Herpes Simplex Virus and the Alimentary Tract

Eric A. Lavery, MD, and Walter J. Coyle, MD

Corresponding author
Walter J. Coyle, MD
Division of Gastroenterology and Hepatology Scripps Clinic
Torrey Pines, 10666 North Torrey Pines Road, N203, La Jolla, CA 92037, USA.
E-mail: Coyle.Walter@scrippshealth.org

Current Gastroenterology Reports 2008, **10:**417–423
Current Medicine Group LLC ISSN 1522-8037

Herpes simplex virus (HSV) infection is well known as a sexually transmitted disease. However, relatively little has been published concerning the presentations and treatment of HSV infection within the gastrointestinal tract, where HSV most commonly affects the esophagus in both immunocompromised and immunocompetent patients. HSV proctitis is not uncommon and occurs primarily in males having sex with males. In patients with normal immune systems, gastrointestinal HSV infections are generally self-limited and rarely require antiviral therapy. Treatment of infection is suggested for immunocompromised patients, though no large randomized controlled trials have been performed. This article reviews the manifestations of HSV infection within the luminal gastrointestinal tract and options for diagnosis and treatment.

Introduction

Herpes simplex virus (HSV) infection is common throughout the world, with both HSV-1 and HSV-2 infections being well documented, especially in immunocompromised patients. Abundant literature exists concerning HSV-2 genital infections and HSV-1 orolabial infections in immunocompetent patients, but the medical literature includes relatively little information related to HSV infections of the gastrointestinal tract. Increasingly, case reports, case series, and reviews have shown HSV to be an infrequent cause of gastrointestinal infections in immunocompetent hosts. In addition, HSV has been investigated as a possible cause of gastrointestinal conditions such as peptic ulcer disease (PUD), toxic megarectum, and achalasia [1]. The purpose of this review is to summarize the available literature on HSV infections of the gastrointestinal tract in both immunocompromised and immunocompetent patients.

Background

HSV is a member of the Herpesviridae family of viruses, which also includes varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesvirus (HHV) 6, 7, and 8 [2•]. Members of this family contain linear, double-stranded DNA within a protein capsid, which is surrounded by a tegument and an outer glycoprotein layer [2•,3••]. HSV-1 and HSV-2 have 70% genomic homology but tend to affect different areas of the body. HSV-1 tends to cause most oral and esophageal herpetic lesions; it is commonly acquired during childhood, though it has been associated with proctitis in a minority of cases. HSV-1 is primarily transmitted via oral secretions and has a higher seroprevalence in lower socioeconomic communities. HSV-2 is most often sexually transmitted; it primarily causes genital and rectal infections. Estimates suggest that HSV-1 has a worldwide seroprevalence of 80% to 90%, whereas HSV-2 has a 22% seroprevalence rate in the United States [3••,4]. However among patients infected with HIV, HSV is the most common viral coinfection, and 95% of males who have sex with males (MSM) are seropositive for HSV-1, HSV-2, or both [4]. Incubation periods for primary HSV infections range from 2 to 12 days [5].

Primary infections, diagnosed by antibody seroconversion or a fourfold rise in HSV IgG levels between acute and convalescent serum antibody titers, may produce constitutional symptoms but are frequently asymptomatic [2•]. After primary infection, viral particles are transported retrograde from the peripheral site of infection to dorsal root ganglia via nerve axons [3••]. The virus may become latent for an unpredictable period. At any time, the virus may be reactivated, traveling from the ganglia through sensory neurons and replicating in the target cells. Asymptomatic reactivation (recurrence) may cause viral shedding; symptomatic reactivation (recrudescence) frequently causes symptoms that are less severe and shorter in duration than the symptoms of the primary infection but that have a similar distribution. Most cases of gastrointestinal HSV infection in immunocompromised

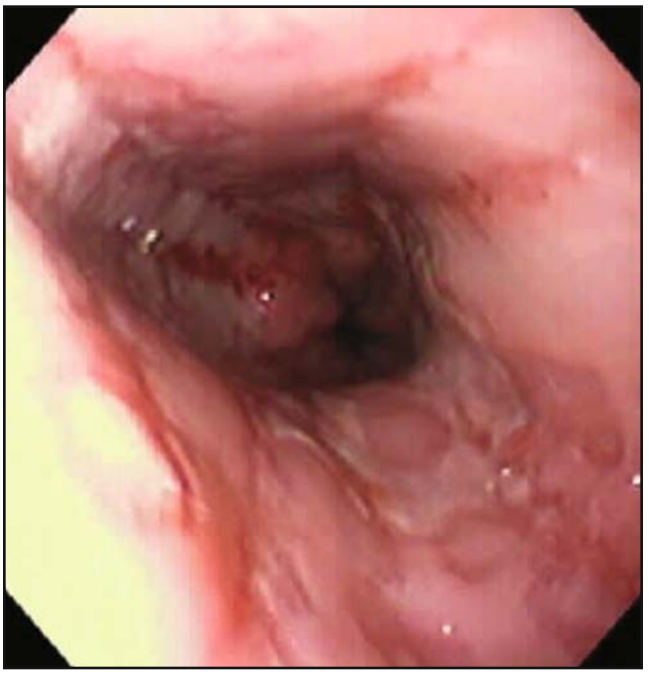

Figure 1. Herpes simplex virus esophagitis with ulcerations. Endoscopic view of the distal esophagus with mucosal ulceration typical for herpes simplex virus infection. (*Courtesy of* Glen Arluk, MD.)

patients represent recrudescence, as these patients have higher baseline seroprevalence rates. Primary infection is the most common cause of HSV gastrointestinal infections in those who are immunocompetent. The underlying mechanism for reactivation is unknown, but multiple factors have been suggested, including stress, immunosuppression, and sun exposure.

Esophagus

Within the gastrointestinal tract, HSV involvement is most frequently recognized within the esophagus. In a recent case report, Kato et al. [6] discussed a 26-year-old immunocompetent man who presented after developing cough, sore throat, fever, and rash on his chest and abdomen. Three days later, the patient complained of odynophagia and hematemesis [6]. Esophagogastroduodenoscopy (EGD) revealed multiple ulcers in the mid and distal esophagus and a Mallory-Weiss tear. Repeat endoscopy several days later showed whitish exudates, and esophageal biopsies showed Cowdry type A inclusion bodies in the epithelial cells. HSV IgM was elevated by day 7 with low IgG levels, and the patient was suspected of having primary HSV-1 infection. The patient recovered without the use of antiviral medications.

This report is a typical presentation of HSV esophagitis in an immunocompetent patient. Symptoms frequently have an acute onset, and dysphagia is a frequent complaint [7]. Odynophagia, the most common symptom, occurs in over 76% of patients [8]. Other common symptoms are retrosternal chest pain, heartburn (50%), and fever (44.7%). Almost one quarter of patients have preceding cough or sore throat; 27% have oral lesions, and 13% have herpetic skin rashes [6]. Hematemesis is unusual in HSV esophagitis, though it has been reported in several case reports [9,10].

The incidence of HSV esophagitis by gender depends upon age [6,8]. In a review of 38 cases of HSV esophagitis in immunocompetent hosts, the mean age of presentation was 28.5 ± 20.4 years. Almost 79% of those affected were younger than 40, and of these, 76% were male [8]. Above the age of 40, however, there was no gender predilection.

Although the esophagus is the most common site of HSV infection in the gastrointestinal tract, autopsy data suggest that HSV esophagitis is uncommon overall. In one Japanese autopsy series, it was found in 24 (1.8%) of 1307 serial autopsies [11]. In a separate Japanese autopsy series of 145 cases, 9 patients (6%) were found to have HSV esophagitis [12]. This diagnosis was based on the macroscopic appearance of esophageal erosions or ulcerations and positive immunohistochemical staining. All affected patients were immunocompromised: eight had a malignancy and the ninth was using steroid therapy for rheumatoid arthritis. All these patients had HSV-1 as the etiologic agent. Consistent with the Japanese autopsy series, the vast majority of documented cases of HSV esophagitis are due to HSV-1, though at least one case report documents HSV-2 esophagitis secondary to heterosexual orogenital contact in an immunocompetent patient [7,13]. One Western autopsy series reviewed 3000 consecutive autopsies, of which only 55 had microscopic slides of esophageal ulcers. Of these, 14 were consistent with HSV (based on histologic appearance), giving an overall prevalence of HSV esophagitis of about 0.5% [14].

In immunocompetent patients, the distal esophagus is involved 64% of the time, making it the most frequently affected esophageal location [8]. However, extensive esophageal involvement is the norm, occurring over 92% of the time. It is rare for noncontiguous regions to be affected with normal intervening mucosa. The endoscopic appearance typically shows multiple ulcers, which may be superficial or punched out (Fig. 1). Friable mucosa (84.2%) and whitish exudates (39.5%) also are commonly seen [8].

Although esophageal ulceration is the most common endoscopic finding associated with HSV esophagitis (occurring in 86% of immunocompetent patients), this finding is by no means specific for HSV. In a review of 7564 endoscopies performed by a single provider, 88 patients had esophageal ulcerations, but only 1% of these were attributed to HSV. Gastroesophageal reflux disease (GERD) accounted for 65%, 22% were drug induced, and 3% were candidal in origin [15]. GERD ulcers, though frequently larger than herpetic ulcers, are also typically distal in location. In contrast, the drug-induced ulcers appeared in the distal esophagus only 13% of the time.

HSV esophagitis is more common in the immunocompromised patient and is a defining illness for AIDS [16].

Esophageal disease occurs in about 30% of patients with HIV infection; the esophagus is the viscus most commonly involved in disseminated HSV [16,17]. Overall, however, candidiasis is the most common cause of esophageal symptoms in HIV patients, accounting for 52% to 75% of these cases [18,19]. *Candida* is the sole pathogen in 30% to 54% of patients and is frequently a copathogen along with opportunistic viral infections such as CMV or HSV [18]. HSV is either the sole or contributing pathogen causing esophageal symptoms in about 8% of HIV patients. In one series, patients also had perioral ulcers [18].

As with immunocompetent patients, esophageal ulcerations reflect HSV disease in only a small minority of those who are immunocompromised. In a study of 303 consecutive endoscopies performed at a major medical center in patients with AIDS (mean CD4 count 15 cells/mm^3), 100 patients were found to have esophageal ulcers. Odynophagia was the leading symptom. CMV and idiopathic ulcers each accounted for over 40%, and only about 9% were due to HSV (5 with HSV as the sole cause and 4 with HSV/CMV coinfection) [17].

In a retrospective review of 34 cases of herpetic esophagitis in AIDS patients with a mean CD4 count of 15/mm^3, symptoms were similar to those in immunocompetent patients. Over 80% of patients complained of odynophagia or dysphagia, 68% had chest pain, and 44% had fever [16]. However, symptoms may be more severe in AIDS patients, with case reports of esophageal perforation and tracheoesophageal fistulas in the literature [20,21]. Not surprisingly, more AIDS patients have evidence of extraesophageal HSV as well.

Distribution of lesions was also similar in immunocompromised patients, with the distal esophagus being involved over 80% of the time and almost 80% of patients having ulcerations [19]. In one series of AIDS patients with HSV esophagitis, HSV was confirmed by histologic appearance or viral culture in 27 patients, 1 of whom recovered spontaneously; the outcome of 6 patients was not available. Of the remaining 20 patients, 16 (80%) had complete response to acyclovir, 3 (15%) had a partial response, and only 1 treatment failure (5%) was documented. No side effects of acyclovir were documented [16].

Diagnosis of HSV esophagitis has been accomplished by multiple methods involving tissue biopsies and serologic testing. Biopsies have a higher diagnostic yield for HSV when samples are obtained from the edge of ulcers, as specimens from ulcer craters often lack epithelial cells [22]. In one small series of immunocompetent patients, virus isolation from tissue biopsies was the best diagnostic method, being positive 95.8% of the time [8]. Immunocytochemistry also had excellent diagnostic yield, being positive in 87.5% of patients. Characteristic viral cytopathology (ballooning degeneration of epithelial cells, multinucleated giant cells, Cowdry type A inclusion bodies) was seen in about 68% of cases. These histologic findings are nonspecific and may be found with infections caused by other members of the Herpesviridae family (VZV, CMV), but esophageal infections with VZV or CMV are unusual in immunocompetent patients, making these findings more clinically relevant. HSV serology may be diagnostically useful in patients suspected of having primary infection.

Similar results regarding diagnostic yield of HSV by various laboratory tests have been reported from a dermatology cohort of 48 patients. In this series, HSV was most reliably detected by viral culture (83%), followed by polymerase chain reaction (PCR) (73% of stained smears and 83% of unstained smears) [23]. Least reliable was the Tzanck smear (60%).

HSV esophagitis is self-limiting in most immunocompetent patients. Scattered case reports of bleeding and esophageal perforation secondary to HSV esophagitis are clearly unusual [24]. Because of the generally benign and self-limited course of HSV esophagitis, treatment with acyclovir is rarely required [7,8,22]. On average, symptoms resolve over about 7 days. Some authors have recommended treatment if the diagnosis is made early, but studies showing benefit from treatment in this population are lacking [25]. Treatment is recommended for immunocompromised patients with HSV esophagitis, who may have more complications, more severe symptoms, and worse outcomes. For example, in a case report by Cattan et al. [9], a 74-year-old man with neutropenia (absolute neutrophil count 600/mm^3) following chemotherapy presented with hematemesis, dysphagia, and epigastric pain. On endoscopy, most of the patient's esophagus appeared black and ulcerated, consistent with acute necrotizing esophagitis. Biopsies revealed necrosis and clusters of multinucleated giant cells with ground-glass nuclei, suggesting a viral infection. Immunostaining was positive for HSV; cultures grew HSV-1. The patient was treated with 2 weeks of acyclovir, and resolution was endoscopically documented 6 weeks later. Overall, patients with complicated courses, ongoing severe symptoms, or immunocompromise should be treated with acyclovir, whereas routine infections in immunocompetent patients may be managed conservatively [22].

Stomach

Significant HSV infection is much rarer in the stomach than in the esophagus. Scattered case reports of HSV-associated gastritis are available. One particularly interesting case report describes a 65-year-old man with Ménétrier's disease associated with HSV. The patient presented with hematemesis, and initial endoscopy showed a distal esophageal ulcer and gastric findings consistent with Ménétrier's disease. Both esophageal and gastric biopsies immunostained for HSV; gastric biopsies were negative for both CMV and *Helicobacter pylori*. After 10 days of treatment with acyclovir, the patient underwent a repeat endoscopy, which showed healed esophageal ulcerations and a markedly improved gastric appearance [26•].

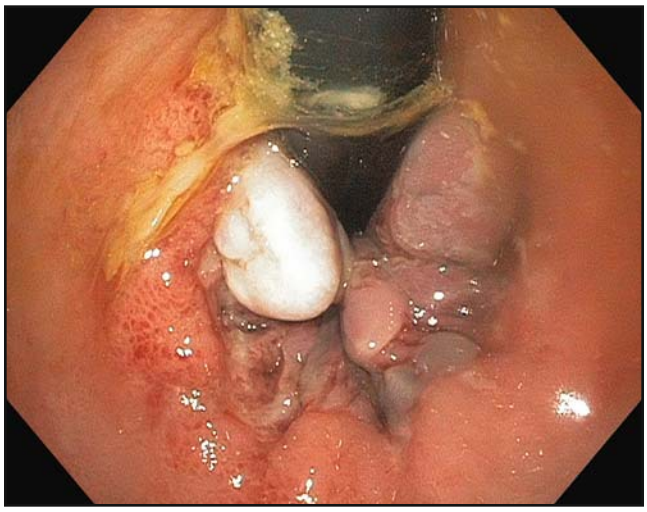

Figure 2. Mild proctitis due to herpes simplex virus infection. Endoscopic view of the rectum with mucosal erosions and erythema due to herpes simplex virus infection. (*Courtesy of* Glen Arluk, MD.)

Most medical literature regarding HSV and the stomach revolves around the possible role of HSV in some patients with PUD. Although most PUD is attributable to *H. pylori* or the use of NSAIDs, a significant minority of ulcers and erosions have no clear etiology [27••]. Proponents suggest that the ability of HSV to remain latent in nerve ganglia explains the occasional recurrence of PUD and erosions in this subset of patients. A further argument for an etiologic role for HSV in some PUD includes the notable reduction in recurrent ulcers and erosions after vagotomy. Proponents of this theory suggest that HSV in the vagal ganglia is unable to reach the gastric mucosa after vagotomy, contributing to the decrease in recurrent ulcers.

Initial serologic studies in the 1980s and early 1990s compared HSV-1 seropositivity in patients with PUD versus controls. Data were conflicting, with some studies showing no difference in HSV seropositivity rates and others showing statistically significant differences in patients with duodenal ulcers versus controls. Further serologic studies have focused on HSV antibody titers in the presence of PUD. Once again, data conflict, but most series show a significantly higher antibody titer in patients with active ulcers than in controls [28–32].

Toljamo et al. [33] studied patients with persistent erosions or ulcerations. In a group of 52 patients with erosions at initial endoscopy, the only predictor of persistent erosions (seen at repeat endoscopy an average of 15 years later) was an initial high HSV antibody titer. The presence of *H. pylori*, smoking, and the use of NSAIDs or alcohol were not associated. These investigators also found that high HSV titers at follow-up endoscopy were correlated with concurrent erosions, but HSV was not identifiable in tissue specimens from the chronic erosions that were tested with PCR and immunohistochemistry.

However, other series have found HSV-1 in gastric mucosa. In a small series of 22 patients with PUD, 4 patients (18%) were found to have evidence of HSV-1 nucleic acid and proteins by in situ hybridization and PCR of gastric or duodenal ulcer tissue [34]. *H. pylori* was identified by histopathology in only 1 of these 4 patients. Immunocytochemistry showed that the HSV was predominantly localized close to the ulcers, and further series have confirmed this finding [35]. Neither the patients with ulcers from other causes nor the 33 controls had positive immunocytochemical staining for HSV.

In this study, many of the HSV-positive immunostained cells were in the base of crypts, and some had co-staining for cholecystokinin and HSV [34]. The presence of cholecystokinin suggests that these cells are neuroendocrine in origin. The authors hypothesized that HSV migrates from the vagal and celiac ganglia, initially infecting neuroendocrine cells. The virus may then replicate, spread to other epithelial cells, and cause ulceration.

Perhaps the most informative data regarding a possible role of HSV in a PUD subset is in the prospective study of 90 patients with PUD by Tsamakidis et al. [27••]. Biopsy specimens were obtained from 56 patients with duodenal ulcers, 34 patients with gastric ulcers, and 50 controls. Using PCR, 31.1% of PUD patients were positive for HSV-1, versus 0% of controls. The prevalence of HSV-1 was similar between patients with duodenal ulcer (30.4%) and those with gastric ulcer (32.4%, $P = 0.843$). HSV was detected only in biopsy specimens from the crater and ulcer rim, not in specimens of adjacent or distant tissue. *H. pylori* was detected in only 68% of the patients with positive HSV PCR, compared with 92% of patients with negative HSV PCR. Thus, the presence of HSV in patients with PUD decreased the likelihood of *H. pylori* infection, suggesting a possible etiologic role for HSV in these ulcerations. However, though these studies are provocative, they fail to definitively demonstrate that HSV causes a subset of PUD, as it remains possible that HSV migrates to the site of ulceration rather than being the underlying cause.

Colon and Rectum

HSV does not commonly affect the small and large intestine, but there are scattered case reports of HSV colitis and jejunitis after bone marrow and solid organ transplantation [36–39]. In fact, among 45% to 73% of patients undergoing bone marrow transplantation who are seropositive for HSV, the latent virus is reactivated in various tissue sites [40]. This finding has led to prophylactic treatment with acyclovir in this set of patients, which has dramatically decreased clinical cases of HSV. A recent Cochrane review found that the incidence of HZV or HSV infection after solid organ transplantation was reduced by 73% with antiviral prophylaxis [41].

Most cases of HSV infection involving the rectum and colon involve immunocompromised patients or MSM and frequently represent reactivation of latent virus rather than primary infection. Proctitis is often described in MSM,

and HSV is the most common cause of nongonococcal proctitis. Most HSV proctitis cases (70%) are related to HSV-2 [42]. Typical endoscopic findings in HSV proctitis include friable mucosa, diffuse distal ulcerations, and vesicular lesions (Fig. 2) [5].

In a study of 119 MSM presenting to a sexually transmitted disease clinic complaining of anorectal pain or discharge, tenesmus, hematochezia, increased stool frequency, or abdominal cramping with bloating or nausea, anoscopy found proctitis in 102; the other 17 patients had normal anoscopy and symptoms more consistent with enteritis (diarrhea, abdominal pain and cramping). These 119 symptomatic patients were compared with an asymptomatic cohort of 75 MSM patients. In the symptomatic group with positive anoscopy, 80% were found to have an enteric infection; HSV accounted for 19% of this group. HSV was detected in only 4% of the asymptomatic group and was not detected in any of the symptomatic patients with enteritis and negative anoscopy [43]. All herpetic infections were due to HSV-2. Of the symptomatic patients, 85% were suspected of having a primary infection rather than reactivation, reinforcing the idea that primary infections tend to cause more severe symptoms than reactivation [44].

HSV involvement of the colon and rectum is much less common in immunocompetent patients who do not participate in anoreceptive intercourse. Colemont et al. [45] described a 78-year-old woman (taking no medications) who had acute onset of bloody diarrhea and abdominal discomfort 2 months after transverse colectomy of a Dukes' B colonic adenocarcinoma. She was found to have extensive HSV-1 colitis, which resolved without therapy [45]. Other than her previous malignancy, the patient was felt to be immunocompetent.

Although this woman's symptoms resolved without therapy, treatment with acyclovir has been shown to be beneficial for herpes proctitis in MSM. In a study of 29 HIV-negative MSM with their first episode of HSV proctitis, treatment with acyclovir (400 mg five times daily) reduced the duration of rectal lesions and shedding. After 3 days of therapy, 80% of the treated patients and only 25% of those given placebo had cessation of viral shedding from the rectum. Symptomatic relief was noted in the treated patients, but was not statistically significant [46].

HSV proctitis is more likely than other forms of infectious proctitis to cause constipation, severe anorectal pain, difficulty urinating, sacral paresthesias, and diffuse ulcerations of the distal rectal mucosa [44]. Nonherpetic forms of proctitis are more likely to extend endoscopically beyond 10 cm from the anal verge. MSM coinfected with HIV and HSV-2 shed HSV-2 on 9% of days, whereas MSM infected only with HSV-2 shed virus less frequently (3.1%). Risk factors for increased shedding among HIV-infected patients include lower CD4 counts and seropositivity for HSV-1 and HSV-2 [4].

It is widely accepted that CMV may cause severe, steroid-refractory colitis in patients with underlying inflammatory bowel disease. In a small series of 19 patients, Cottone et al. [47] showed that 36% of such cases were due to CMV. The role of HSV in inflammatory bowel disease is less clear, however. There are several reports of HSV colitis related to known underlying Crohn's disease, but whether HSV was an exacerbating or complicating factor of the colitis is unclear [48,49].

Conclusions

HSV infections of the gastrointestinal tract occur predominantly in immunocompromised patients but may also affect those who are immunocompetent. Of the visceral organs involved in herpetic infections, the esophagus is most commonly affected. In MSM, HSV-2 proctitis is not uncommon, and frequent viral shedding occurs even in asymptomatic patients. Involvement of the stomach, small intestine, or colon is unusual. Symptomatic HSV infection in immunocompetent individuals tends to reflect primary infection, whereas reactivation of latent virus is the typical cause of symptoms in those who are immunocompromised. Treatment is recommended for the immunocompromised patients, but infection tends be self-limited in those with an intact immune system. Prophylaxis is recommended for severely immunocompromised patients such as recipients of bone marrow and solid organ transplants.

Disclaimer

The opinions and assertions contained herein are the sole views of the authors and should not be construed as official or as representing the views of the US Navy, Department of Defense, or Department of Veterans Affairs.

Disclosures

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Castagliuolo I, Brun P, Constantini M, et al.: **Esophageal achalasia: is the herpes simplex virus really innocent?** *J Gastrointest Surg* 2004, **8:**24–30.

2.• Fatahzadeh M, Schwartz RA: **Human herpes simplex virus infections: epidemiology, pathogenesis, symptomatology, diagnosis, and management.** *J Am Acad Dermatol* 2007, **57:**737–763.

This is a very thorough review of herpesvirus infections, diagnosis, and treatment, though it focuses on dermatologic conditions.

3.•• Steiner I, Kennedy PG, Pachner AR: **The neurotropic herpes virus: herpes simplex and varicella-zoster.** *Lancet* 2007, **6:**1015–1028.
This is an excellent resource for understanding the virology of HSV, including the mechanism of HSV primary infection and reactivation.
4. Schacker T, Zeh J, Hu H, et al.: **Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivation among human immunodeficiency virus–infected men.** *J Infect Dis* 1998, **78:**1616–1622.
5. Drew WL, Buhles W, Erlich KS: **Herpesvirus infections (cytomegalovirus, herpes simplex virus, varicella-zoster virus). How to use ganciclovir (DHPG) and acyclovir.** *Infect Dis Clin North Am* 1988, **2:**495–509.
6. Kato S, Yamamoto R, Yoshimitsu S, et al.: **Herpes simplex esophagitis in the immunocompetent host.** *Dis Esophagus* 2005, **18:**340–344.
7. Galbraith JC, Shafran SD: **Herpes simplex esophagitis in the immunocompetent patient: report of four cases and review.** *Clin Infect Dis* 1992, **14:**894–901
8. Ramanathan J, Rammouni M, Baran J, Khatib R: **Herpes simplex virus esophagitis in the immunocompetent host: an overview.** *Am J Gastroenterol* 2000, **95:**2171–2176.
9. Cattan P, Cuillerier E, Cellier C, et al.: **Black esophagus associated with herpes esophagitis.** *Gastrointest Endosc* 1999, **49:**105–107.
10. Fishbein PG, Tuthill R, Kressel H, et al.: **Herpes simplex esophagitis: a cause of upper-gastrointestinal bleeding.** *Dig Dis Sci* 1979, **24:**540–544.
11. Itoh T, Takahashi T, Kusaka K, et al.: **Herpes simplex esophagitis from 1307 autopsy cases.** *J Gastroenterol Hepatol* 2003, **18:**1407–1411.
12. Matsumoto J, Sumiyoshi A: **Herpes simplex esophagitis—a study in autopsy series.** *Am J Clin Pathol* 1985, **84:**96–99.
13. Wishingrad M: **Sexually transmitted esophagitis: primary herpes simplex virus type 2 infection in a healthy man.** *Gastrointest Endosc* 1999, **50:**845–846.
14. Nash G, Ross JS: **Herpetic esophagitis: a common cause of esophageal ulceration.** *Hum Pathol* 1974, **5:**339–345.
15. Higuchi D, Sugawa C, Shah SH, et al.: **Etiology, treatment, and outcome of esophageal ulcers: a 10-year experience in an urban emergency hospital.** *J Gastrointest Surg* 2003, **7:**836–842.
16. Genereau T, Lortholary O, Bouchard O, et al.: **Herpes simplex esophagitis in patient with AIDS: report of 34 cases.** *Clin Infect Dis* 1996, **22:**926–931.
17. Wilcox CM, Schwartz DA, Clark WS: **Esophageal ulceration in human immunodeficiency virus infection: causes, response to therapy and long term outcome.** *Ann Intern Med* 1995, **123:**143–149.
18. Connolly GM, Hawkins D, Harcourt-Webster JN, et al.: **Oesophageal symptoms, their causes, treatment, and prognosis in patients with the acquired immunodeficiency syndrome.** *Gut* 1989, **30:**1033–1039.
19. Bonacini M, Young T, Laine L: **The causes of esophageal symptoms in human immunodeficiency virus infection: a prospective study of 110 patients.** *Arch Intern Med* 1991, **151:**1567–1572.
20. Dieckhaus KD, Hill DR: **Boerhaave's syndrome due to herpes simplex virus type 1 esophagitis in a patient with AIDS.** *Clin Infect Dis* 1998, **26:**1244–1245.
21. Cirillo NW, Lyon DT, Schuller AM: **Tracheoesophageal fistula complicating herpes esophagitis in AIDS.** *Am J Gastroenterol* 1993, **88:**587–589.
22. Becker K, Lubke HJ, Borchard F, Haussinger D: **Inflammatory esophageal diseases caused by herpes simplex virus infections—overview and report of 15 personal cases.** *Z Gastroenterol* 1996, **34:**286–295.
23. Nahass GT, Goldstein BA, Zhu WY, et al.: **Comparison of Tzanck smear, viral culture, and DNA diagnostic methods in detection of herpes simplex and varicella-zoster infection.** *JAMA* 1992, **268:**2541–2544.
24. Cronstedt JL, Bouchama A, Hainau B, et al.: **Spontaneous esophageal perforation in herpes simplex esophagitis.** *Am J Gastroenterol* 1992, **87:**124–127.
25. Van Ongeval J, Rutgeerts L, Ghillebert G: **Herpetic esophagitis in 5 immunocompetent patients.** *Ned Tijdschr Geneeskd* 1996, **140:**1367–1371.
26.• Jun DW, Kim DH, Kim SH, et al.: **Ménétrier's disease associated with herpes infection: response to treatment with acyclovir.** *Gastrointest Endosc* 2007, **65:**1092–1095.
This is a fascinating case report of HSV infection causing Ménétrier's disease, which improved after therapy with acyclovir.
27.•• Tsamakidis K, Panotopoulou E, Dimitroulopoulos D, et al.: **Herpes simplex virus type 1 in peptic ulcer disease: an inverse association with Helicobacter pylori.** *World J Gastroenterol* 2005, **11:**6644–6649.
This is the most provocative and recent article relating the possible connection of a subset of PUD patients with HSV.
28. Kang JY, Lee TP, Guan R, et al.: **Antibody to herpes simplex virus type 1 in peptic ulcer patients.** *J Gastroenterol Hepatol* 1990, **5:**387–390.
29. Archimandritis A, Markoulatos P, Tjivras M, et al.: **Herpes simplex virus types 1 and 2 and cytomegalovirus in peptic ulcer disease and non-ulcer dyspepsia.** *Hepato-Gastroenterol* 1992, **39:**540–541.
30. Rand KH, Jacobson DG, Cottrell R, et al.: **Antibodies to herpes simplex type 1 in patients with active duodenal ulcer.** *Arch Intern Med* 1983, **143:**1917–1920.
31. van der Merve CF, Alexander JJ: **Herpes simplex virus and duodenal ulceration [letter].** *Lancet* 1982, **2(8301):**762.
32. Vestergaard BF, Rune SJ: **Type-specific herpes-simplex-virus antibodies in patients with recurrent duodenal ulcer.** *Lancet* 1980, **1(8181):**1273–1274.
33. Toljamo KT, Niemelä SE, Karttunen TJ, et al.: **The role of Herpes simplex and Helicobacter pylori infection in the etiology of persistent or recurrent gastric erosions: a follow-up study.** *Dig Dis Sci* 2002, **47:**818–822.
34. Lohr JM, Nelson JA, Oldstone MB: **Is herpes simplex virus associated with peptic ulcer disease?** *J Virol* 1990, **64:**2168–2174.
35. Kemker BP Jr, Docherty JJ, De Lucia A, et al.: **Herpes simplex virus: a possible etiologic agent in some gastroduodenal ulcer disease.** *Am Surg* 1992, **58:**775–778.
36. Kingreen D, Nitsche A, Beyer J, Siegert W: **Herpes simplex infection of the jejunum occurring in the early post-transplantation period.** *Bone Marrow Transplant* 1997, **20:**989–991.
37. Naik HR, Chandrasekar PH: **Herpes simplex virus (HSV) colitis in a bone marrow transplant recipient.** *Bone Marrow Transplant* 1996, **17:**285–286.
38. Delis S, Kato T, Ruiz P, et al.: **Herpes simplex colitis in a child with combined liver and small bowel transplant.** *Pediatr Transplant* 2001, **5:**374–377.
39. Adler A, Goldman M, Liesnard C, et al.: **Diffuse herpes simplex virus colitis in a kidney transplant recipient successfully treated with acyclovir.** *Transplantation* 1987, **43:**919–921.
40. Hann IM, Prentice HG, Blacklock HA, et al.: **Acyclovir prophylaxis against herpes virus infections in severely immunocompromised patients: randomised double blind trial.** *Br Med J (Clin Res Ed)* 1983, **287:**384–388.
41. Hodson EM, Barclay PG, Craig JC, et al.: **Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients.** *Cochrane Database Syst Rev* 2005, CD003774.
42. Rompalo A: **Diagnosis and treatment of sexually acquired proctitis and proctocolitis: an update.** *Clin Infect Dis* 1999, **28(Suppl 1):**S84–S90.
43. Quinn TC, Walter ES, Goodell SE, et al.: **The polymicrobial origin of intestinal infections in homosexual men.** *N Engl J Med* 1983, **309:**576–582.

44. Goodell SE, Quinn TC, Mkrtichian E, et al.: **Herpes simplex virus proctitis in homosexual men: clinical sigmoidoscopic and histopathological features.** *N Engl J Med* 1983, **308:**868–871.
45. Colemont LJ, Pen JH, Pelckman PA, et al.: **Herpes simplex virus type 1 colitis: an unusual cause of diarrhea.** *Am J Gastroenterol* 1990, **85:**1182–1185.
46. Rompalo AM, Mertz GJ, Davis LG, et al.: **Oral acyclovir for treatment of first-episode herpes simplex virus proctitis.** *JAMA* 1988, **259:**2879–2881.
47. Cottone M, Pietrosi G, Martorana G, et al.: **Prevalence of cytomegalovirus infection in severe refractory ulcerative and Crohn's colitis.** *Am J Gastroenterol* 2001, **96:**773–775.
48. El-Serag HB, Zwas FR, Cirillo NW, Eisen RN: **Fulminant herpes colitis in a patient with Crohn's disease.** *J Clin Gastroenterol* 1996, **22:**220–223.
49. Ruther U, Nunnensiek C, Muller HA, et al.: **Herpes simplex-associated exacerbation of Crohn's disease. Successful treatment with acyclovir.** *Dtsch Med Wochenschr* 1992, **117:**46–50.