Endoscopy in acquired immunodeficiency syndrome patients with diarrhea and negative stool studies

Shu-Chen Wei, MD, Chien-Ching Hung, MD, Mao-Yuan Chen, MD, Cheng-Yi Wang, MD, PhD, Che-Yen Chuang, MD, PhD, Jau-Min Wong, MD, PhD

Taipei, Taiwan

Background: Diarrhea is a frequent gastrointestinal symptom in patients with acquired immunodeficiency syndrome (AIDS) and is a major source of morbidity and mortality. A stepwise diagnostic approach is often recommended to search for treatable causes. However, whether the stepwise diagnostic approach is adequate for planning treatment and whether specific treatment for infectious etiologies will affect the survival of patients with AIDS remain unknown.

Methods: From March 1996 to September 1997, endoscopy was performed in AIDS patients with diarrhea, the etiology of which was not identified by noninvasive methods. Specific treatment was given according to the identified etiologies and symptomatic treatment was given for those without definite diagnosis. The clinical symptoms, signs, and duration of follow-up were recorded and survival patterns were analyzed.

Results: Etiologic diagnoses were made in 26 of 40 patients (65%) who underwent endoscopic studies. Amebic colitis and cytomegalovirus colitis were the 2 leading causes of prolonged diarrhea in patients with AIDS. Thirty-five patients (87.5%) recovered after treatment. The difference in survival time after diarrhea between patients whose symptoms resolved after treatment and those who continued to have diarrhea was statistically significant ($p < 0.001$).

Conclusions: Endoscopic studies were helpful for the diagnosis of prolonged diarrhea in AIDS patients who had negative stool studies and did not respond to 2 weeks of empiric treatment. Specific treatment according to the results of endoscopy may improve survival in these patients. (Gastrointest Endosc 2000;51:427-32.)

Two thirds of patients with acquired immunodeficiency syndrome (AIDS) develop diarrhea at some time during the course of their illness.¹⁻³ Diarrhea itself is a cause of major morbidity and may contribute to the death of these patients. Infectious etiologies account for 30% to 80% of the diarrhea in patients with AIDS and the chance of finding an infectious agent depends on patient characteristics and extent of evaluation.⁴⁻⁹ As with other clinical syndromes in AIDS, the approach to the patient with diarrhea is oriented toward diagnosing treatable causes and avoiding unnecessary invasive procedures. In clinical practice a stepwise diagnostic approach is often recommended in which less invasive investigations are used first (stool analysis), and more invasive tests (endoscopy with biopsy) are

reserved for patients in whom a pathogen is not identified by stool examinations or those who fail to respond to treatment of symptoms.¹⁰⁻¹⁵ However, it is not clear whether endoscopy with other associated studies will influence the survival of these patients. Therefore, this study was designed to determine how often an identifiable pathogen can be recognized by endoscopy in AIDS patients in whom stool analysis has been negative, and the impact that specific therapy might have on the outcome for these patients.^{11,15}

PATIENTS AND METHODS

A 9-bed AIDS unit was established on June 24, 1994, at our university hospital. It has since become the largest referral center for the management of complications associated with human immunodeficiency virus (HIV) infection in Taiwan. As of December 31, 1997, there were 390 admissions for 210 HIV-infected patients, the great majority being patients with advanced HIV infection, for the management of HIV-related complications. Before mid-April 1997, patients were treated with two non-nucleotide reverse transcriptase inhibitors (zidovudine, dideoxycytidine, or didanosine). Protease inhibitors (indinavir, ritonavir, hard-gel saquinavir) were not available until mid-April 1997. Since then, protease inhibitors were freely provided to all HIV-infected patients at any stage of infection. For those patients with CD4 lymphocyte counts less than 200/mm³ or previous episodes of pneumocystosis,

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From the Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.

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Reprint requests: Jau-Min Wong, MD, Associate Professor, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan, R.O.C.

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Table 1. Clinical characteristics of the 40 HIV-infected patients with diarrhea and negative stool studies

Clinical characteristics	Number
Gender (M/F)	37/3
Age (yr, mean) (range)	36 (21-64)
Routes of transmission	
Homosexual	13
Heterosexual	23
Bisexual	4
Intravenous drug use	5
Duration of anti-HIV (+) to diarrhea (mo)*	31.9 ± 33.4 (0-132)
Duration of postendoscopy follow-up (mo)*	9.0 ± 6.4 (1-24)
Serum albumin (g/dL)*	3.2 ± 0.7 (1.7-4.5)
CD4 (μL)*	75 ± 143 (1-794)
Recovery from diarrhea after treatment	35/40
Recurrence of diarrhea	13/35

*Values are expressed as mean ± standard deviation (range).

trimethoprim-sulfamethoxazole was given for primary or secondary prophylaxis. Rifabutin and newer macrolides were not routinely given for primary prophylaxis against *Mycobacterium avium* complex disease, and ganciclovir was not given for cytomegalovirus (CMV) disease.

Inclusion criteria

From March 1, 1996, to September 30, 1997, AIDS patients who had diarrhea had stool studies repeated 3 times at first. The studies included staining (wet mount, gram stain and modified acid fast stain) and cultures (cultures for *Campylobacter*, *Salmonella*, *Shigella*, and *Yersinia* species and *Clostridium difficile*). One stool specimen was obtained routinely from each patient for determination of *C difficile* toxin A by immunoassay. Diarrhea was defined as the presence of at least 3 liquid bowel movements per day. The patients whose stool examinations were nondiagnostic and those who did not respond to 2 weeks of antidiarrheal medications (albumin tannate, loperamide) were included in this study. Endoscopy was performed to search for the possible etiologies.

Endoscopy

For colonoscopy, patients were prepared with oral magnesium citrate solution and bisacodyl. Meperidine and hyoscine butylbromide were given before the procedure. The examiner and assistant wore masks, eyeglasses and gowns. The endoscope was disinfected using a standard procedure. Multiple biopsies from the gut lesions were obtained. Biopsies were obtained randomly if no lesions were visualized. The specimens were submitted for cultures of viruses, fungi and mycobacteria, and histopathologic studies. For the latter, stains used included hematoxylin-eosin, Gomori-methenamine silver, Ziehl-Neelson, and modified acid fast stain. Immunohistochemical staining for CMV was routinely performed whether or not intranuclear or intracytoplasmic inclusion bodies were present. EGD was performed if the colonoscopy did not define the etiology for diarrhea. The rules for obtaining biopsies and manipulation of the specimens were the same as those for colon-

Table 2. Final diagnoses in 40 HIV-infected patients with diarrhea and negative stool studies

Diagnosis	Number
Made by colonoscopy and biopsy:	n = 21
CMV colitis	6
Amebic colitis	4
Mixed amebic and CMV colitis	2
<i>C difficile</i> -associated disease	1
Cryptosporidiosis	1
<i>Histoplasma capsulatum</i> colitis	1
Lymphoma	1
Kaposi's sarcoma	1
<i>Penicillium marneffe</i> colitis	1
Mixed <i>P marneffe</i> and CMV colitis	1
Tuberculous colitis	1
<i>Candida</i> -related colitis	1
Made by colonoscopy, abdominal sonography and operation:	n = 1
Appendiceal abscess	1
Made by colonoscopy, subsequent stool study and antibiotic treatment:	n = 1
Nontyphoid <i>Salmonella</i> colitis	1
Made by colonoscopy and adjustment of antibiotics:	n = 3
Antibiotic-related colitis and diarrhea	3
Unknown etiology after all studies	n = 14

oscopy. For random biopsies sites sampled were the gastric body, antrum and proximal duodenum. Oral lidocaine for local anesthesia, intramuscular injection of meperidine and hyoscine butylbromide were given before EGD.

Treatment

Specific therapy was administered when an etiology was identified. Amebic colitis was treated with orally administered metronidazole 500 mg every 8 hours for 10 days, followed by iodoquinone 650 mg 3 times per day for 21 days. CMV colitis was diagnosed only when there were changes of colitis by endoscopy and the inclusion body identified by histopathologic study. CMV colitis was treated with intravenous ganciclovir 5 mg/kg twice per day for 2 to 3 weeks, followed by 5 mg/kg once per day as maintenance therapy. For tuberculous colitis, 4-drug combined antituberculous therapy (isoniazid, rifampin, ethambutol, and pyrazinamide) was continued for 2 months, followed by 7 months of 3-drug combined therapy (isoniazid, rifampin, and ethambutol). Amphotericin B was administered at a daily dose of 0.7 to 1.0 mg/kg for those patients with invasive fungal colitis, followed by itraconazole (400 mg/d) or fluconazole (400 mg/d).

Follow-up and statistical analysis

Duration of time required for recovery was recorded as from the date of the colonoscopy to that of resolution of diarrhea. After discharge, patients were regularly followed in our outpatient department by two of the investigators (C-C.H., M-Y.C.). The duration of survival of our patients was censored at the date of last follow-up or the date of death. The postendoscopy follow-up period was defined as from the date of colonoscopy to the date of last

Table 3. Comparison between dead and surviving patients

	Dead (n = 7)	Surviving (n = 33)	p Value
Age (yr)*	34.0 ± 5.6	36.5 ± 9.4	0.676
Albumin (g/dL)*	2.7 ± 0.4	3.3 ± 0.7	0.022
CD4 (μL)*	26.6 ± 52.0	85.4 ± 154.3	0.277
Anti-HIV (+) noted for (mo)*	42.9 ± 36.6	29.5 ± 32.8	0.192
Gender (M/F)	7/0	30/3	0.552
Anal sexual practice	3	20	0.326
Recovery	3	32	0.002
Duration needed for recovery (days)*	9.6 ± 9.4	8.5 ± 4.7	0.577
Recurrence	2	11	0.592
Follow-up period (mo)*	4.7 ± 6.9	10.0 ± 6.0	0.013

*Values are expressed as mean ± standard deviation.

follow-up or the date on which the patient died. To analyze the benefits of treatment, the patients were divided into 3 groups. Group A included patients with a definitive diagnosis in whom appropriate treatment could be administered. Group B included patients with a definitive diagnosis in whom treatment was less than fully effective. Group C included patients without a definitive diagnosis who received only treatment for control of symptoms. Student *t* test and ANOVA were used for the comparison of continuous variables. Fisher exact test was used for comparing the categorical variables. Cox regression and Kaplan-Meier methods were used for the survival analysis.

RESULTS

A total of 40 patients were enrolled (Table 1). Six had been treated with 2 non-nucleoside reverse transcriptase inhibitors and 1 protease inhibitor for a median duration of 8 weeks (range 3 to 20 weeks) before endoscopy. Seven patients died during the follow-up period, 5 of respiratory failure and 2 of multiple organ failure. The final diagnosis and method of diagnosis are summarized in Table 2. Among the 14 patients with chronic diarrhea of unknown etiology, 9 had nonspecific colitis and 5 had no abnormal findings at colonoscopy. Randomly obtained biopsies from the patients with no colonoscopic findings did not provide more information for diagnosis. EGD was performed in 18 patients without diagnostic lesions at colonoscopy. Only the patient with lymphoma had gastric and duodenal lesions, which were confirmed by histopathologic study. The others had no positive finding or gastritis at EGD. Randomly obtained biopsies did not provide diagnostic information.

Of the 22 patients who had diagnostic colonoscopic findings, the distribution of the lesions at colonoscopy was also recorded and analyzed. Ten patients had colonoscopic lesions only proximal to the splenic flexure, 3 had lesions only distal to the splenic flexure, and 9 had lesions in both the proximal and distal colon. Two of 4 patients had amebic colitis only in the proximal colon; 2 of 6 had CMV colitis only in the proximal colon.

Thirty-five of the 40 patients (87.5%) recovered after treatment. Of the 5 patients who did not recover after treatment, 1 had non-Hodgkin's lymphoma of stomach and intestine, and 1 had disseminated Kaposi's sarcoma. Both underwent chemotherapy without benefit and died 5 and 30 months later, respectively, of respiratory failure. Two others had nonspecific colitis and 1 had normal endoscopic findings. These 3 patients had intermittent diarrhea during the entire follow-up period. One died of septic shock 4 months later, another died of respiratory failure 1½ months later, and the other was followed regularly at our clinic for 7 months.

Thirteen of 35 patients (37.1%) had recurrences of diarrhea during the follow-up. Six of them recovered spontaneously within 2 weeks of treatment to control symptoms. Another 7 patients (3 CMV colitis, 2 amebic colitis, 1 *Salmonella* infection and 1 colitis without definite diagnosis) had 9 episodes of recurrent diarrhea necessitating repeated endoscopic studies. Of the 9 episodes, 2 were due to *C. difficile*-associated disease, 4 to CMV colitis, 1 to CMV colitis with cryptosporidiosis, and 2 remained undiagnosed. Most of the patients recovered again, except 1 patient with CMV colitis and 1 with CMV and *Cryptosporidium* infection. They had intermittent diarrhea and were still followed regularly with antidiarrheal treatment as needed.

Because CMV and amebic colitis were the two most common causes of diarrhea, we tried to identify the characteristics associated with CMV or amebic colitis. In comparing the patients with CMV colitis and non-CMV colitis, there was no statistically significant difference in age, gender, serum albumin level, CD4 counts, sexual practice, the number of patients recovering from diarrhea, duration of time needed for recovery, recurrence rate after treatment, mortality rate, or duration of follow-up. But patients with CMV colitis appeared to be diagnosed with HIV later than those without CMV colitis (15.3 ± 19.4 vs. 37.4 ± 35.5 months, *p* = 0.033). There was

Figure 1. The survival analysis of patients who recovered and those who did not by Kaplan-Meier method.

also no significant difference with respect to these characteristics between patients with and without amebic colitis. But the patients with amebic colitis were diagnosed with HIV infection earlier than those without amebic colitis (56.7 ± 26.8 vs. 27.5 ± 32.9 months, $p = 0.015$). Amebic colitis occurred more frequently in patients who had had anal sex ($p = 0.003$).

Lower serum albumin values and failure of recovery after treatment were associated with a worse prognosis (Table 3). Comparisons between the 3 patient subgroups are shown in Table 4. Group A included patients with diarrhea due to ameba, CMV, *Clostridium*, *Histoplasma*, *Penicillium*, *Mycobacteria*, *Salmonella*, and *Candida* infection, as well as antibiotic-related colitis, and appendiceal abscess. Group B included the patients with Kaposi's sarcoma, lymphoma, and cryptosporidiosis. The 14 patients with diarrhea of uncertain etiology belonged to group C. Only recovery rate showed a statistically significant difference among these 3 groups (Fisher exact test). Further analysis by independent t test showed that the difference came from group A and group C ($p = 0.046$). Using Cox's proportional hazard model, we estimated the hazard ratios of recovery for death with adjustment of anti-HIV (+) duration. The hazard ratios were 0.059 (16.95^{-1}) with 95% confidence interval as $[0.0085, 0.4082]$ ($2.45^{-1}, 117.6^{-1}$). The survival difference between the patients who recovered from diarrhea after treatment and those who did not was statistically significant ($p < 0.001$) (Fig. 1).

DISCUSSION

To make the correct diagnosis in AIDS patients with diarrhea, a combination of investigations and a stepwise diagnostic approach are often recommended, starting with less invasive investigations while reserving more invasive tests for those without an identified etiology.¹⁰⁻¹⁵ However, the benefits of such a strategy have not been established. According to our study results, colonoscopy could help to make the etiologic diagnosis in 65% (26 of 40) of AIDS

patients with diarrhea and negative stool studies. EGD, instead, was not of assistance in making the etiologic diagnosis in these patients. After diagnosis and treatment, diarrhea resolved in 87.5% of patients. Although 37.1% (13 of 35) developed recurrences, only 20% (7 of 35) needed additional endoscopic studies to further identify the cause of the recurrence and 84.6% (11 of 13) of them recovered again after treatment.

The etiology of diarrhea in 35% (14 of 40) of the patients remained unidentified after our stepwise studies. This rate was comparable to that of previous studies (30% to 40%) after all diagnostic efforts.¹¹ Randomly obtained biopsies from the endoscopically normal area did not aid in the diagnosis. In our study, the major causes of chronic diarrhea in AIDS patients undiagnosed by stool studies or unrelieved after 2 weeks of treatment to control the symptoms were CMV and amebic colitis. Both were treated successfully with specific treatment. Other unusual causes of chronic diarrhea, such as intestinal histoplasmosis and penicilliosis, could not be identified until colonoscopy with histopathology and microbiology studies were performed.

Gay bowel syndrome was initially described in sexually active homosexual men who were at increased risk for infection with a variety of enteropathogens, including *Salmonella*, *Shigella*, *Campylobacter*, *Giardia*, and ameba.¹⁶⁻¹⁸ In our study, 6 of 40 patients (15%) had amebic colitis, which appeared to be associated with longer duration of anti-HIV antibody positivity and anal sexual practice.

Invasive fungal colitis is rarely described in patients with HIV infection in areas that are endemic for both HIV infection and fungal infection, such as histoplasmosis in the Midwest of the United States¹⁹ and penicilliosis marneffeii in Southeast Asia.²⁰ Through endoscopy, we were able to diagnose 3 cases of invasive fungal colitis due to these 2 endemic fungi.²¹ All 3 patients with invasive fungal colitis might have acquired the infection during travel to Southeast Asia and Mainland China. It is likely that invasive fungal colitis is underdiagnosed because not all patients with diarrhea undergo endoscopy.

In considering sigmoidoscopy versus colonoscopy for AIDS patients with diarrhea, colonoscopy seemed to be a better choice based on our study because 45.5% (10 of 22) of patients would have remained undiagnosed if sigmoidoscopy alone had been performed. This might be due to the fact that most of the patients who entered our study had already been screened by stool cultures and routine studies, and that distal colon lesions had already been excluded even though they could be more easi-

Table 4. Comparisons between subgroups A, B and C

	Group A (n = 23)	Group B (n = 3)	Group C (n = 14)	p Value
Age (yr)*	35.6 ± 7.1	33.3 ± 8.5	37.4 ± 11.6	0.730
Albumin (gm/dL)*	3.2 ± 0.7	2.6 ± 0.10	3.3 ± 0.8	0.315
CD4 (μL)*	77.8 ± 164.8	52.7 ± 79.3	75.4 ± 119.7	0.962
Gender (M/F)	22/1	2/1	13/1	
Anal sex	11	1	5	0.789
Anti-HIV (+) noted for (mo)*	32.6 ± 31.2	52.0 ± 59.2	26.3 ± 32.3	0.488
Duration needed for recovery (days)*	7.5 ± 3.5	15.0 ± 13.2	9.4 ± 5.9	0.076
Recovery	23	1	11	0.045
Recurrence	6	1	6	0.245
Died	2	2	3	0.053
Postendoscopy follow-up (mo)*	9.3 ± 6.8	8.2 ± 9.9	8.8 ± 5.4	0.065

Group A included patients with definitive diagnosis in whom appropriate treatment could be administered. Group B included patients with definitive diagnosis but for whom treatment was not fully effective. Group C included patients without definitive diagnosis who received only treatment to control symptoms.

*Values are expressed as mean ± standard deviation.

ly diagnosed with stool studies. In accordance with the most common causes of diarrhea in our patients, ameba and CMV were both frequently seen in proximal colon or both the most proximal and most distal ends of colon.^{22,23}

Although the onset of diarrhea in AIDS patients may be a sign of worsening of immune function,¹² Smith et al. reported that specific therapy could lead to symptomatic improvement.¹⁸ However, there has been no report as yet to indicate whether the specific treatment will affect survival in AIDS patients. Previous studies had reported that patients with advanced AIDS and "pathogen negative" diarrhea seemed to have a slightly better prognosis than those for whom a cause was detected.^{24,25} In our study, no statistical difference was detected between these two groups (group A and group C) in terms of the duration of recovery, the postendoscopy follow-up period, or the mortality rate. But a statistically significant difference ($p = 0.046$) was detected with regard to the rate of recovery. As 2 of the 3 patients in group B had malignant GI tract tumors, their prognosis was the worst among the 3 groups. Similar experience has been reported.¹¹ Therefore, specific treatment for the colitis group of patients is beneficial. In considering the effect of treatment on survival status, we used the Cox proportional hazard model to estimate the hazard ratio of recovery for mortality with the adjustment of positive anti-HIV test period. The hazard ratio was 0.059, which meant that the mortality rate was 16.95 times greater for the nonrecovery group than the recovery group. Kaplan-Meier analysis also showed that the survival between the recovery group and the nonrecovery group was significantly different ($p = 0.0004$). Our results showed that specific treatment for AIDS patients with diarrhea improved the recovery rate, duration of recovery, and prolonged the survival time.

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