acidic stools with a large osmotic gap (osmolality of the stool cannot be accounted for by the concentration of Na^+, K^+ and accompanying anions) as would be expected with a fermentative osmotic diarrhea.

In many patients, however, large volume diarrhea (> 1 l/d) continues even when the patient is completely fasted and maintained on parenteral fluids. Fasting diarrhea of this magnitude indicates that net secretion of isosmotic fluid into the lumen of the bowel is occurring. Secretory diarrhea is usually associated with organisms capable of elaborating an enterotoxin. Such a mechanism has never been reported for cryptosporidium, however. How cryptosporidium produces such a severe functional derangement of the gut while neither invading the mucosa nor elaborating an enterotoxin remains to be determined.

In addition to the bowel, the hepatobiliary system may also be affected by cryptosporidium in patients with AIDS (27-29). These patients usually present

with right upper quadrant pain, nausea, vomiting and an elevated alkaline phosphatase. Radiologic findings include a thickened gallbladder wall or dilated bile ducts, often with strictures and luminal irregularities suggestive of sclerosing cholangitis. Cryptosporidial organisms have been found attached to the gallbladder epithelium in symptomatic patients undergoing cholecystectomy and have been recovered in bile obtained from T-tubes or at the time of ERCP. Cholecystectomy or endoscopic papillotomy (if a distal stricture associated with proximal dilatation is observed) has lead to resolution of symptoms and a decrease in the serum alkaline phosphatase in some cases although symptoms often recur. These findings are not specific for cryptosporidium since similar symptoms, laboratory findings and radiographic pictures have been observed in patients with CMV infection of the biliary tract. Biliary tract involvement may occur in up to 10% of patients with cryptosporidium and AIDS. Cryptosporidium may also involve the stomach and in one case produced a gastric outlet obstruction (30).

Diagnosis of cryptosporidial enteritis is usually based on identification of the organisms in stained stool smears. Many techniques for staining cryptosporidium have been described but a modified acid fast stain is most widely used. Because of the heavy parasitic load, direct examination of unconcentrated stool samples are usually positive in AIDS patients with severe diarrhea. Concentration techniques may be useful especially in evaluating formed stool specimens. Currently, there is no known effective therapy for cryptosporidial enteritis. In limited studies, spiramycin, an antiprotozoal drug was shown to be effective in several AIDS patients with cryptosporidium (31); however, subsequent experience has not confirmed these findings. Maintenance of fluid and electrolyte balance is of prime importance and may be accomplished with oral rehydration solutions containing glucose, sodium, bicarbonate and potassium. None of the non-specific antidiarrheal agents such as codeine, immodium and Lomotil have been consistently effective in decreasing the diarrhea in cryptosporidiosis. Furthermore, there have been some anicdotal reports of worsening of symptoms with these agents.

Isospora Belli

Isospora belli, another coccidial parasite, can also produce chronic diarrhea and malabsorption in patients with aids and is particularly common in Haiti and Africa (32,33). Isospora belli is a large organism that invades epithelial cells of the small intestine causing superficial lesions of the villi and destruction of the brush border. Mild peripheral eosinophillia is seen in ~ 50% of cases. Finding the cysts in the stool can be difficult even during periods of severe diarrhea. Recovery of cysts in the stool is enhanced by concentration techniques and acid-fast stains. The diagnosis is more easily made by examining duodenal contents using a duodenal string test (enterotest). In contrast to cryptosporidium, which is really not treatable, Isospora belli usually responds clinically to trimethoprim-sulfamethoxazole although symptoms frequently recur when therapy is discontinued.

Cytomegalovirus

CMV is a ubiquitous organism with seroprevalence rates of higher than 50% in the general population and virtually a 100% in homosexual men (34). Primary infection may be asymptomatic or may produce a mononucleosis-like illness. Following primary infection the virus usually establishes latency in which the

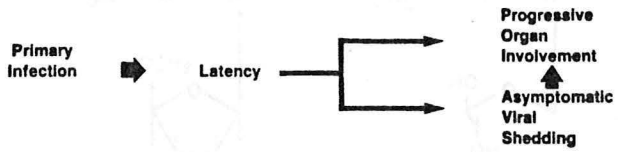
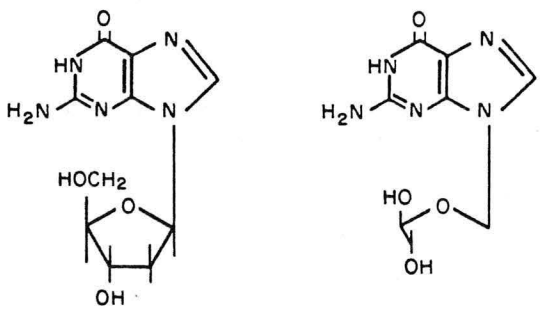


Fig. 6

viral genome is incorporated into host cells but no viral products are produced (Fig. 6). The latent virus may later reactivate and, in particular, immunosuppression commonly produces a change from latent to active infection. Subclinical infection is common in patients with AIDS as well as in healthy homosexual men. Indeed, CMV can be recovered from the saliva, urine, semen or blood in approximately 10% of homosexual men and in the majority of patients with AIDS (34-36).

In addition to asymptomatic shedding of virus, invasive infection of multiple organs including the gastrointestinal tract, eyes, lungs, CNS and adrenal glands may take place. In this case, severe progressive tissue damage occurs which, if not treated, leads to severe disability and death.

In patients with AIDS, CMV may affect the GI tract from the esophagus to the rectum (37-41). In the esophagus and stomach, CMV involvement is usually characterized by discrete ulcers, although diffuse edema and inflammation may also be seen. Esophageal involvement causes odynophagia, retrosternal burning or dysphagia which is indistinguishable clinically from candida, herpes or acid reflux esophagitis. Gastric involvement usually produces epigastric burning or pain. In the small intestine and colon CMV may produce discrete ulcerations or patchy areas of diffuse inflammation and ulceration resembling ulcerative colitis. Patients with CMV involvement of the small bowel and colon usually present with protracted diarrhea and weight loss but may have a severe hemorrhagic colitis or bowel perforation with peritonitis. Endoscopic biopsies of grossly inflammed or ulcerated tissue shows typical viral inclusions primarily in the endothelial cells, and an inflammatory infiltrate. Crypt abscesses, granulomas and lymphoid folicles are notably absent. CMV may induce a vasculitis that affects submucosal capillaries and arterioles resulting in thrombosis and ischemia. This vasculitis is only found in vessels directly infected with CMV and is usually in close association with large ulcers. Initially it was not clear as to whether CMV was a direct pathogen or simply a superinfection of devitalized tissues. In fact, typical CMV inclusions can sometimes be found in apparently completely normal mucosa. However, the finding of enlarged CMV infected endothelial cells in the mucosa and submucosa with frank CMV vasculitis and vessel occlusion along with overlying ulceration and hemorrhage is very strong evidence for the pathogenic potential of CMV. Furthermore, the recent finding of symptomatic improvement with specific antiviral treatment further supports the pathogenic role of CMV in these syndromes. Diagnosis of CMV bowel disease is made by demonstrating CMV inclusions in biopsy material obtained from inflammed or ulcerated mucosa. The



DEOXYGUANOSINE **GANCICLOVIR**

Fig. 7

finding of CMV inclusions histologically correlates very well with the ability to culture CMV from mucosal biopsies. Culturing CMV from stool specimens is not very helpful. Asymptomatic shedding of virus in the stool is common. On the other hand, CMV can be cultured from the stool less than half of the time in patients with CMV enteritis or colitis documented histopathologically.

In addition to involving the bowel, CMV has also been associated with granulomatous hepatitis, acalculous inflammatory disease of the biliary tree and pancreatitis (27,28,42-45).

Until recently, treatment for disseminated CMV infection has been lacking. However, during the past 2-3 years, gancyclovir (DHPG), an agent related to acyclovir, has been reported to show effectiveness (46-50). Gancyclovir is a nucleoside analog (Fig. 7) differing from acyclovir only by the addition of a terminal hydroxymethyl group (51). Gancyclovir is a prodrug that must first be converted intracellularly to gancyclovir triphosphate. Gancyclovir triphosphate competitively inhibits the binding of deoxyguanosine to DNA polymerase inhibiting DNA synthesis and also terminating DNA elongation. Gancyclovir appears to be phosphorylated approximately 10-fold more rapidly in virus infected cells than in uninfected cells affording some selectivity. Nevertheless the potential for suppression of rapidly proliferating cells, especially of the bone narrow and GI tract must be kept in mind. Gancyclovir is 10 to 100 times more active against CMV than is acyclovir.

No placebo controlled trials have been published regarding the efficacy of gancyclovir for CMV gastrointestinal disease. Nevertheless, several uncontrolled series indicate that the majority of patients experience a clinical response to gancyclovir therapy (46-50). Table 2 summarizes the results from the largest series published to date of the efficacy of gancyclovir for CMV gastrointestinal disease (49). In this study, patients received gancyclovir 5 mg/kg intravenously every 12 h for 14 days. The dose was reduced to 3 mg/kg every 12 h if the neutrophil count fell below 1,000 cells per mm^3. Overall, 18 of 41 patients had a complete clinical response defined as complete resolution of diarrhea, abdominal pain or dysphagia for at least 1 month. Thirty of the 41 patients had definite improvement in symptoms. Furthermore, many of the patients who did not respond were bedfast with multiple concurrent opportunistic

Table 2

(from reference 49)

CLINICAL RESPONSE TO GANCYCLOVIR IN 41 PATIENTS WITH AIDS

Site	Patients	Improved	Complete Response	No Response
Colon	31	23	11	8
Esophagus	5	4	4	1
Rectum	4	3	3	1
Small intestine	1	0	0	1
TOTAL	41	30	18	11

infections. Although no control group was included, previous experience indicates that documented invasive CMV involvement of the GI tract is a progressive disease and that 1 month remissions rarely, if ever, occur spontaneously. The major side effect in this study was neutropenia. Neutrophils fell below 1,000 per mm^3 in 5 of the 41 patients. Neutropenia was reversible within 1 week of discontinuing the drug and was not associated with bacterial sepsis. Relapse was common after cessation of the drug and it now appears that the majority of patients will relapse within 3 to 4 months unless maintenance gancyclovir therapy is given. Even less information is available regarding maintenance therapy. Preliminary information suggests that 5 mg/kg administered intravenously 5 days per week is effective in preventing relapse, although at this dose, the gradual development of neutropenia is common. Lower maintenance doses are associated with less neutropenia but higher recurrence rates.

Thus, although no randomized trials of the efficacy of gancyclovir in CMV intestinal disease have been reported, the existing data suggest that many patients will experience symptomatic improvement of dysphagia, abdominal pain or diarrhea. Because of the high relapse rate, most patients will require maintenance therapy. It is not known if such therapy will prolong survival. Furthermore, due to overlapping toxicities, AZT, which has been shown to prolong survival, cannot be taken during gancyclovir therapy. For these reasons, gancyclovir therapy should be reserved for disabling or life threatening gastrointestinal disease that has been documented histopathologically (49,52).

Many other nucleoside analogues have shown activity against human CMV in vitro but pharmacokinetic studies and therapeutic trials have yet to be performed. Another drug, trisodium phosphonoformate (foscarnet), has shown some efficacy in CMV retinitis (50). Foscarnet is a potent inhibitor of all human herpes virus DNA polymerases as well as retrovirus reverse transcriptase. The drug must be given intravenously since oral bioavailability is poor. Myelosuppression does not seem to be a problem with foscarnet therapy. The principle side effect is nephrotoxicity, which is usually reversible.

Herpes Simplex

Primary infection with Herpes simplex virus is a common cause of proctitis in homosexual men (8,9,19). Herpes infection may involve the perianal area,

anal canal and/or the distal 5-10 cm of rectum. Symptoms include pain, constipation and rectal discharge, sometimes bloody. In addition, neurological symptoms such as difficulty with micturation and pain and paresthesias in the distribution of the sacral roots may occur. In homosexual men without AIDS, the clinical course of anorectal herpes is usually self-limited, resolving in 2-3 weeks. Recurrences are frequent but are shorter in duration and less symptomatic. Treatment includes analgesics, stool softeners and sitz baths. Acyclovir is effective in shortening the duration of symptoms and in preventing recurrences. In patients with AIDS, HSV infection of the GI tract may disseminate and cause severe destructive mucocutaneous lesions. Ulcerations may occur around the mouth, in the esophagus and in the distal rectum and perianal area. The remainder of the bowel is rarely involved even in patients with AIDS. Involvement of the liver and pancreas is equally rare. Diagnosis of anorectal herpes is based on the typical appearance of herpetic vesicles or ulcerations and recovery of HSV from rectal swabs. Diagnosis of HSV esophagitis is based on histology and recovery of virus from mucosal biopsies.

Mycobacterium Avium-Intracellulare

Mycobacterium avium-intracellulare, an atypical mycobacterium, is a slow growing organism with relatively little virulence for the immunocompetent host. In patients with AIDS, however, disseminated infection may occur with involvement of lymph nodes, liver, spleen, bone narrow, brain and gut. In fact, in many series over half of AIDS patients coming to autopsy have severe disseminated MAI infection. MAI may colonize the urinary, respiratory or GI tract of AIDS patients without evidence of invasive disease; however, these patients frequently develop severe disseminated disease in subsequent months. Disseminated MAI is characterized by high grade, persistent bacteremia.

Involvement of the gastrointestinal tract usually results in diarrhea, malabsorption and weight loss. The duodenum and small intestine are most commonly involved. Patients may present with a clinical syndrome and histopathologic findings suggestive of Whipple's disease (53,54). In these patients endoscopy may show erythematous macular lesions or small erosions of the duodenum. Biopsy specimens show blunted villi with PAS positive, diastase-resistance macrophages throughout the lamina propria reminiscent of the appearance of Whipple's disease. However, acid-fast organisms can be found in macrophages and free in the lamina propria. By electron microscopy intact rod-shaped bacilli are seen within the cytoplasm of macrophages, whereas in Whipple's disease, the bacilli in mucosal macrophages usually show partial dissolution. MAI may also present with a clinical and radiologic picture resembling Crohn's disease. In one case, barium studies showed a nodular, ulcerated and narrowed terminal ileum. Over the subsequent few weeks the terminal ileal disease progressed to a complete bowel obstruction requiring surgical resection (55).

The liver is often involved in disseminated MAI. MAI infection of the liver is an infiltrating disease usually presenting with fever, hepatomegaly and elevated serum alkaline phosphatase levels. Biopsy usually shows small, poorly formed granulomas with numerous acid-fast bacilli.

There is presently no cure for MAI. When tested in vitro, MAI is highly resistant to most conventional antimycobacterial drugs including INH and rifampin (56). Ansamycin and clofazimine have shown some in vitro activity

against MAI isolates, but clinical experience with these drugs has generally been disappointing (56,57).

Other atypical mycobacterium such as Mycobacterium kansasaii have also produced disseminated infection with bowel involvement in endemic areas (58). In addition, disseminated tuberculosis caused by Mycobacterium tuberculosis is quite common in patients from Haiti and Africa and is often due to drug resistant organisms.

Enteric Bacteremia

Infections with enteric pathogens such as salmonella, shigella and campylobacter are common in homosexual men. Diarrhea caused by these organisms is usually self-limited, bacteremia is unusual and antibiotics are generally effective in eradicating the organisms. In patients with AIDS, however, infection with these organisms can lead to severe, protracted diarrhea accompanied by bacteremia. This is particularly true for salmonella. For example, in one study from San Francisco the annual incidence of non-typhoidal salmonellosis was found to be about 20-fold greater in men with AIDS than in men without AIDS (59). Furthermore, bacteremia was found in 45% of the AIDS patients but in only 9% of men without AIDS. Patients with AIDS had a more severe illness and the diarrhea and bacteremia frequently persisted or recurred despite prolonged antibiotic therapy. Similarly, shigella and campylobacter infections may be unusually severe and persistent with associated bacteremia in AIDS patients, requiring first intensive and then prolonged antibiotic therapy (60,61).

Idiopathic Diarrhea

Diarrhea, alone or in combination with generalized lymphadenopathy, fever and weight loss, may precede the diagnosis of AIDS by months and can remain a chronic debilitative problem throughout the course of the disease. In most patients with AIDS, an infectious or neoplastic cause for the diarrhea can be identified. In some patients with AIDS, however, there is no clear cause for the diarrhea despite aggressive attempts to identify pathogens. The term "AIDS enteropathy" was first used by Kotler et al. in describing 7 AIDS patients who had diarrhea and weight loss but no identifiable bacterial or parasitic infections (62). Malabsorption of d-xylase was found in all patients, and steatorrhea in most. Jejunal biopsy specimens revealed partial villus atrophy and crypt hyperplasia without evidence for MAI or CMV. Viral inclusions were seen in rectal biopsies from several patients, however, and it is possible that the diarrhea and malabsorption in these patients was actually due to CMV involvement of the bowel. In another study, among 72 patients referred for diarrhea, no identifiable cause could be found in 13 (63). Small bowel biopsies were normal or showed nonspecific mononuclear infiltrates. Triglyceride and d-xylose absorption was abnormal in those tested (8 of 13).

The cause of diarrhea in these patients is not known but is probably related to unidentified viral, bacterial or protozoan infections. For example, microsporidia have been found in patients with AIDS, who have diarrhea that after careful evaluation has been termed idiopathic (64). Microsporidia are tiny (1-2 μm) protozoan parasites that are easily missed on light microscopy of intestinal biopsies because of their small size, intracellular location and poor

staining. Microsporidia have not been identified in feces and although associated with diarrhea, have not been proven to cause diarrhea. There is no known treatment.

It is also possible that the HIV itself may play a role in the diarrhea and malabsorption commonly seen in AIDS. In one study, HIV was cultured from mucosal biopsy specimens from 2 out of 4 AIDS patients with chronic diarrhea of unknown cause (65). In addition, in-situ hybridization of biopsy specimens from the duodenum and rectum showed the presence of HIV-infected cells in both the epithelium of the crypts and the lamina propria in 5 of 10 additional patients. In the crypt epithelium, in-situ labeling of HIV RNA was greatest in argentaffin staining cells suggesting that enterochromaffin cells derived from the neural crest are among the target cells. (Labeling of the lamina propria probably reflects the presence of inflammatory cells including $CD4^+$ lymphocytes and macrophages.) These studies raise the possibility that HIV infection of intestinal neuroendocrine cells could give rise to disorders of intestinal motility and function and thus contribute to diarrhea in patients with AIDS.

Retrovirus-like particles have also been found in esophageal ulcers in HIV positive individuals. In one study, 12 homosexual men presented with a viral syndrome, macular-papular rash and severe odynophagia (66). In all patients tested, HIV serology was negative at the time of presentation but positive 2-14 weeks later indicating primary infection with HIV. Endoscopy revealed multiple discrete ulcers in all patients. Cultures, brush cytology and light microscopy of biopsy specimens showed no evidence for fungal, CMV or HSV infection. Biopsy specimens examined by electron microscopy, however, showed enveloped, virus-like particles exhibiting morphologic features consistent with retroviruses in the cytoplasm of esophageal epithelial cells.

NEOPLASMS ASSOCIATED WITH AIDS

The profound deficiency of cell-mediated immunity in patients with AIDS predisposes these individuals not only to a wide spectrum of opportunistic infections but also leads to conditions conducive to the development of secondary neoplasms (67). Although a number of neoplasms have been reported in AIDS patients, approximately 95% of the malignancies are either Kaposi's sarcoma or non-Hodgkin's malignant lymphoma.

Kaposi's Sarcoma

Kaposi's sarcoma, a neoplasm with an incidence of 0.02% in the general population and approximately 5% in transplant patients, is the malignancy most commonly seen in AIDS patients and eventually develops in about 40% of patients. In the general population Kaposi's sarcoma is generally seen in elderly men and follows an indolent course with a mean survival of 10-13 years after diagnosis (68). Kaposi's sarcoma in AIDS patients is much more aggressive with widespread cutaneous involvement and a high incidence of visceral disease.

Endoscopic studies have demonstrated typical Kaposi's sarcoma lesions in 40% of patients with known skin or lymph node involvement. Endoscopic evidence of Kaposi's sarcoma is associated with increased mortality. The gastrointestinal tract may be involved from the esophagus to the rectum. At endoscopy several types of lesions may be seen (64). Most common are small

(less than 5 mm in diameter) reddish-purplish lesions with minimal elevation from the surface. Nodular lesions, which may have central ulcerations, are also common. Diffuse involvement of the colon reminiscent of ulcerative colitis has also been described (70,71). Biopsy of Kaposi's sarcoma lesions is safe but the yield is low due to the submucosal location of these tumors.

The bowel lesions are usually asymptomatic; however, a wide variety of complications have been reported, sometimes in patients with no visible skin lesions. The most frequent manifestation is gastrointestinal blood loss which is usually occult but may be massive. Less common manifestations include diarrhea, malabsorption, protein losing enteropathy, toxic megacolon, intestinal obstruction, intussusception, and bowel perforation (72-75). Some of these complications require surgical intervention.

Therapy for progressive Kaposi's sarcoma includes radiotherapy, chemotherapy or interferon therapy depending on the overall clinical presentation of the patient (73,74). The use of cytotoxic chemotherapy in the treatment of AIDS-related Kaposi's sarcoma is complicated by the underlying immune deficiency. Nevertheless, excellent responses have been seen with tolerable single agent regimens with vinblastine, vincristine, doxrubicin or etoposide. Aggressive combination chemotherapy is generally toxic and not clearly superior to single agent therapy. An alternating regimen of vincristine and vinblastine may diminish the toxicity of each without compromising overall efficacy. Trials of high dose recombinant α-2 interferon have shown response rates of 30-50% or higher in patients without a history of opportunistic infections. Remission can usually be sustained during maintenance therapy administered 3 days per week.

Lymphomas Associated with AIDS

An increased incidence of non-Hodgkin's lymphoma has been recognized in patients with AIDS, particularly those with preceding lymphadenopathy syndrome (65,78,79). In fact, approximately 4 to 10% of AIDS patients have been diagnosed with non-Hodgkin's lymphomas. These tumors are predominately of the high-grade B-cell type and frequently present in extranodal locations. An increased incidence of lymphomas has previously been recognized in patients with inherited or iatrogenic immunodeficiency. For example, between 2% and 13% of renal transplant recipients develop a secondary neoplasm at a mean interval of 3 years from the onset of immunosuppression and about one-third of these tumors are high grade B-cell non-Hodgkin's lymphomas.

In a multicenter study, Ziegler et al. described the clinical features of 90 homosexual men with non-Hodgkin's lymphoma (78). At the time the lymphomas were diagnosed, all but two men were found to have extranodal disease including 38 in the CNS, 30 in bone marrow, 15 in the bowel, and 8 in the liver. Several patients had involvement of more than one extranodal site. Histologically, 62% had high-grade lymphomas, primarily large cell immunoblastic (diffuse histiocytic) and small non-cleaved cell Burkitt's-like lymphoma (diffuse undifferentiated); 29% had intermediate-grade malignant lymphomas, primarily diffuse large-cell lymphoma (diffuse histiocytic lymphoma). In a smaller series of 18 patients with non-Hodgkin's lymphoma (79), 4 presented with primary CNS disease and 6 with primary bowel involvement (1 stomach, 3 small intestine and 1 colon). Again, all lymphomas were high-grade B-cell lymphomas. In both series patients were treated with multi-drug chemotherapy. The most commonly used

DIFFERENTIAL DIAGNOSIS OF DIARRHEA IN AIDS

1. Bacterial: salmonella, shigella, campylobacter, chlamydia, C. difficile, MAI
2. Protozoan: cryptosporidium, isospora, giardia, amoeba, blastocystis
3. Viral: CMV
4. Neoplasms: Kaposi's sarcoma, lymphoma
5. Idiopathic: "AIDS enteropathy"

Fig. 8

regimens were CHOP (cyclophosphamide, doxrubicin, oncovin and prednisone) with or without methyltrexate and/or bleomycin. In general, the response to treatment, and survival were poor relative to treatment results in historical controls with similar histologic subtypes of lymphoma.

Initial presentation in bowel or liver is seen in 17-28% of those AIDS patients with non-Hodgkin's lymphoma. A number of patients have been reported who presented initially with small bowel obstruction or bowel perforation that on exploration was found to be due to intestinal lymphoma (79-81). There are also many case reports of patients with anorectal symptoms found to be due to large primary lymphomas of the rectum. In some cases, staging revealed no other evidence of tumor. Local radiation therapy may give symptomatic relief for these rectal lymphomas (82-84).

Thus, the non-Hodgkin's lymphomas observed in AIDS patients have been unusual in several important respects. First, the tumors are frequently extranodal at presentation and often primary to the brain and GI tract. Second, the vast majority of AIDS-related lymphomas are high-grade B-cell lymphomas which ordinarily comprise only 1 to 2% of all cases of spontaneous non-Hodgkin's lymphomas in the U.S. Third, response to chemotherapy and survival is poor relative to historical controls even when histology and stage of disease is taken into account.

EVALUATION OF GASTROINTESTINAL SYMPTOMS IN AIDS

Diarrhea

Diarrhea is the most common GI symptom in patients with AIDS. The differential diagnosis of diarrhea in these patients is wide as illustrated in Fig. 8. Two recent reports deal with the relative importance of these various infections and neoplasms in causing diarrhea in patients with AIDS. Table 3 shows the frequency with which various enteric pathogens were recovered from stool and rectal swabs in AIDS patients from the Baltimore area being followed at Johns Hopkins University (85). In patients with diarrhea, cryptosporidium was the most common organism identified. Furthermore, cryptosporidium was seen

Table 3

(from reference 85)

RECOVERY OF ENTERIC PATHOGENS IN STOOL

Organism	AIDS with Diarrhea (n=49)	AIDS without Diarrhea (n=28)
	N (%)	N (%)
Cryptosporidium	7/45 (16)	0/19
Campylobacter	5/47 (11)	2/24 (8)
Chlamydia	5/44 (11)	2/16 (13)
Shigella	2/41 (5)	0/20
Giardia	2/45 (4)	1/19 (5)
Vibrio parahemolyticus	2/47 (4)	0/26
Isospora belli	1/45 (2)	0/19

only in AIDS patients with diarrhea and was never recovered from patients without diarrhea. A number of other organisms including campylobacter, chlamydia, C. difficile, shigella, giardia, V. parahemolyticus, and isospora were also encountered though less frequently than cryptosporidium. Several of these organisms were seen as frequently in AIDS patients without diarrhea as in AIDS patients with diarrhea. Nevertheless, it seems clear that these known pathogens do cause diarrhea since eradication of the organism by specific antimicrobial therapy usually leads to resolution of symptoms. How an organism can be asymptomatic in one person and cause disease in another is not known but may be related to host factors, virulence factors acquired by the organism or simply to a quantitative phenomena where mild infection is asymptomatic while more extensive infection causes diarrhea. In all, approximately half of the patients had some recognized enteric pathogen recovered from the stool or rectal swabs.

In addition to these known enteric pathogens, a number of other organisms of uncertain significance were recovered from the stool (Table 4) including candida, CMV, Herpes simplex, MAI and Blastocystis hominis. Stool cultures for candida are not helpful clinically since the finding of candida in the stool usually reflects oral or esophageal candidiasis; candidal enteritis or colitis is rare. Similarly, the recovery of CMV from the stool is of questionable clinical significance since this may indicate invasive CMV bowel disease or simply asymptomatic viral shedding. The recovery of Herpes simplex from stool or rectal swabs is also of doubtful significance with respect to diarrhea since anorectal herpes is usually (~ 80% of the time) associated with constipation rather than diarrhea. On the other hand, the recovery of MAI from the stool almost always signifies invasive bowel involvement or disseminated disease. The finding of large numbers of Blastocystis hominis organisms in the stool is also significant in that these patients will usually respond to therapy with Flagyl.

In another recent study, 20 selected patients with AIDS and diarrhea being followed at the NIH underwent an extensive diagnostic evaluation that included microbiologic studies of the stool, as well as endoscopy and colonoscopy with

Table 4

(from reference 85)

ORGANISMS OF UNCERTAIN SIGNIFICANCE IN STOOL

Organism	AIDS with Diarrhea (n=49)	AIDS without Diarrhea (n=28)
	N (%)	N (%)
Candida	20/38 (53)	4/17 (24)
CMV	9/34 (27)	2/13 (15)
HSV	7/38 (18)	8/20 (40)
Blastocystis hominis	7/44 (15)	3/19 (16)
Mycobacterium	1/44 (2)	0/19

Table 5

(from reference 86)

DIAGNOSTIC FINDINGS IN 20 PATIENTS WITH AIDS AND DIARRHEA

Diagnosis	Cases
	n(%)
One or more pathogenic process	17(85)
Cytomegalovirus enteritis, colitis, or both	9(45)
Entamoeba histolytica	5(25)
Cryptosporidium	3(15)
Salmonella typhimurium	3(15)
Giardia lamblia	3(15)
Campylobacter jejuni	2(10)
Salmonella flexneri	2(10)
Mycobacterium avium-intracellulare	1(5)
Herpes simplex	1(5)
Kaposi sarcoma	1(5)
No pathogens	3(15)
Total	20(100)

biopsies for pathology and cultures (86). The diagnostic findings in these 20 patients with AIDS and diarrhea are illustrated in Table 5. Overall a specific diagnosis could be made in 17 of the 20 patients. CMV enteritis, colitis or both was documented by endoscopy or colonoscopy in 9 of the 20 patients. The next most frequently identified intestinal pathogen was E. histolytica (5 patients), followed by cryptosporidium, salmonella and Giardia (3 patients each), campylobacter and shigella (2 patients each), and MAI (1 patient). One patient had circumferential Kaposi's sarcoma throughout the proximal small bowel. Duodenal aspirates showed no evidence for bacterial overgrowth in these patients. The high incidence of CMV GI disease in this series may reflect selection bias or simply the the fact that all patients underwent endoscopy and colonoscopy.

Thus, from these studies it appears that a specific infection can be diagnosed by stool studies alone in about 50% of AIDS patients with diarrhea. About half of these infections are treatable. Definitive diagnosis of invasive CMV, MAI or neoplastic involvement of the bowel generally requires endoscopic procedures with biopsies for histopathology.

An algorithm for evaluating AIDS patients with diarrhea is presented in Figs. 9-11. In evaluating AIDS patients with diarrhea (Fig. 9), the history and physical examination are not specific for any single diagnosis but may aid in localizing the problem to a particular region of the bowel. Unfortunately, opportunistic infections frequently affect more than one region of the bowel and, in addition, infection with multiple organisms is common. Thus, all patients with significant diarrhea should have fresh stool specimens sent for fecal leukocytes, O&P, bacterial cultures including salmonella, shigella and campylobacter and AFB smears looking for cryptosporidium and isospora. If prominent anorectal symptoms are present, rectal swabs for gonorrhea, Herpes simplex and chlamydia, as well as syphilis serologies, should be obtained. Based on these studies specific antimicrobial therapy is given when available. Empiric antibiotic therapy may be indicated if acute bacterial colitis is suspected (acute onset of small volume bloody diarrhea with lower abdominal cramps and fever). In this case a fluoroquinolone such as ciprofloxacin is a good choice while awaiting bacterial cultures since it covers salmonella and shigella as well as campylobacter and all other enteric bacterial pathogens except C. difficile. Blood cultures prior to starting antibiotics are useful since if enteric bacteremia is documented, the patient will almost certainly require long-term antibiotics to prevent relapse.

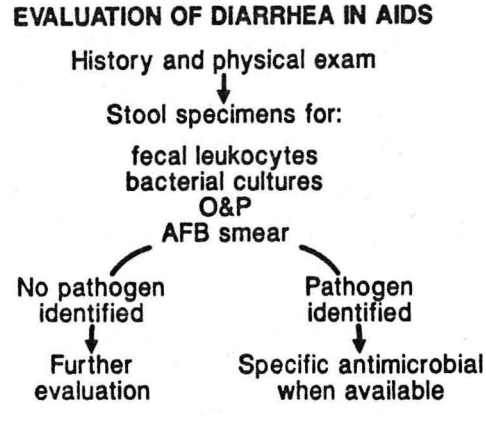


Fig. 9

If no enteric pathogen is recovered on initial stool studies or if the diarrhea persists after specific therapy, further evaluation can be undertaken as outlined in Fig. 10 and 11. Watery diarrhea without tenesmus, blood or leukocytes (Fig. 10) suggests

an enteritis caused by noninvasive organisms such as giardia or cryptosporidium. Accordingly, the stool should be reexamined for O&P including AFB smears for cryptosporidium and isospora. In addition, stool cultures for those bacterial pathogens that may occasionally cause an enteritis in patients with AIDS (V. parahemolyticus, Yersinia enterocolitica, salmonella and aeromonas) should be considered. If no treatable organism is recovered, attention should be focused on supportive care. Some patients, especially those with cryptosporidiosis, may have several liters of stool per day and this cholera-like state would obviously be fatal if not for the ability to replace fluid and electrolytes on an around-the-clock basis with rehydration solutions containing sodium, glucose, potassium and bicarbonate. Aside from fluid and nutritional supplements, a number of therapeutic trials may be of benefit. Since Giardia is a common and treatable cause of enteritis and may be missed on stool examinations, a therapeutic trial of Flagyl is usually indicated. Nonspecific antidiarrheals such as lomotil are also usually given and may or may not be helpful. Patients with enteritis are generally intolerant of lactose and all patients should be tried on a lactose-free diet. A few patients may have pancreatic insufficiency and if gross steatorrhea is present, a trial of pancreatic enzymes may be indicated. Finally, a few patients with severe secretory diarrhea have had an apparent clinical response to prostaglandin synthesis inhibitors such as indomethacin or naproxen.

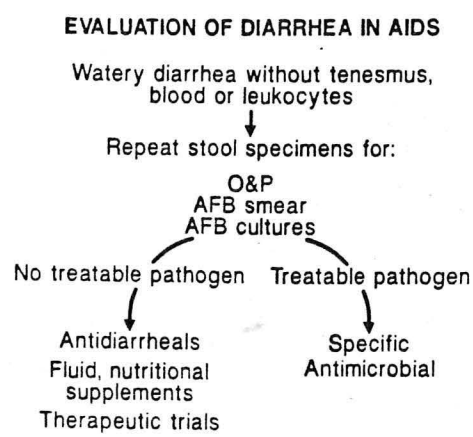


Fig. 10

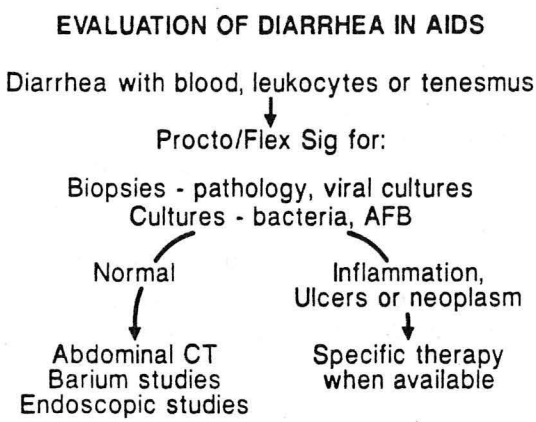


Fig. 11

Patients with tenesmus, or with fecal blood or leukocytes should be further evaluated with proctoscopy or flexible sigmoidoscopy (Fig. 11). Areas of inflammation or ulceration should be biopsied for pathology and viral cultures. Further stool specimens should be sent for bacterial cultures, O&P and AFB cultures. If inflammation or ulceration is seen at proctoscopy, a specific

diagnosis can be made in nearly every case and therapy administered if available. In some cases, proctoscopy will be normal despite the presence of blood and/or leukocytes in the stool indicating that an invasive infection or neoplasm is involving the bowel proximal to reach of the sigmoidoscope. CMV, MAI, Kaposi's sarcoma or intestinal lymphoma are the most likely possibilities and further investigation can be undertaken if differentiating between these etiologies would affect management. At this point, an abdominal CT scan is often very helpful at directing subsequent evaluation. Thickening of the bowel wall indicating inflammation, and even ulcers or tumors may be seen by CT. In addition, mesenteric or retroperitoneal lymphadenopathy may be observed. Lymph nodes greater than 1.5 to 2 cm in diameter almost always indicate involvement with MAI, lymphoma or Kaposi's sarcoma and differentiation can be made by CT guided fine needle aspirate. Depending on the results of the CT scan further evaluation of the GI tract using endoscopic or barium studies can be considered.

Odynophagia/Dysphagia/Retrosternal Burning

The differential diagnosis of odynophagia/dysphagia in patients with AIDS includes candida, cytomegalovirus, Herpes simplex, MAI, neoplasms, and non-AIDS esophageal diseases such as reflux esophagitis (Fig. 12). By far the most common cause of esophageal symptoms in patients with AIDS is candida esophagitis. Accordingly, a practical approach to odynophagia/dysphagia in patients with AIDS is to treat all patients with ketoconazole 200 mg/BID. Endoscopy would be reserved for those patients who do not respond symptomatically in 7 to 10 days. At endoscopy multiple biopsies should be taken for pathology and for viral cultures, and brush cytology should be obtained to look for candida.

ODYNOPHAGIA/DYSPHAGIA/ RETROSTERNAL BURNING

1. Differential diagnoses
   - Candida, HSV, CMV, neoplasm, MAI, non-AIDS esophageal disease
2. Evaluation/Treatment
   - Ketoconazole (200 mg bid)
   - Endoscopy if no response in 7-10 d
     Biopsies for histology and viral cultures
     Brush cytology

Fig. 12

Jaundice/RUQ Pain/Hepatomegaly

Mild elevations in serum alkaline phosphatase or in the hepatic aminotransferase levels are very common in patients with AIDS and if asymptomatic are usually not investigated. Jaundice, or a progressively rising alkaline phosphatase, especially if associated with RUQ pain should be evaluated. Jaundice and/or RUQ pain may be due to hepatic parenchymal disease or to biliary tract disease. In patients with AIDS, the liver is frequently involved with disseminated infections and neoplasms. In addition, virtually all AIDS patients are taking one or more potentially hepatotoxic drugs. Three groups have recently reported their experience with liver biopsies in patients with AIDS and hepatobiliary symptoms (44,45,87). Table 6 shows the histopathologic findings found on 26 percutaneous liver biopsies performed in AIDS patients at the San Francisco General Hospital over a 4-year period (87). Biopsies were performed primarily for abnormal liver function studies, hepatomegaly or unexplained

fever. Nonspecific changes including macrovesicular fat and mild portal inflammation were the most common findings. Poorly formed granulomas were noted in 10 of the 26 patients; acid-fast bacilli were demonstrated in 8 of these biopsies and CMV in 2. (Other less common causes of hepatic granulomas not seen in this series include M. tuberculosis, histoplasmosis, cryptococcus, toxoplasmosis and drug reactions.) Non-Hodgkin's lymphoma was found on two biopsies. Only 1 of the 26 biopsies was histologically normal. Overall, a specific diagnosis was made on 12 of the 26 biopsies (8 with MAI, 2 with CMV and 2 with lymphoma). In terms of patient management, however, in only two patients was a diagnosis made that had not previously been made by other means. An autopsy series from the same institution confirms the fact that opportunistic infections and neoplasms frequently involve the liver but that the liver is rarely the only site of involvement (Table 7). Thus, the usefulness of liver biopsy in directing the management of AIDS patients is very limited.

Table 6

(from reference 86)

HEPATIC HISTOLOGY AND PATHOLOGY IN AIDS

Finding	n=26
Normal	1
Portal inflammation	14
Steatosis	10
Granulomas	10
Fibrosis/cirrhosis	4
Specific infection	10
Lymphoma	2
Diagnosis not previously made by other means	2

Table 7

(from reference 87)

INTRAHEPATIC INVOLVEMENT WITH COMMON PATHOGENS AND NEOPLASMS AT AUTOPSY

	Intrahepatic Involvement	Intrahepatic Only
MAI	5/12	1/12
KS	11/32	0/32
CMV	6/26	0/26
Lymphoma	7/7	1/7

Biliary disease is much less common than hepatic parenchymal disease but may require specific therapy. Acalculous cholecystitis in association with CMV, cryptosporidium or campylobacter infection of the gallbladder has been reported in several patients (27,29). Patients present with prominent RUQ pain and tenderness and on ultrasound or CT of the abdomen are found to have a dilated thick-wall gallbladder which is usually nonfilling by OCG or HIDA scan. In addition, some patients may present with clinical, biochemical and radiological features of sclerosing cholangitis with or without papillary stenosis. Eight such cases were recently reported from the San Francisco General Hospital (28). All patients presented with prominent RUQ pain and marked elevations of serum alkaline phosphatase levels. Abdominal ultrasound showed a dilated common bile duct in all cases and ERCP showed irregularities and beading of the bile ducts

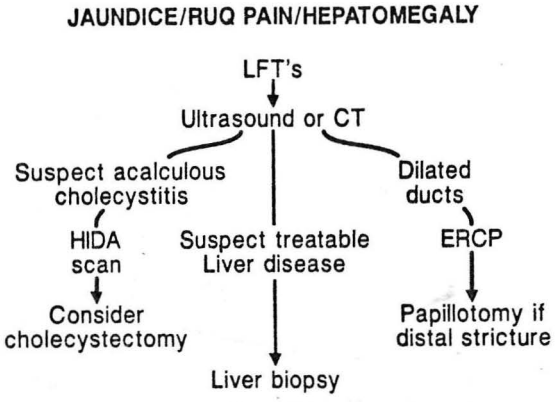


Fig. 13

with distal obstruction. Endoscopic papillotomy was performed in all patients leading to prompt resolution of clinical symptoms. Biliary infection with CMV or cryptosporidium can be documented in most of these cases and superimposed bacterial cholangitis may occur.

Hepatobiliary symptoms are usually investigated as outlined in Fig. 13. Liver function tests are nonspecific, although a very high serum alkaline phosphatase level suggests MAI involvement of the liver or extrahepatic obstruction. Abdominal ultrasound or CT should be obtained to evaluate the gallbladder, bile ducts and hepatic parenchyma. Acalculous cholecystitis is suggested by a dilated thick-wall gallbladder and if the clinical presentation is consistent, cholecystectomy should be considered since progression to gangrenous cholecystitis and perforation may occur. If the ultrasound or CT scan shows a dilated common bile duct, an ERCP should be considered and a papillotomy performed if distal obstruction is demonstrated. A liver biopsy may occasionally be helpful if undiagnosed, treatable liver disease is suspected.

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