Viral Infections of the Gastrointestinal Tract

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INTRODUCTION

Viral infections of the gastrointestinal (GI) tract predominantly arise in the setting of immune deficiency. Although they may occur at random following exposure to a pathogen in a normal host, these are mostly self-limited. In contrast, these infections typically result in significant morbidity and mortality in immunocompromised patients (eg, patients with HIV/AIDS or organ transplant) if untreated. Despite significant improvements in targeted immunosuppression and antimicrobial prophylaxis in the transplant setting, viruses remain important causes of disease.

The GI tract is a natural portal of entry for pathogens into the body, but numerous protective mechanisms, most importantly the mucosal immune system, help prevent or attenuate infections from these pathogens. In immunocompromised patients, these protective mechanisms are either impaired or lost, thereby predisposing to local or systemic infections, termed opportunistic infections, oftentimes by unusual pathogens. The 2 groups of patients who most commonly develop opportunistic viral GI infections are those with HIV/AIDS and those who have undergone organ transplantation. In patients with HIV, the incidence of viral GI infections rises markedly as immune function deteriorates and is inversely related to the absolute CD4 lymphocyte count. However, the risk of these infections in patients with iatrogenic immune suppression after transplantation falls over time, as drug-induced immune suppression is tapered. When organ rejection occurs, thus requiring a boosting of immune suppression, the risk of infection markedly escalates. In both groups of patients, the degree of immune suppression/dysfunction determines the incidence of infection.

For any immunocompromised patient with GI symptoms, the differential diagnosis depends on the suspected organ(s) involved and the type, severity, and duration of immune compromise. Timing of viral infections correlates with the interval after transplant; herpes simplex virus (HSV) is seen in the first 30 days, cytomegalovirus (CMV) between days 30 and 90, and herpes zoster after day 100. These observations mandate targeted antimicrobial prophylaxis during periods of greatest vulnerability to these infections. Improvements in immunosuppressive medications as well as the use of CMV-seronegative organs and blood products for seronegative recipients have reduced the incidence of CMV infections in the post-transplant setting. In HIV-infected patients, the use of highly active antiretroviral therapy (HAART) has dramatically reduced the incidence of opportunistic infections, especially CMV.

This review takes a symptom/organ-based approach in a case study format to review the epidemiology, clinical features, diagnosis, and therapy for viral GI infections seen mostly in persons immunocompromised by AIDS and those with iatrogenic disease associated with organ transplantation or chemotherapy.

CASE PRESENTATIONS

CASE 1

A 20-year-old man presents for evaluation of a “white tongue.” He has noted painless white “fuzzy” patches on the side of his tongue for several weeks. He denies local pain, itching, difficulty swallowing, fevers, or chills. His past medical history is significant for an episode of genital herpes 6 months prior to presentation. He reports having a single male sexual partner but denies ever using alcohol or illicit drugs. He is not taking any prescription or over-the-counter medications at this time. Physical examination reveals corrugated white lesions on the lateral borders of the tongue without erythema or other discoloration. The lesions cannot be scraped off (see Figure 1, page 6).

• Which of the following is consistent with this lesion?
  (A) Oral hairy leukoplakia (OHL)
  (B) Squamous cell carcinoma
  (C) Candidiasis
  (D) All of the above

  The correct answer is A. The differential diagnosis includes all of the above, but the diagnosis is OHL. OHL is an asymptomatic lesion that may be a sign of HIV
infection and is thought to be associated with progression to AIDS. In this disorder, the lingual squamous epithelium is infected with Epstein-Barr virus (EBV), an opportunistic agent that proliferates in patients with underlying immunodeficiency. It may also involve the floor of the mouth, the palate, or the buccal mucosa. Unlike candida, the lesions adhere to the surface and cannot be scraped off easily. Although anticandidal therapy may be given initially if there is suspicion of candidal infection, the similar appearance of other lesions may warrant a biopsy to confirm the diagnosis and exclude dysplasia. Predominantly seen in homosexual and bisexual men, OHL may also be observed in organ transplant recipients.

HSV should be suspected and tested for in individuals with hairy leukoplakia. OHL is not considered a premalignant lesion and does not progress to squamous cell carcinoma. Among HIV-infected patients, studies have shown a higher incidence in men, patients with CD4 cell counts below 200/mm$^3$, and those with a higher HIV viral load. Specific treatment is usually not indicated, except for treating the underlying immunodeficiency condition and any candidal superinfection. The use of HAART has reduced the incidence of OHL.

**CASE 2**

A 43-year-old woman presents with a 3-day history of severe burning and tingling on the lips and pain with chewing or swallowing food. She also reports some reddish bumps on her lips. She reports similar episodes in the past, associated with stress. Physical examination reveals multiple small vesicles with surrounding erythema on her lips and shallow serpiginous ulcerations on the hard palate (see Figure 2, page 6).

- **This presentation is consistent with which of the following entities?**
  - (A) Aphthous ulcers
  - (B) Cold sores/fever blisters
  - (C) Crohn’s ulcers
  - (D) Vitamin deficiency
  - (E) Behçet’s syndrome

  **The correct answer is B.** Although all of these conditions can manifest with oral ulcers, the typical history of burning and pain preceding the development of vesicles and ulcers is suggestive of orolabial HSV infection, commonly known as cold sores or fever blisters. HSV-1 causes ulcers on keratinized mucosa such as the hard palate and gingival mucosa in contrast to aphthous ulcers, which involve unkeratinized surfaces such as the labial or buccal mucosa, soft palate, and the floor of the mouth. Immunocompromised patients may develop larger pseudomembrane covered ulcers, and HSV should be suspected in all perineal and orolabial ulcerations in HIV-infected patients. Fever, sunlight, and physical or emotional stress precipitate recurrences by causing reactivation of dormant HSV in the regional ganglia.

  A cytologic (Tzanck) smear showing multinucleated giant cells supports the diagnosis of HSV infection, while viral cultures and monoclonal antibody stains are confirmatory tests. Topical antivirals are of little benefit, and systemic acyclovir (3 g orally in divided doses or 5 mg/kg intravenously [IV] 3 times daily until the lesions heal) is used for primary infection or recurrences in immunosuppressed patients. Famiciclovir 125 mg twice daily and valacyclovir 500 mg twice daily are equivalent alternatives. Topical anesthetics may provide relief of pain. Suppression of recurrences is accomplished with acyclovir 200 mg orally 3 times daily or 400 mg twice daily.

**CASE 3**

A 46-year-old woman with a history of acute myeloid leukemia presents 4 weeks after allogenic bone marrow transplantation with painful swallowing, decreased appetite, and 10-lb weight loss. She also reports a sensation of food sticking in her chest and substernal chest pain with eating. She denies nausea, vomiting, fever, or abdominal pain. She had thrush about a week prior to this presentation. Multiple small vesicles are noted on the upper lip, with surrounding erythema. On examination, the pharynx is clear without any ulcers or thrush.

- **All of the following are in the differential diagnosis for her esophageal symptoms EXCEPT**
  - (A) HSV esophagitis
  - (B) CMV esophagitis
  - (C) Schatzki’s ring
  - (D) Gastroesophageal reflux disease (GERD)
  - (E) Candida esophagitis

  **The correct answer is C.** All of the above can cause the patient’s symptoms of odynophagia (painful swallowing) and dysphagia (difficulty swallowing) except Schatzki’s ring, which is typically painless. Mechanical obstruction of the esophagus results in difficulty swallowing solids more than liquids, whereas motility disorders typically result in difficulty swallowing both solids and liquids. Infections may cause dysphagia or odynophagia with both solids and liquids. Viral esophagitis causes ulcerations and thus characteristically results in odynophagia that may be severe, limiting oral intake.

- **The patient is completing a course of empiric fluconazole without relief of her symptoms. What is the best diagnostic test for this patient?**
(A) Barium swallow
(B) Endoscopy with biopsy
(C) Computed tomography (CT) scan of the chest
(D) Serologic tests for CMV
(E) Empiric antiviral therapy

The correct answer is B. Although empiric treatment may be tried in cases of suspected candida esophagitis, this patient has not responded to fluconazole. The presence or absence of oral thrush does not predict the underlying pathology, fungal or otherwise. Barium swallow may demonstrate diffuse mucosal involvement or ulcer(s); however, it cannot differentiate between the various causes of esophageal disease and thus is not diagnostic. For a definitive diagnosis, endoscopy with biopsy is required. CMV viral cytopathic effect is seen in the granulation tissue at the base of the ulcer, while HSV is mostly recovered from the ulcer margins. Hence, biopsy of both the ulcer base and margins is required to evaluate for different viruses.

- Upper endoscopy reveals multiple small, shallow esophageal ulcers (see Figure 3, page 6), and biopsy samples taken from the ulcer edge show multinucleated giant cells with Cowdry type A inclusion bodies (see Figure 4, page 6). What is the appropriate initial treatment based on these findings?
  (A) Acyclovir (C) Foscarnet
  (B) Ganciclovir (D) Amphotericin B

The correct answer is A. The endoscopic findings are characteristic of HSV esophagitis. The differential diagnosis for odynophagia in immunocompromised patients is esophagitis caused by HSV or CMV, pill-induced esophagitis, GERD, and, in patients with AIDS, idiopathic esophageal ulcer (IEU). Histologic confirmation is essential to differentiate between these diverse causes, as the endoscopic appearance may be similar. HSV infection is generally localized to squamous cells and hence is manifested mostly as esophageal and perianal disease. Small, sharply demarcated vesicles may be an early finding, while numerous small ulcerations resembling volcanoes that may become confluent are common endoscopic features. Cytologic brushings and mucosal biopsies are used to identify a characteristic viral cytopathic effect, while viral histochemical stains and cultures may provide additional diagnostic utility in the presence of diffuse erosive disease. The endoscopic findings in this patient do not suggest GERD or CMV, and she does not have a history of taking any medications linked with pill-induced esophagitis (eg, doxycycline, potassium, bisphosphonates, nonsteroidal anti-inflammatory drugs, iron). IEU is a diagnosis of exclusion.

Once a diagnosis of HSV is established, generic acyclovir for 7 to 10 days is the least expensive regimen and is effective; famciclovir and valacyclovir are also effective. Prophylaxis against HSV mucositis with acyclovir from the beginning of the conditioning regimen until the patient recovers from neutropenia is standard therapy in both autologous and allogenic transplant recipients.

CASE 4

A 51-year-old man presents 3 weeks after bone marrow transplantation with symptoms of painful swallowing and intermittent chest pain. Multiple deep ulcers with normal intervening mucosa are noted at endoscopy and on a barium swallow (see Figure 5, page 6), and biopsy of these ulcers reveals large intracellular eosinophilic inclusions.

- These pathologic findings are most suggestive of which of the following?
  (A) HSV infection (C) HIV infection
  (B) CMV infection (D) Candida infection

The correct answer is B. Large solitary or multiple deep ulcers at endoscopy are typical for CMV esophagitis. The viral cytopathic effect of CMV is observed in endothelial and mesenchymal cells as large eosinophilic inclusions in the nucleus or basophilic inclusions in the cytoplasm. The cells are characteristically enlarged (“cytomegalos”). Although odynophagia is commonly reported (unlike in candida esophagitis), dysphagia is rare, especially as the predominant symptom. Nausea, vomiting, or GI bleeding may occur. The presence of altered vision, abdominal pain, or diarrhea suggests concurrent retinal, intestinal, or colonic involvement, respectively. Ophthalmic involvement is frequent, a retinal examination should be performed in AIDS patients.

- This patient has a white blood cell count of 1.2 × 10^9/mm^3 (normal, 4–10 × 10^9/mm^3) and a creatinine level of 0.6 mg/dL (normal, 0.6–1.2 mg/dL). What is the ideal treatment for this patient?
  (A) Ganciclovir (C) Acyclovir
  (B) Foscarnet (D) Amphotericin B

The correct answer is B. Various treatments are available for CMV infection (Table 1). Ganciclovir is associated with bone marrow suppression and leukopenia (responsive to granulocyte colon-stimulating factor), while foscarnet may result in renal insufficiency (acute tubular necrosis). Given this patient’s neutropenia and normal renal function, ganciclovir is contraindicated and foscarnet may be most appropriate. Intravenous hydration reduces the frequency of renal complications. Electrolyte monitoring is essential to monitor for hypocalcemia (caused by transient chelation of calcium by foscarnet),
hypomagnesemia, hypokalemia, and hypophosphatemia or hyperphosphatemia.

CMV prophylaxis is rarely utilized for HIV patients but is commonly instituted for high-risk organ transplant patients (eg, CMV-negative recipients of CMV-positive donors).

CASE 5

A 28-year-old man with AIDS who is noncompliant with HAART presents with complaints of watery diarrhea for 3 weeks, with intermittent bleeding, tenesmus, and mild lower abdominal pain. He also reports low-grade fever and 15-lb weight loss over the last month. His past medical history is significant for Pneumocystis jiroveci pneumonia, and he is currently on prophylaxis with trimethoprim/sulfamethoxazole and azithromycin. He denies any recent travel outside the United States. Physical examination reveals an ill-appearing man with mild diffuse abdominal tenderness and normal bowel sounds. His laboratory studies are significant for a CD4 cell count of 44/mm$^3$ and hemoglobin of 10 g/dL.

**Which of the following initial investigations are indicated for this patient’s symptoms?**

(A) Fecal leukocyte smear  
(B) Routine stool culture and sensitivity  
(C) Stool *Clostridium difficile* toxin assay  
(D) Examination of the stool for ova and parasites  
(E) All of the above

**The correct answer is E.** Fecal leukocyte assay is indicated to evaluate for inflammatory/infectious causes of diarrhea and to differentiate these from chronic osmotic or secretory causes. In a patient presenting with bloody diarrhea, abdominal pain, and fever, routine stool bacterial culture and sensitivity is recommended for diagnosing acute bacterial colitis. CMV colitis typically causes a chronic watery diarrhea, although bloody diarrhea has been described. *Cryptosporidium, Microsporidium,* and *Giardia* are common parasitic infections in AIDS. *C. difficile* is an important cause of diarrhea that should be excluded in hospitalized patients and those reporting recent use of antibiotics.

**Case Continued**

The studies are negative except for the presence of fecal leukocytes. Sigmoidoscopy reveals mucosal edema, patchy subepithelial hemorrhage, and discrete deep ulcers (see Figure 6, page 7). Biopsy samples taken from the ulcers reveal multiple cells containing eosinophilic intranuclear inclusions (see Figure 7, page 7).

**What is the diagnosis?**

Although the endoscopic findings are nonspecific in this patient, the eosinophilic inclusions are diagnostic for CMV colitis. CMV is the most common opportunistic cause of colonic disease. In patients with AIDS, GI involvement is the second most common site of disease, following the eyes. This marked frequency of disease is related to high prevalence of prior exposure to CMV and reactivation of the latent virus rather than primary infection. Occurring in HIV patients with CD4 cell counts below 100/mm$^3$, CMV-related disease, such as megacolon and bowel perforation, is the most common reason for emergent or elective abdominal surgery in patients with AIDS.\textsuperscript{15,18} Abdominal CT may show focal or diffuse thickening suggestive of colitis. As there is usually pancolonic involvement, sigmoidoscopy has a high diagnostic yield. Endoscopically, diffuse colitis or multiple ulcerations may be observed.\textsuperscript{19}

Histological diagnosis or immunohistochemical stains are needed for diagnosis, as serologic testing is uniformly positive in this patient population.\textsuperscript{20} A characteristic cytopathic effect is noted in cultured fibroblasts in the setting of CMV infection, but this may take days to weeks to appear, depending on the viral titer in the clinical specimen. Shellvial assay is a technique where the diagnosis can be made within 24 to 48 hours after inoculation. The clinical specimens are inoculated onto adherent cell

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**Table 1. Antivirals Used for Treatment of Enteric Viral Infections**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Main Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Orogenital HSV, herpes zoster</td>
<td>GI side effects, nephrotoxicity</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>CMV treatment and prophylaxis</td>
<td>Bone marrow suppression</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Acyclovir-resistant HSV, herpes zoster, and ganciclovir-resistant CMV</td>
<td>Nephrotoxicity, electrolyte disorders, GI side effects</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>Herpes zoster, herpes labialis</td>
<td>CNS and GI side effects</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>CMV, acyclovir-resistant HSV</td>
<td>Nephrotoxicity</td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; CNS = central nervous system; GI = gastrointestinal; HSV = herpes simplex virus.
monolayers grown on round coverslips in small vials, centrifuged at low speed to facilitate viral adsorption, and incubated. Viral infection is then detected by staining with a fluorescein-labeled anti-CMV antibody or with an antibody against CMV, followed by a fluorescein-labeled anti-Ig.

Ganciclovir, foscarnet, or cidofovir are the antiviral agents used for treatment of CMV colitis (Table 1).

CASE 6

A 29-year-old man with a history of poorly controlled ulcerative colitis (UC) presents with a 3-week history of bloody diarrhea, abdominal pain, and low-grade fever. He reports being compliant with a regimen of azathioprine and mesalamine. Physical examination is significant for mild diffuse abdominal tenderness. Laboratory studies, including complete blood count, are unremarkable. Fecal leukocytes are increased, but routine stool cultures and C. difficile toxin assay are negative. Institution of IV steroids and hydrocortisone enemas for 1 week does not result in improvement of the patient’s symptoms.

Flexible sigmoidoscopy reveals inflamed mucosa in the rectum and the descending colon, thought to be consistent with UC. Biopsy of the colon reveals active UC with crypt distortion as well as multiple large cells with abundant granular cytoplasm.

- **What is the next step to consider in the management of this patient?**
  - (A) IV infliximab
  - (B) IV cyclosporine
  - (C) Immunohistochemical staining of the mucosal biopsies for CMV
  - (D) Total colectomy

  **The correct answer is C.** Although CMV colitis is observed more commonly in immunocompromised patients, the association between CMV and UC is well recognized. The exact nature of the association is unknown, and there is debate as to whether CMV is an innocent bystander in UC or causes disease. Although some studies have shown increased frequency of anti-CMV antibodies in UC patients without documented CMV colitis (suggesting that CMV is not pathogenic in UC), there have been multiple cases of CMV in UC that respond to ganciclovir, thus suggesting a pathogenic
role for CMV. Steroid treatment may be a risk factor for CMV colitis, although up to one third of patients may be steroid-naïve at the time of diagnosis. For individuals with apparent UC flares not responding to standard UC therapy, CMV should be considered and endoscopy with biopsy and immunohistochemical staining should be performed before considering surgery for refractory UC. Early and appropriate management may prevent complications and unnecessary surgery.

CASE 7

A 29-year-old college student presents with nausea, vomiting, and diarrhea for 2 days. He reports similar symptoms among 3 of his friends that developed after eating at the college cafeteria. He has mild abdominal discomfort but denies fever or chills. He reports 4 episodes of vomiting and 3 to 4 watery, non-bloody bowel movements per day. He appears uncomfortable and has mild diffuse abdominal tenderness on examination. Rectal examination reveals brown liquid stool without blood.

- What is the most common infectious cause of sporadic acute GI illness in the United States?
  (A) Bacterial  (C) Protozoal
  (B) Viral       (D) Parasitic

The correct answer is B. In the United States, the United Kingdom, northern Europe, and Japan, caliciviruses (eg, the Norwalk and Sapporo viruses) are the most common cause of sporadic acute gastrointestinal illness in patients of all age-groups, except infants and toddlers, in whom rotaviruses predominate.\(^{23,24}\) The other common viral causes of diarrhea in healthy adults are adenovirus types 40 and 41 and astrovirus. Other causes predominate in the developing world. Caliciviruses, of which Norwalk-like viruses (NLV) or noroviruses are the prototypes, cause almost 90% of the outbreaks, mostly reported in restaurants, nursing homes, cruise ships, and school campuses. The Farmington Hills strain is the predominant circulating strain in the United States.\(^ {25} \) NLV causes explosive emesis and voluminous stools with a large number of organisms in the stool as well as in the vomitus. The attack rate is high, as the inoculum required to produce infection is small (fewer than 100 viral particles). Contaminated food and
water as well as person-to-person transmission have been recognized as important for the spread of infection. Caliciviruses and astroviruses are more prevalent among outpatients, whereas rotavirus is a common cause of hospitalization.²⁷

• How does viral gastroenteritis compare to bacterial gastroenteritis?

Viral gastroenteritis has an abrupt onset of loose, watery stools without blood, mucus, or fecal leukocytes. These patients may have low-grade fever, nausea, abdominal cramping, and myalgias. Compared to bacterial toxin-mediated disease, the incubation period is longer, ranging from 10 to 51 hours, and the secondary attack rates are high, commonly resulting in community outbreaks (Table 2). The duration of symptoms (1–5 days) and postinfectious malabsorption (2–3 weeks) are more prolonged with NLV than with bacterial disease. Viral shedding occurs in the stool as well as the vomitus. Electron microscopy or polymerase chain reaction techniques on stools have been used to establish the diagnosis during outbreaks. Supportive management is adequate for recovery, without the need for any specific treatment.

CASE 8

A 10-month-old child is brought to the emergency department for vomiting and watery, nonbloody diarrhea of 2 days’ duration. The child is lethargic and febrile and appears dehydrated. There are no sick contacts at home, including his older brothers 3 and 5 years of age, who are in good health and attend day care.

• Which of the following infectious agents is known to cause symptomatic diarrheal disease only in infants or very young children?
  (A) *Shigella* 
  (B) *Salmonella* 
  (C) Rotavirus 
  (D) Amebiasis 
  (E) *Giardia*

The correct answer is C. Rotaviruses are a prominent cause of severe diarrheal disease in children between 4 and 24 months of age (maternal antibodies are thought to be protective in the first 3 months of life). Infection is highly contagious, indicating that a very small inoculum is infectious, since the feces of infected children usually contain no more than 100 colony-forming units/g. Rotavirus causes self-limited or asymptomatic infection in older children and adults, unless they are immunocompromised.²⁸,²⁹

Most adults acquire the infection from within the family, whereas young children acquire the infection from day care or other outside sources. The presence of 1 or more of the following risk factors results in an increased risk of hospitalization and death: age less than 18 months, poor socioeconomic status, malnutrition, immunodeficiency, or the presence of other systemic disease. Management involves fluid repletion and adequate dietary intake during acute diarrhea; antibiotics and antimitotic agents should be avoided.

Rotaviruses and noroviruses are difficult to control as they survive common cleansing agents and spread easily due to the small inoculum required to cause infection. Sanitary measures to both prevent and control the spread of infections in daycare centers and other settings include proper hand washing, diaper hygiene, using gloves, and proper disposal of contaminated material.

CASE 9

A 25-year-old man with untreated AIDS presents with diarrhea and lower extremity edema of 4 weeks’ duration. He reports having 10 to 12 watery, nonbloody bowel movements per day and denies tenesmus, fever, or greasy stools. He reports a 30-lb weight loss over this period. Physical examination reveals a cachectic man with marked lower extremity edema and multiple purplish macules and plaques on the skin and scalp and in the oropharynx.

• Which of the following is included in the differential diagnosis for diarrhea in this patient?
  (A) *Cryptosporidium/Microsporidium* enteritis 
  (B) *Mycobacterium avium* enteritis 
  (C) Protein-losing enteropathy 
  (D) CMV colitis 
  (E) All of the above

The correct answer is E. HIV/AIDS predisposes patients to numerous opportunistic infections—bacterial, viral, protozoal, and fungal—resulting in diarrhea and malabsorption. Routine stool studies (as described in case 5) are indicated prior to endoscopy or abdominal

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**Table 2. Selected Comparisons of Viral Versus Bacterial Gastroenteritis**

<table>
<thead>
<tr>
<th></th>
<th>Viral</th>
<th>Bacterial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>Hours–days</td>
<td>Hours</td>
</tr>
<tr>
<td>Infectious dose</td>
<td>Smaller than for bacterial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gastroenteritis</td>
<td></td>
</tr>
<tr>
<td>Symptom duration</td>
<td>1–5 days</td>
<td>1–2 days</td>
</tr>
<tr>
<td>Viral shedding</td>
<td>Feces, vomitus</td>
<td>Feces</td>
</tr>
</tbody>
</table>

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imaging. The clinical presentation and severity of immunodeficiency are useful in predicting which patients with negative stool tests may benefit from endoscopic examination. In one study, patients without an identifiable pathogen after endoscopic examination had fewer systemic symptoms (weight loss) and a higher CD4 cell count. Indeed, diarrhea remained unexplained in patients who had not lost weight, and no opportunistic infection was found in those patients with a CD4 cell count of more than 50 cells/mm³.

**Case Continued**

This patient's laboratory studies are significant for a serum albumin below 1.0 g/dL. Stool studies are negative for leukocytes, ova, and parasites, with a normal fat concentration. Fecal α1-antitrypsin concentration is elevated.

- The diagnosis of protein-losing enteropathy explains which of the following?
  - (A) Diarrhea
  - (B) Low serum albumin
  - (C) Elevated fecal α1-antitrypsin
  - (D) Lower extremity edema
  - (E) All of the above

**The correct response is E.** Protein-losing enteropathy may be a result of ulcerative diseases (eg, inflammatory bowel disease, graft versus host disease), nonulcerative diseases (eg, Ménétrier’s disease, Whipple’s disease) or lymphatic obstruction/increased pressure (eg, Kaposi’s sarcoma [KS], primary intestinal lymphangiectasia) and causes significant protein loss, resulting in hypoalbuminemia, edema, and ascites.

α1-Antitrypsin has a moderately higher molecular weight than albumin (50,000) and is excreted intact in the stool because it is resistant to proteolysis and degradation in the intestinal lumen. Hence, its rate of intestinal clearance helps to quantify total intestinal protein loss. Simultaneous plasma and stool measurements of this protein are required to estimate net protein loss. Plasma α1-antitrypsin clearance is a product of daily stool volume and stool α1-antitrypsin concentration divided by serum α1-antitrypsin concentration.

**Case Continued**

Further evaluation of this patient with abdominal CT reveals diffuse enhancement of the small bowel, and upper endoscopy reveals multiple flat and raised reddish purple lesions in the duodenum (see Figure 8, page 7). Biopsy of these lesions as well as the skin lesions is consistent with KS.

- Management of KS includes
  - (A) HAART for AIDS patients
  - (B) Intralesional chemotherapy
  - (C) Cryotherapy/laser therapy/local radiation
  - (D) Systemic chemotherapy
  - (E) All of the above

**The correct answer is E.** KS is an AIDS-defining illness caused by human herpes virus 8 and is the most common tumor arising in HIV-infected patients. Although KS is a neoplasm, it is considered an opportunistic disease in HIV-infected and other immunosuppressed patients because it is caused by a virus. The characteristic appearance of the skin lesions aids in the diagnosis; however, biopsy is needed to differentiate KS lesions from bacillary angiomatosis lesions. KS may result in a variety of lesions and symptoms but is mostly asymptomatic. Oral KS lesions may be seen in one third of patients with skin involvement and may be the initial manifestation. The GI tract is involved in approximately 40% of cases, independent of the presence of skin lesions. Gut involvement by KS may be manifested clinically as nausea, vomiting, GI bleeding, diarrhea, or malabsorption, depending upon the location of the tumor. Fortunately, in the era of HAART, this disease has almost disappeared in patients with AIDS.

The primary treatment of AIDS-related KS is improvement of immune function with HAART. Several studies have shown improvement in KS treated with HAART, concurrent with decrease in HIV RNA and improvement of CD4 cell count. In some patients, apparent cure has been observed with HAART alone. Because of an unpredictable response to HAART, specific local or systemic therapy may also be required. Radiation therapy yields improvement of skin or oral mucosal lesions. Systemic chemotherapy is used for patients with widespread mucocutaneous disease, lymphedema, or visceral disease. Etoposide, vinblastine, and doxorubicin have some efficacy. Liposomal doxorubicin has been found to be more effective and less neurotoxic than a combination of vincristine, bleomycin, and doxorubicin. Paclitaxel has also been shown to be an excellent second-line agent.

Biologic agents such as interferon alfa are considered first-line therapy for some patients with epidemic cutaneous KS and result in remission in 20% to 60% of cases. The response rates correlate with baseline CD4 counts and the use of antiretroviral therapy.

**CASE 10**

A 35-year-old woman presents with mild pruritus in the perianal area. She denies any pain or bleeding but has “felt a growth.” She reports that this is the first time
The incidence of anal cancer is higher in patients with anal canal condylomata than in the general population. There are many subtypes of HPV, and some are highly associated with cancer (HPV types 16, 18, and 33), whereas others generally produce benign warts (types 6 and 11). Patients coinfected with HIV and HPV have a higher risk of developing high-grade anal dysplasia, a precancerous lesion. HPV-related squamous cell cancers occur with increasing incidence with immunosuppression, as in transplant patients and HIV-infected patients. Immunosuppression, HIV

**Table 3. Treatment of Anal Warts**

<table>
<thead>
<tr>
<th>Chemical agents</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Podophyllin</td>
<td>Cryotherapy</td>
</tr>
<tr>
<td>Trichloroacetic acid</td>
<td>Laser therapy</td>
</tr>
<tr>
<td>5-Fluorouracil epinephrine gel</td>
<td>Infrared coagulation</td>
</tr>
</tbody>
</table>

**Immune modulation**

- Imiquimod
- Interferon alfa

**The correct answer is B.** Condylomata acuminata, or anal and genital warts, caused by human papilloma virus (HPV) are the most common sexually transmitted disease in the United States. HPV is a double-stranded DNA virus with multiple subtypes. HPV infects the basal cells of the squamous epithelium, and viral shedding occurs from the completely differentiated cells of the upper epithelium because cellular differentiation is necessary for the HPV growth cycle. Sometimes they may be differentiated into external warts, which are visible on the skin, and internal warts, which may extend into mucosal surfaces with squamous epithelium (eg, the vagina and anal canal) and may require anoscopy or colposcopy to be seen. The prevalence of condylomata is higher in HIV-infected patients and patients with other sexually transmitted infections. The risk of disease increases with the number of sexual partners in men and women. Receptive anal intercourse is common in patients with anal warts, and coital trauma is thought to allow entry of latent virus into the anal epidermis. In women, anal condylomata can occur by extension from vulvar or perineal infection or by receptive anal intercourse. Mostly seen in homosexual men, condylomata acuminata have also been recognized in heterosexual men.

Usually seen as raised lesions, condylomata acuminata may be smooth, verrucous, filiform, fungating, or cauliflower-like, and need to be differentiated from flat lesions (condylomata lata) seen in syphilis. They may be asymptomatic or present with pruritus, bleeding, burning, pain, or vaginal discharge in women.

- All of the following are acceptable for the initial management of this condition EXCEPT
  - (A) Anoscopy
  - (B) Tissue biopsy
  - (C) Colposcopy
  - (D) Evaluation for other sexually transmitted infections
  - (E) Surgical removal

The correct answer is E. Table 3 lists the common treatments available for anal and genital warts. Colposcopy and anoscopy may be indicated to evaluate the extent of disease; if limited, topical therapy is indicated. Although a biopsy may confirm the diagnosis, clinical diagnosis is generally sufficient to initiate treatment. While multiple treatment options exist, there is no single satisfactory therapy. Recurrence occurs in 30% to 70% of cases within 6 months of treatment. Spontaneous regression may occur in 20% to 30% cases. Most local treatments are indicated for external warts, while cryotherapy is indicated for both external and internal warts. Topical podophyllin 25% in tincture of benzoin is tried first, and CO₂ laser, cryosurgery, or electrocautery may be necessary for resistant cases. Surgical treatment is usually reserved for extensive disease or after conservative treatment has failed. Podophyllin contains the antimitotic agent podophyllotoxin, which arrests cell cycle in metaphase and causes cell death. It may cause skin irritation or ulceration and is teratogenic. Trichloroacetic acid causes wart destruction by protein coagulation and can be used for mucosal/internal lesions as well as in pregnancy. 5-Fluorouracil is a pyrimidine antimetabolite that interferes with DNA synthesis; imiquimod and interferon alfa are immunomodulators used in the treatment of condylomata acuminata.

- What is the risk of anal cancer in patients with anal warts?

The incidence of anal cancer is higher in patients with anal canal condylomata than in the general population. There are many subtypes of HPV, and some are highly associated with cancer (HPV types 16, 18, and 33), whereas others generally produce benign warts (types 6 and 11). Patients coinfected with HIV and HPV have a higher risk of developing high-grade anal dysplasia, a precancerous lesion. HPV-related squamous cell cancers occur with increasing incidence with immunosuppression, as in transplant patients and HIV-infected patients.
infection, and the serotype of HPV are important factors in the development of anal cancer, but the location and/or extension of warts is not.

**CASE 1**

A 29-year-old man presents with a 3-day history of severe anal pain, tenesmus, mucoid discharge per rectum, and constipation. He also reports vague lower abdominal pain and painful urination. He denies blood per rectum, fever, or chills. He is accompanied by his male partner with whom he admits to having anal intercourse. He does not take any medications but has tried IV drugs and has alcohol on weekends. His past medical history is significant for appendicitis and oral candidiasis.

- All of the following are potential causes of this patient’s symptoms EXCEPT
  - (A) HSV
  - (B) Chlamydia trachomatis
  - (C) Neisseria gonorrhoea
  - (D) Anal fissure
  - (E) Diverticular disease

  **The correct answer is E.** Except for diverticular disease, all of these may result in the patient’s symptoms. While diverticulitis may cause lower abdominal pain, tenesmus and anal pain suggest another diagnosis. Anal fissure typically causes severe pain with defecation (dyschezia) and results in constipation due to fear of having pain with a bowel movement. *N. gonorrhoea, C. trachomatis,* and HSV are the most common causes of pain/proctitis in this setting.

**Case Continued**

The patient does not allow examination of the anal region until local anesthesia is provided. Perianal erythema with multiple small fluid-filled vesicles is seen, with tenderness to palpation (see Figure 10, page 7). Anoscopy reveals similar vesicles and focal ulcerations in the anal canal. Biopsy show inflammation with microabscesses and multinucleated giant cells by Giemsa stain.

- All of the following are indicated in the management EXCEPT
  - (A) Acyclovir
  - (B) Sitz baths
  - (C) Local anesthetic
  - (D) Local steroids
  - (E) Analgesics

  **The correct answer is D.** A presumptive diagnosis of HSV proctitis may be made from the physical examination and anoscopic findings as well as the multinucleated giant cells, which are characteristic of HSV infection. Symptomatic treatment should be initiated with all of the above except steroids. Immunofluorescent staining and PCR or viral culture from rectal swabs or biopsy specimens will confirm the diagnosis. Topical acyclovir 6 times daily for 7 days will accelerate healing of lesions. Acyclovir, 400 mg 5 times daily orally or 5 to 10 mg/kg every 8 hours IV, may be used for severe disease. Recurrences may be prevented in HIV-infected patients with acyclovir or famciclovir maintenance therapy.

  - How does the immune status of the host affect the presentation and course of HSV infection?

  The tendency for self-limited lesions is linked to the immune status of the patient. Therefore, HSV infection is often chronic when associated with advanced immunodeficiency. HSV infection of longer than 1 month’s duration in HIV patients is a criterion for the US Centers for Disease Control diagnosis of AIDS. In HIV infected patients, HSV infection can be more severe with systemic symptoms and results in more frequent HSV shedding and recurrences than in immunocompetent persons. The degree of immunodeficiency determines the frequency of recurrences, severity of the disease, and likelihood of spontaneous remission. Recurrence rates increase dramatically when immunodeficiency is advanced (CD4 cell count < 50/μL).

**SUMMARY POINTS**

- The clinical presentation of gastrointestinal disease is dictated by the infecting pathogen(s) and the organ(s) involved, and there is overlap among these.

- The severity and chronicity of infection is dictated by the underlying cause, duration, and type of immunodeficiency.

- The radiographic and endoscopic features of gastrointestinal infections are variable and overlapping, making definitive diagnosis by biopsy essential.

- Relapse is common despite effective antiviral therapy when immunodeficiency persists.

**REFERENCES**


4. Boeckh M. Current antiviral strategies for controlling cytomegalovirus in hematopoietic stem cell transplant recipients: prevention and