

Practice guidelines

Diagnosis and Treatment of Esophageal Diseases Associated with HIV Infection

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PREAMBLE TO ALL GUIDELINES

Guidelines for clinical practice are intended to suggest preferable approaches to particular medical problems as established by interpretation and collation of scientifically valid research, derived from extensive review of published literature. When data are not available that will withstand objective scrutiny, a recommendation may be made based on a consensus of experts. Guidelines are intended to apply to the clinical situation for all physicians without regard to specialty. Guidelines are intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated. Given the wide range of choices in any health care problem, the physician should select the course best suited to the individual patient and the clinical situation presented.

These guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee. These guidelines are also approved by the governing boards of the American Gastroenterologic Association and the American Society of Gastrointestinal Endoscopy. Expert opinion is solicited from the outset for the document. Guidelines are reviewed in depth by the Committee, with participation from experienced clinicians and others in related fields. The final recommendations are based on the data available at the time of the production of the document and may be updated with pertinent scientific developments at a later time.

INTRODUCTION

According to the Centers for Disease Control, the number of HIV-infected individuals in the U.S. ranges from 0.8 to 3 million. The World Health Organization estimates that as many as 40 million people worldwide may be infected by the year 2000, if the pandemic continues unabated. The

health care costs associated with HIV in the U.S. alone are projected at \$15 billion in 1995. The enormity of the problem and the importance of efficient, accurate diagnosis are clear. It is vital that we strive for prompt delivery of effective therapy. This guideline is a review of the management of esophageal disease in those with HIV infection.

BACKGROUND

The esophagus may be the site of the first AIDS-defining opportunistic infection in a significant number of patients (1). At some point in their HIV disease, at least one third of patients will suffer from esophageal disease (2). This number may be understated considering the prevalence of oropharyngeal candidiasis in the HIV-infected population. Opportunistic infection of the esophagus is also a predictor of poor survival (1).

The most common esophageal symptoms described by patients with HIV is odynophagia, or painful swallowing and dysphagia, a feeling of food "sticking" in the retrosternal area. Frequently, odynophagia and dysphagia occur simultaneously. Uncommon manifestations of esophageal disease include singultus or "hiccups," substernal chest pain, and gastrointestinal bleeding. These symptoms are usually caused by inflammation of the esophagus by either acid reflux or infection. Strictures may form, when esophageal ulcers heal. When esophageal symptoms prevent the patient from eating or drinking, severe malnutrition or dehydration may result.

ETIOLOGY

The majority of HIV-infected patients with esophageal symptoms have opportunistic infections and they should be excluded early in the course of investigation. *Candida albicans* is the most frequently identified cause of esophageal symptoms (3, 4). It is usually, but not always associated with oropharyngeal candidiasis (5). Asymptomatic esopha-

geal candidiasis may also occur in the presence of oropharyngeal disease. *Torulopsis globrata* and *Histoplasma capsulatum* may rarely cause esophageal disease (6, 7).

The most common viral pathogen causing esophageal disease is cytomegalovirus (CMV), seen in 10 to 40% of endoscopic biopsies of the esophageal lesions (8). Cytomegalovirus infection may not be found in the patient until after treatment for severe *Candida* esophagitis. CMV and *Candida* may coexist in up to 20% of patients (9). Less commonly occurring viral pathogens include Epstein-Barr virus, herpes simplex virus, and papovavirus (10, 11). Human herpes virus 6 (HHV-6) has been recently isolated from the esophagus in patients with AIDS (12). The human immunodeficiency virus itself has been postulated to cause both acute and chronic esophageal disease (13–15). However, in one recent study (10), only 36% of 25 patients with esophageal symptoms had HIV identified in biopsies by *in situ* hybridization, whereas 100% had other infectious etiologies for their symptoms, and in another study (15) 56/88 (64%) had an infectious etiology for esophageal symptoms on endoscopic biopsy. Of those, 46% had candida, 16% had a viral cause, and one had Kaposi's sarcoma.

Bacterial and mycobacterial esophageal involvement are uncommon (16–24). *Mycobacterium tuberculosis* causes esophageal symptoms usually due to erosion of a contiguous mediastinal lymph node into the esophagus (16). There have been reports of bronchoesophageal, tracheoesophageal, and mediastinal fistulas as well as perforations caused by *M. tuberculosis* (16–20). *Mycobacterium avium* complex causes direct esophageal infection. Superinfection with actinomyces has also been reported in esophageal ulcers caused by other pathogens (21, 22). Dysphagia due to bacterial and nocardial esophagitis has been described (23, 24). Extremely rare protozoal causes of esophagitis include *Cryptosporidium parvum*, *Pneumocystis carinii*, and leishmania (25–28).

Lymphoma and Kaposi's sarcoma are the most common HIV-related neoplastic lesions found in the esophagus. Kaposi's sarcoma is usually submucosal and rarely causes symptoms unless it (1) occurs at a sphincter, (2) obstructs the lumen, or (3) ulcerates (10, 29). The esophagus can be the primary or secondary site of lymphoma and it may coexist with other pathogens (30).

Idiopathic ulceration of the esophagus is a significant problem. Commonly, a large ulcer is identified. Biopsies reveal only ulcer with granulation tissue and no identifiable pathogens. These ulcers may be caused by established pathogens missed by biopsy, by HIV itself, or possibly by unknown pathogens (31).

Gastroesophageal reflux disease is uncommon in HIV-infected individuals (2). Acid production has been reported to be diminished in these patients in one early report (32), but in several later reports (33, 34) was found to be normal. There was no difference in basal acid output, maximal acid output, or peak acid output regardless of the stage of HIV (35). Most patients with HIV take a large variety of common

medications, any one of which can cause esophagitis. Pill esophagitis has been described for HIV-specific drugs including zidovudine (AZT) and zalcitabine (ddC) (36, 37).

DIAGNOSIS

Recommendation

If, after a thorough history and physical, the etiology of esophageal symptoms is not obvious, then an empiric trial of a systemic antifungal agent (like fluconazole 200 mg orally once daily) is warranted. If there is little or no response to therapy in 7–10 days, upper gastrointestinal endoscopy with brushing and/or biopsy is indicated.

In patients with odynophagia or dysphagia, the history and physical examination should include a search for clues to the diagnosis, such as a history of pill ingestion, gastroesophageal reflux, and infections. Physical examination should include evaluation for oropharyngeal candidiasis and infectious retinitis. In one study (2), 100% of patients with *Candida* esophagitis had thrush. In another (3), only 50% of patients who had *Candida* esophagitis on endoscopy had thrush. If the complaints resolve on anti-fungal therapy in 2–5 days, no further testing is required. If odynophagia or dysphagia do not resolve on empiric therapy, endoscopy should be performed. Barium esophagography is not helpful. It can detect *Candida* esophagitis but the diagnosis of CMV, herpes, lymphoma or two simultaneous pathogens is usually missed (38). When two pathogens are involved, the radiologic procedure missed at least one in 100% of the cases (38). The endoscopic appearance of candidiasis can range from small white plaques to overwhelming infection, obstructing the lumen. It can be so extensive as to obscure an underlying infection like CMV. *Candida* rarely causes ulcers. Biopsy of an esophageal ulcer in the patient with severe *Candida* esophagitis is necessary to identify other pathogens like CMV, or to suggest an idiopathic cause (39, 40).

CMV infection can appear in many forms, and may appear in conjunction with *Candida* or lymphoma. The endoscopic appearance of CMV can be diffuse esophagitis, or as single or multiple ulcers, usually in the distal esophagus. Rarely, giant (>2 cm) ulcers will be present. It is common practice to biopsy esophageal ulcers both from the periphery and the crater (40). Viral culture of biopsy material is not useful in diagnosing CMV since cultures are commonly positive when there is no histopathologic evidence of CMV and vice versa (41). In some centers, less experienced in the pathology of AIDS in the gastrointestinal tract, the use of immunohistochemical and *in situ* DNA staining, may increase the diagnostic yield (40–42). Herpes simplex lesions appear endoscopically as vesicles, as a diffuse erosive esophagitis or small discrete “volcano” ulcers (38). Herpes virus can be identified on biopsy, cytology, and culture.

TREATMENT

Recommendation

Oral fluconazole is the treatment of choice for *Candida* esophagitis in patients with HIV. The role of maintenance therapy of *Candida* esophagitis is yet to be established. In patients already taking fluconazole, high dose fluconazole or amphotericin B may be required.

Many agents have been used to treat *Candida* esophagitis such as topical agents including nystatin, clotrimazole, and miconazole; oral agents such as ketoconazole, fluconazole, itraconazole, and 5-flucytosine; and parenteral agents such as amphotericin-B and fluconazole. Topical agents are usually effective against oropharyngeal candidiasis, however esophageal disease requires systemic therapy.

Until recently, ketoconazole was the treatment of choice for *Candida* esophagitis (2, 43). Problems associated with ketoconazole, include hepatotoxicity, resistance, and poor absorption (44, 45). The incidence of hypochlorhydria in HIV-infected patients may not be as high as previously reported (33, 34). This can be clinically relevant because the absorption of ketoconazole and itraconazole are pH dependent (35, 43). Ketoconazole is also an agent that can have interactions with commonly prescribed drugs like terfenadine, cisapride, zalcitabine, zidovudine, and others. Fluconazole is a newer triazole that has greater *in vivo* activity against *Candida albicans* than does ketoconazole and is much better absorbed, even at neutral pH (46, 47). A recent randomized trial compared the two drugs and showed an endoscopic cure in 91% of the fluconazole-treated versus 52% of the ketoconazole-treated patients with no difference in adverse events (48). In another comparative study, itraconazole, which is now FDA approved for the treatment of histoplasmosis, was shown to have no advantages over ketoconazole for the treatment of *Candida* esophagitis (49). Although fluconazole is approximately three times as costly as ketoconazole, it is considered by many to be the drug of choice (47).

Low-dose maintenance antifungal therapy with either ketoconazole or itraconazole may prevent a recurrence of *Candida* esophagitis. However, the cost and potential for inducing drug resistance must be taken into account before implementing this strategy in all patients (50). Many patients with advanced HIV infection are already taking fluconazole or itraconazole for prevention of recurrence of cryptococcosis or histoplasmosis (51). Azole resistant *Candida* species are emerging (52, 53). Resistance can be overcome by tripling the dose, but switching to amphotericin B may be the only solution in many cases.

Recommendation

Initial therapy of esophageal CMV infection should be tailored to the patient. Both ganciclovir and foscarnet are effective as initial therapy. Therapy should be given for 3 to 4 wk initially, depending on severity. The role of maintenance therapy after initial therapy is yet to be established. If

relapse occurs, retreatment with the same drug is reasonable and then maintenance is suggested. For further recurrence, switching to the alternative drug is recommended. After relapse on the alternative drug, combination therapy is recommended for both treatment and maintenance.

Two intravenous drugs are available in the U.S. for the treatment of CMV disease, ganciclovir and foscarnet. Both have been approved for the treatment of CMV retinitis. There is every reason to believe that the systemic treatment of retinitis and colitis is applicable to gastrointestinal disease. Ganciclovir was superior to placebo in treating CMV colitis (54). In four uncontrolled studies (55–59), the response of CMV esophageal disease to intravenous ganciclovir is about 80%, equivalent to the response rate for CMV retinitis. Ganciclovir frequently induced neutropenia especially in the presence of zidovudine (60). This problem can now be treated with colony stimulating factors successfully, but at considerable expense or by switching to foscarnet. Foscarnet is effective in treating both “new” CMV esophageal disease (58, 61, 62) and relapses failing ganciclovir (63). A longer course of initial therapy of 3 to 4 wk may be more effective (62). Foscarnet’s principal side effects are renal failure and electrolyte abnormalities. The manufacturer recommends that foscarnet be administered thrice daily, although a twice daily schedule for foscarnet in gastrointestinal disease, has been studied and appears to be equivalent both in efficacy and in pharmacokinetics (62). Esophageal strictures have been reported after treatment with both drugs (63, 64), presumably as a result of healing. If a patient has a normal creatinine clearance and neutropenia, foscarnet may be the drug of choice at a dose of 90 mg/kg *i.v. b.i.d.* because of its toxicity profile. If a patient has an elevated creatinine, decreased creatinine clearance, or electrolyte disturbances, then ganciclovir is the drug of choice. If none of these abnormalities exist, then the choice is up to the treating physician. There is at least one report that indicated that patients randomized to treatment with foscarnet had a significantly better survival than those randomized to ganciclovir (65). At present, ganciclovir is the least expensive treatment by half, and may have fewer side effects.

When a CMV esophageal ulcer recurs after multiple courses of therapy with both ganciclovir and foscarnet individually, there is evidence to suggest that both drugs can be used together successfully. The drugs can be used in standard doses concurrently, both in treatment and maintenance of CMV infection (66). Whether to use maintenance treatment after initial therapy is still controversial. Many factors enter into the decision and there are no absolute guidelines. After one or at most two relapses, maintenance therapy is recommended. Oral ganciclovir has been approved by the FDA for maintenance therapy of CMV retinitis. The role of oral ganciclovir in the treatment of CMV gastrointestinal disease is yet to be established.

Recommendation

Herpes esophagitis should be treated with acyclovir intravenously. Foscarnet is active against acyclovir-resistant herpes simplex.

Herpes esophagitis is rare in AIDS patients. Acyclovir is the treatment of choice for herpes esophagitis. It usually needs to be given intravenously at first and then orally (67). If acyclovir fails due to drug resistance, foscarnet is quite effective against herpes simplex (68).

Recommendation

If no pathogen is found on multiple adequate biopsies of an esophageal ulcer, after thorough review by an experienced pathologist, the patient should be treated with prednisone 40 mg *p.o.* daily until symptoms improve and then taper at 10 mg/wk.

Treatment of idiopathic ulcers of the esophagus is extremely difficult and controversial. Symptomatic therapy with antacids and sucralfate may help. H-2 blockers or proton pump inhibitors may also alleviate symptoms. Treatment of underlying HIV disease is an important adjunct to therapy of the esophageal disease. There have been reports of successful treatment with corticosteroids (69–72). In several reports of prednisone therapy, a 90% response rate has been noted with few side effects (69–71). Concomitant ketoconazole or fluconazole is sometimes given as *Candida* prophylaxis (50, 69–71). Corticosteroid use may increase the risk of clinical CMV in patients with AIDS (73, 74). Simultaneous antifungal therapy is controversial although vigilance for opportunistic infections must be maintained while on corticosteroids. Recently, thalidomide has been reported to improve idiopathic esophageal ulcers (75, 76). Thalidomide is experimental in the United States.

ACKNOWLEDGMENT

This practice guideline has been officially endorsed by the American Gastroenterological Association and the American Society of Gastrointestinal Endoscopy.

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