Gastrointestinal Infections

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ABSTRACT Gastrointestinal infections in the immunocompromised host are caused by the common bacterial, viral, fungal, and parasitic agents that also cause infections in the immunocompetent host. Of special consideration is that immunocompromised patients may be at increased risk for infection or disease severity and by pathogens not seen in the competent host. This chapter reviews the various agents, risk factors, and diagnostic approaches to detect gastrointestinal infections in this patient population.

BACKGROUND Gastrointestinal (GI) infections in the immunocompromised host include the common bacterial, viral, fungal, and parasitic agents that also cause infections in the immunocompetent host (Table 1). Of special consideration is that immunocompromised patients may be at increased risk for, or experience, increased disease length and severity caused by many common GI pathogens. As the stomach is a major barrier to colonization by some enteric pathogens, it is not surprising that there may be changes in gastric microbiota in the immunocompromised patient that could be involved in increasing the risk of infection (1). Patients with human immunodeficiency virus (HIV) infection, recipients of solid-organ and bone-marrow transplant, patients with hematologic or other malignancies, or with diabetes, or patients receiving immunosuppressive chemotherapy and corticosteroid therapy, as well as patients with poor nutritional status, and/or at the extremes of age, are all at risk for conventional and opportunistic infections of the GI tract. Patients with primary immunodeficiencies may have GI lesions that are similar to other noninfectious diseases (2). Additionally, certain microorganisms cause infection in the compromised host but rarely, if ever, are observed in the normal, immunocompetent population (Fig. 1). Some infections that may indicate an underlying immunodeficiency include Candida spp. esophagitis or microsporidial enteritis, which may be the first acquired immunodeficiency syndrome (AIDS)-defining illness experienced by patients with HIV infection.

Infections of the GI tract can be categorized as either upper, affecting the oral cavity, esophagus, or stomach, or lower tract, affecting the small and large intestine. Oral mucositis resulting from chemotherapy or radiation therapy for a variety of malignancies can be a debilitating complication but does not have a particular infectious cause (3). Esophagitis may be characterized by dysphagia (difficulty in swallowing), odynophagia (painful swallowing), heartburn, and sometimes chest pain, and are common features for the more frequent infectious causes of esophagitis (primarily Candida spp.) in the compromised host. Gastritis may be either acute or chronic. Symptoms include epigastric pain, nausea, and vomiting. Infections such as salmonellosis or cytomegalovirus (CMV) infection may cause acute gastritis in the compromised host; Helicobacter pylori is the prototype infection for chronic gastritis (4). Necrotizing enterocolitis is a serious disease affecting low-birthweight neonates, with high morbidity and mortality without a known microbial etiology (5). Lower-GI infections may be associated with fever, abdominal pain,
nausea, vomiting, and diarrhea. Microbial agents that cause diarrhea and enterocolitis are numerous and may cause direct damage to the intestinal mucosa or may be mediated through the production of toxins. Diarrhea of unknown etiology is common in the neutropenic host (neutropenic enterocolitis, typhilitis) and occurs in adults and pediatric populations, mainly associated with acute leukemia and use of cytotoxic drugs (6). Proctitis is mainly due to the manifestations of common sexually-transmitted diseases, such as lymphogranuloma vene-

<table>
<thead>
<tr>
<th>Agent</th>
<th>Disease Associations</th>
<th>Diagnostic Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Salmonella</em> spp.</td>
<td>enterocolitis, bacteremia</td>
<td>culture, NAAT</td>
</tr>
<tr>
<td><em>Campylobacter</em> spp.</td>
<td>enterocolitis, bacteremia</td>
<td>fecal Gram stain, culture, NAAT</td>
</tr>
<tr>
<td><em>Shigella</em> spp.</td>
<td>enterocolitis</td>
<td>culture, NAAT</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>enterocolitis</td>
<td>culture, fecal-toxin assays, NAAT</td>
</tr>
<tr>
<td><em>Aeromonas</em> spp.</td>
<td>diarrhea, serious extraintestinal disease</td>
<td>culture, fecal-toxin assays, NAAT</td>
</tr>
<tr>
<td><em>Plesiomonas shigelloides</em></td>
<td>enterocolitis</td>
<td>culture, fecal-toxin assays, NAAT</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>diarrhea, pseudomembranous colitis</td>
<td>culture, fecal-toxin assay, immunoassay, NAAT</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>enterocolitis, bacteremia</td>
<td>histopathology, culture, NAAT</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>enterocolitis, esophagitis less common</td>
<td>histopathology, culture, NAAT</td>
</tr>
<tr>
<td><em>Mycobacterium spp.</em></td>
<td>enterocolitis (MAC), esophagitis and gastritis less common</td>
<td>histopathology, culture, NAAT</td>
</tr>
<tr>
<td><em>Helicobacter</em> spp.</td>
<td>gastritis, no increased risk factors in HIV for <em>H. pylori</em>. Other species may cause gastroenteritis</td>
<td>histopathology, culture, NAAT</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>proctitis</td>
<td>culture, NAAT, serology</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida</em> spp.</td>
<td>oropharyngeal, esophagitis</td>
<td>Gram or fungal stain, histopathology</td>
</tr>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>enterocolitis, esophagitis</td>
<td>histopathology, culture, urinary antigen</td>
</tr>
<tr>
<td><em>Pneumocystis</em></td>
<td>esophagitis uncommon, extrapulmonary disease is rare</td>
<td>histopathology, immunofluorescence</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>upper and lower GI disease, uncomon</td>
<td>histopathology, culture, NAAT</td>
</tr>
<tr>
<td><em>Aspergillus</em> spp.</td>
<td>localized infection uncomom, usually in context with disseminated disease</td>
<td>histopathology, culture</td>
</tr>
<tr>
<td><em>Penicillium marneffi</em></td>
<td>diarrhea</td>
<td>histopathology, culture</td>
</tr>
<tr>
<td><em>Zygomycetes</em></td>
<td>upper and lower GI tract</td>
<td>histopathology, culture</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Cytomegalovirus</em></td>
<td>upper and lower GI tract</td>
<td>histopathology, culture, antigenemia, viral load</td>
</tr>
<tr>
<td><em>HIV</em></td>
<td>esophagitis uncommon</td>
<td>histopathology, NAAT</td>
</tr>
<tr>
<td><em>Herpes simplex</em></td>
<td>esophagitis</td>
<td>histopathology, NAAT</td>
</tr>
<tr>
<td><em>Varicella zoster</em></td>
<td>esophagitis and enterocolitis uncomom</td>
<td>histopathology, NAAT</td>
</tr>
<tr>
<td><em>HHV-8</em></td>
<td>gastric involvement complicating skin disease</td>
<td>NAAT</td>
</tr>
<tr>
<td><em>HHV-6</em></td>
<td>gastro-duodenal disease, colitis</td>
<td>immunoassay (enteric adenovirus 40, 41), culture, NAAT</td>
</tr>
<tr>
<td><em>Adenovirus</em></td>
<td>hemorrhagic colitis</td>
<td>histopathology, viral load</td>
</tr>
<tr>
<td><em>EBV</em></td>
<td>PTLD, intestinal obstruction, bleeding oral hairy leukoplakia</td>
<td>culture, NAAT</td>
</tr>
<tr>
<td><em>Enterovirus</em></td>
<td>prolonged diarrhea</td>
<td>electron microscopy, NAAT</td>
</tr>
<tr>
<td><em>Norovirus/Sapovirus</em></td>
<td>severe diarrhea, dehydration</td>
<td>immunoperoxidase, NAAT</td>
</tr>
<tr>
<td><em>Astrovirus</em></td>
<td>severe diarrhea, dehydration</td>
<td>histopathology, NAAT</td>
</tr>
<tr>
<td><em>Rotavirus</em></td>
<td>severe diarrhea, dehydratation</td>
<td>histopathology, NAAT</td>
</tr>
<tr>
<td><em>Human papilloma virus</em></td>
<td>oropharyngeal lesions</td>
<td>histopathology, NAAT</td>
</tr>
<tr>
<td><strong>Parasites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Cryptosporidium</em></td>
<td>diarrhea common, gastritis uncomom</td>
<td>histopathology, immunoassay, O&amp;P with special stains, DFA, NAAT</td>
</tr>
<tr>
<td><em>Giardia lamblia</em></td>
<td>chronic diarrhea in IgA deficiency</td>
<td>immunoassay, O&amp;P, DFA, NAAT</td>
</tr>
<tr>
<td><em>Microsporidium</em></td>
<td>enterocolitis</td>
<td>histopathology, O&amp;P with special stains</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
<td>enterocolitis, extraintestinal disease</td>
<td>histopathology, immunoassay, O&amp;P, NAAT</td>
</tr>
<tr>
<td><em>Leishmania</em></td>
<td>upper and lower gastrointestinal disease</td>
<td>histopathology, immunoassay, O&amp;P</td>
</tr>
<tr>
<td><em>Strongyloides</em></td>
<td>autoinfection and dissemination</td>
<td>histopathology, O&amp;P</td>
</tr>
<tr>
<td><em>Cyclospora cayetanensis</em></td>
<td>severe diarrhea</td>
<td>histopathology, O&amp;P</td>
</tr>
<tr>
<td><em>Isospora belli</em></td>
<td>severe diarrhea</td>
<td>histopathology, O&amp;P</td>
</tr>
</tbody>
</table>

*NAAT, nucleic acid-amplification tests; MAC, Mycobacterium avium complex; HIV, human immunodeficiency virus; LGV, lymphogranuloma venerum; GI, gastrointestinal; HHV, human herpesvirus; EBV, Epstein-Barr virus; PTLD, posttransplantation lymphoproliferative disease; O&P, ova and parasite examination; DFA, direct fluorescent antibody.
reum, and may be associated with rectal pain, tenesmus, pruritus, and fever in invasive disease (7). Graft-versus-host disease (GVHD) is a common complication in patients undergoing hematopoietic stem-cell transplants (HSCT) and also occurs in patients receiving solid-organ transplants. GVHD may be associated with nausea, vomiting, diarrhea, and abdominal pain and it can mimic a variety of infectious diseases (8).

Opportunistic infections in the compromised host usually occur during the first year following a decrease in host immunity. The greatest risk after solid-organ transplant occurs during the first year, particularly in the first 6 months (9, 10). Opportunistic infections have dramatically decreased in patients with HIV receiving highly active antiretroviral therapy (11). Infections of the GI tract in particular appear to be decreasing in patients with HIV; however, infections still occur, mainly Candida spp. esophagitis, CMV esophagitis, or colitis (12). Noncompliance with medications is a major risk factor for developing opportunistic infections in this population (12).

Other risk factors for developing GI infections in the compromised host include the use of cytokine antagonists and newer immunotherapies that deplete lymphocyte subpopulations (13). In solid-organ transplant patients at the University of Pittsburgh receiving alemtuzumab (anti-CD52), for example, 10% of patients developed opportunistic infections, including CMV GI disease (enteritis, gastritis) and esophageal candidiasis (14). CMV ileitis and listeriosis have been reported following infliximab (anti-TNF-α) therapy (15, 16).

**AGENTS**

**Bacteria**

The common microbial agents of foodborne diarrheal illness, Salmonella spp., Campylobacter spp., Shigella spp., Escherichia coli, and Listeria monocytogenes, all affect the compromised host, but with increased risk of infection and severity. Salmonellosis may be self-limited, severe, and persistent with fever, bloody diarrhea, and weight loss, or septicemic (with or without GI symptoms) (17). The incidence of salmonellosis in patients with HIV is 20 to 100 times greater compared to the general population without HIV (17). Recurrent bacteremia also occurs at a higher rate in patients with AIDS. Patients with campylobacteriosis may exhibit persistent
diarrhea, bacteremia, and extraintestinal involvement \((18)\). Patients with HIV infection are estimated to have a 39-fold increased risk for developing *Campylobacter* infection over the general population, particularly in men who have sex with men (MSM) \((17)\). Development of antimicrobial resistance in *C. jejuni* while on therapy appears to be more frequent in HIV-positive patients \((17)\). *C. fetus* subspecies *fetus* causes serious infection in patients who are pregnant, or in patients with other underlying disorders such as cirrhosis, diabetes, hematologic malignancies, or HIV \((19)\). Although gastroenteritis occurs with *C. fetus* subspp *fetus*, the incidence is probably underestimated because the organism may not grow well in routine stool cultures used for *C. jejuni* \((20)\). There is also an increased risk of shigellosis in MSM and *Shigella* bacteraemia is more common in patients with HIV \((17)\). In the transplant population, listeriosis may occur with increased frequency, particularly during the first few months posttransplant \((10)\). The most serious complications from *Listeria* infection are sepsis and infection of the central nervous system; however, patients with listeriosis may initially have abdominal cramps and diarrhea \((21)\). Additionally, there may be an increased risk of serious *Listeria* infections in patients treated with anti-TNF-α therapeutic agents \((22)\). *Aeromonas* spp. are a cause of diarrhea in the normal host, but cause serious extraintestinal disease in the compromised host, particularly in patients with malignancies and hepatobiliary disease \((23, 24)\). *Plesiomonas shigelloides* may cause more severe diarrhea in the compromised host, but this has not been well studied \((25)\). *Clostridium difficile*-associated diarrhea and colitis occur in both competent and compromised hosts and nosocomial infections in compromised hosts are common. Populations at greater risk for *Clostridium difficile* infection (CDI) include those with advanced HIV and HSCT and solid-organ transplant recipients \((26)\). Refractory *C. difficile* disease is associated with a lack of antibody response to *C. difficile* toxins and may respond to infusion of intravenous immunoglobulin \((27)\), suggesting that patients with disorders affecting immunoglobulin production may be at risk for persistent disease.

The most common mycobacterial infections causing GI disease in the compromised host are those caused by *Mycobacterium avium-intracellulare* complex (MAC). The incidence of disseminated MAC in AIDS is 20% to 40% in the absence of antiretroviral therapy (ART) or prophylaxis \((17)\), with an incidence rate of 2 per 100 person-years in patients with CD4+ T cells >100–200/µL and receiving effective prophylaxis or responding to ART treatment \((17)\). In children with AIDS, disseminated MAC appears to be more common among children with hemophilia or transfusion-acquired HIV infection (~14%), compared with those with perinatal HIV infection (5%) \((28)\). Symptoms include fever, night sweats, weight loss, fatigue, chronic diarrhea, and abdominal pain. Gastric ulceration, enterocolitis, enteric fistulae, and intra-abdominal abscess and hemorrhage are common manifestations of disseminated MAC, with the duodenum being the most common site affected \((29)\). Esophagitis and gastritis are uncommon manifestations of non-tuberculous mycobacterial infections in this population. *M. tuberculosis* may cause extrapulmonary disease affecting the GI tract as a result of disseminated disease or primary intestinal involvement \((30)\). Intestinal tuberculosis has been increasingly seen in the compromised patient, associated with the HIV epidemic, and in patients from outside the U.S. from endemic areas of tuberculosis, such as the Indian subcontinent and Southeast Asia \((31)\). The most common sites are the ileocecal and jejuni-ileum sites, and less commonly include the esophagus, stomach, and duodenum \((32, 33)\). Patients may have signs suggestive of acute appendicitis or intestinal obstruction and can have rectal lesions presenting as perirectal abscess, fistulae, or fissures \((32)\).

*H. pylori* is the most common cause of chronic active gastritis in the competent host and there is no evidence that patients with underlying immunodeficiencies are at increased risk for infection. Other species of *Helicobacter* such as *H. cinaedi* and *H. fennelliae*, are associated with proctocolitis and enteritis in the compromised host and may be associated with bacteremia \((34)\). A number of other *Helicobacter* species have been isolated infrequently from patients with gastroenteritis, but may be difficult for most laboratories to isolate \((35)\). Lymphogranuloma venereum is associated with anorectal syndrome with symptoms of anal pruritus, bloody mucopurulent rectal discharge, and localized tenderness \((7)\). *Treponema pallidum* causes syphilis in both competent and immunocompromised patients and is a rare cause of GI infection; gastric syphilis has been reported in patients with HIV infection, but whether there is an increased risk is unknown \((36)\).

**Fungi**

*Candida* spp., most commonly *C. albicans*, are the most common cause of esophagitis in the compromised host. Oral candidiasis is frequently associated with radiotherapy and chemotherapy for treatment of solid tumors and hematologic malignancies and is particularly common in HIV-positive patients with low CD4+ T-cell counts, occurring in about 10% to 15% of patients and
associated with frequent recurrences (3, 37). The incidence of Candida esophagitis has declined in the ART era, with increasing CD4+ T-cell counts accounting for the dramatic improvement (38). Oral thrush is common among HIV-infected children. Candida esophagitis occurs in 12% to 16% of children aged <13 years in the United States (28). A related species, C. dubliniensis, has been reported with increasing frequency as a cause of oral candidiasis in HIV and non-HIV patients, in primary and refractory infections (39, 40).

GI histoplasmosis, caused by Histoplasma capsulatum, occurs mostly in the competent host, but risk increases in patients with HIV and is predominant in males (41). Patients receiving anti-TNF-α therapy for diseases like inflammatory bowel disease (IBD) are also at increased risk for histoplasmosis (42). The first year following solid-organ transplants is also high risk for histoplasmosis (43). GI disease occurs in less than 10% of patients with AIDS and disseminated histoplasmosis (17). Esophageal histoplasmosis may occur following acute infection or affecting other parts of the GI tract in disseminated disease (41). Esophageal ulcers with dysphagia or bleeding (41) are seen in patients with immunosuppression. The organism may affect all sites of the GI tract, but primarily affects the colon (44). There is high mortality associated with GI histoplasmosis and the disease is fatal in about one-fourth of cases (44).

Although patients with HIV are at increased risk for disseminated coccidioidomycosis, GI involvement occurs uncommonly (45). Intestinal disease caused by Talaromyces (Penicillium) marneffei, a dimorphic fungus, is an uncommon manifestation of disseminated infection, which is endemic in Southeast Asia and has been reported in patients with HIV, renal transplantation, and corticosteroid treatment (46, 47).

Disseminated cryptococcal infections affecting the esophagus, stomach, duodenum, and colon are rarely reported in the immunocompromised host (48). Localized cryptococcal infection of the esophagus and colon without evidence of disseminated disease has been reported in two patients with Job’s syndrome (49, 50). Extrapulmonary Pneumocystis jirovecii infection affecting the GI tract is rare among adults and children (28, 51).

Invasive aspergillosis of the GI tract usually occurs in the context of disseminated disease in the compromised host affecting both the upper and lower GI tract. In a postmortem study, approximately 30% of patients with disseminated invasive aspergillosis had evidence of GI involvement (52). Localized infection of the GI tract is uncommon (53). Fusarium species may cause GI disease that is indistinguishable clinically and histologically from aspergillosis (2). GI mucormycosis is relatively common in the compromised host and has a very high mortality rate. Of 929 patients with mucormycosis, primarily in low-birth-weight infants, patients with malnutrition and patients receiving peritoneal dialysis, 7% had GI infection (54). In patients receiving solid-organ transplants, GI mucormycosis occurred in 11% of patients with mucormycosis infections (55).

Viruses
Cytomegalovirus is by far the most common viral agent causing GI disease in the compromised host and may cause esophagitis, gastritis, and enterocolitis. CMV enterocolitis is common in advanced HIV, solid-organ, bone-marrow and HSCT recipients, and common-variable immunodeficiency. Esophagitis may occur in <5% to 10% of patients with AIDS and CMV end-organ disease, presenting with fever, odynophagia, nausea, and mid-epigastric or retrosternal discomfort (17). The most common site affected is the colon, occasionally affecting more than one GI site and sometimes becoming disseminated (56). The prevalence of GI CMV disease appears to be steady over the past decade (56). In a study of cancer patients over an 18-year period, the incidence of GI disease caused by CMV was 20 per 100,000 cases, with a higher incidence among patients with hematologic cancers (102/100,000) compared to patients with solid tumors (6/100,000) (56). Patients receiving allogeneic stem-cell transplants had significantly higher incidence (608/100,000) than autologous transplants (58/100,000). Of seropositive allograft recipients who developed late CMV disease, 26.2% had GI disease (57). Colitis is the most common GI manifestation among HIV-infected children with CMV end-organ disease, also causing oral and esophageal ulcers, hepatic involvement, ascending cholangiopathy, or gastritis (28). In patients receiving organ transplants, seronegative recipients (R-) receiving organs from seropositive donors (D+) are at the highest risk for severe acute disease and thus, CMV should be strongly considered in acute GI disease in this setting (58).

Herpes-simplex virus can cause esophagitis in HIV-infected patients and solid-organ transplant patients (59). It is usually seen in the oropharynx in patients receiving bone-marrow transplants. There may be vesicles and punched out ulcerations with an adherent pseudo-membrane (4). Varicella-zoster virus is a less common cause of GI disease in the compromised host, and may cause esophagitis and enterocolitis. Human herpesvirus (HHV)-8, associated with Kaposi’s sarcoma, may cause gastritis as a complication of primary skin disease.
Epstein-Barr virus-associated posttransplant lymphoproliferative disorder (PTLD) may have a GI component; the clinical presentation of which may include GI bleeding, obstruction, and perforation (60). The incidence of PTLD affecting the bowel in solid-organ allograft recipients is estimated at 11% overall, but is 31% in children less than 5 years of age (61). HHV-6 has been reported to cause colitis in patients following renal transplant and is suggested as an etiologic agent of gastro-duodenal disease and colitis following HSCT (62, 63). HIV may be associated directly with enterocolitis with histologic features similar to celiac disease (2).

Noroviruses are commonly associated with infection and gastroenteritis in both immunocompromised as well as immunocompetent individuals, causing more significant disease in compromised individuals (52). The characteristics of norovirus illness in this patient population include persistent diarrhea with prolonged viral shedding, particularly in immunosuppressed children (64, 65). Noroviruses, along with sapoviruses, have also been associated with chronic diarrhea in transplant recipients (66). Astroviruses are also a common cause of gastroenteritis, accounting for up to 9% of nonbacterial gastroenteritis in pediatric populations worldwide (67). While most cases are self-limiting, there have been recent reports of strains of astrovirus, in particular the VA1/HMO clade, that can cause encephalitis in severely compromised patients (68, 69).

Adenovirus infections usually cause self-limited GI disease in the immunocompetent host. Adenovirus may cause diarrhea and hemorrhagic colitis in bone-marrow transplant patients and solid-organ transplant recipients, particularly small-bowel transplant recipients, and may also lead to serious disseminated disease (70, 71). The compromised host is susceptible to GI infection with rotavirus and infection may be associated with prolonged diarrhea and dehydration (72). Whether compromised patients are at greater risk for rotavirus infection is not clear.

Parasites

A number of parasitic agents cause disease in the immunocompromised host. Cryptosporidiosis is caused by Cryptosporidium parvum and C. hominis, which are indistinguishable morphologically (73). The incidence of cryptosporidiosis is less than 1 per 100 person-years in developed countries with good hygiene and available ART (12). The disease is not self-limited in the compromised patient, and is mostly seen in HIV, but other groups (Hodgkin’s lymphoma, renal transplant, other solid-organ transplant) may also be at risk. The greatest risk is in HIV patients with CD4+ T-cell counts of <100 cells/μl (17). Biliary disease is more common in HIV patients, associated with low CD4+ T-cell counts of <50 cells/μl (74). Watery and persistent diarrhea is the most common manifestation in children; fever and vomiting are also relatively common (28).

Microsporidiosis is unique to patients with profound immunosuppression, particularly seen in patients with HIV infection. In the pre-ART era, 2% to 70% of HIV patients with diarrhea were infected with microsporidia, but the prevalence has dropped in the post-ART era. Infection is mostly seen when the CD4+ T-cell count is <100/μl (5). While not reported frequently, other individuals receiving solid-organ transplant and with other underlying diseases associated with various degrees of immunosuppression have developed microsporidiosis (75). Two species are particularly associated with gastrointestinal infection. Enterocytozoon bieneusi is associated with persistent diarrhea, fever, weight loss, malabsorption, and cholangitis. Encephalitozoon intestinalis is associated with diarrhea, disseminated infection, and superficial keratoconjunctivitis (24).

Giardia lamblia infections may have a chronic course in patients with immunodeficiencies, particularly patients with IgA deficiency or other disorders associated with immunoglobulin deficiencies (76). E. histolytica causes enterocolitis and extraintestinal disease (liver abscess) and may be more common in the compromised patient, particularly in malnourished children (77). Acute necrotizing colitis is a rare complication with high mortality seen predominantly in developing countries (78). Toxic megacolon is also a rare complication and associated with corticosteroid use (78). Strongyloides causes severe hyperinfection in immunosuppressed patients – patients at risk include those treated with immunosuppressive drug therapies and patients with other conditions such as leukemia, lymphoma, and solid-organ transplants and also in HSCT (59, 79, 80). GI symptoms occur most frequently in hyperinfection as well as extraintestinal manifestations (80). Cyclospora cayetanensis is a foodborne illness causing persistent diarrhea in the compromised host, but usually self-limited in competent hosts. Cystoisospora belli (Isospora) may cause severe diarrhea in patients with AIDS, affecting primarily the small intestine, and is often associated with severe dehydration (17).

Leishmania spp. are an uncommon cause of GI infection in the compromised host. Disseminated visceral disease syndrome is the most common clinical presentation in AIDS (~70%) (17). Advanced immunosuppression (CD4+ T-cell count <100) in HIV-positive patients is a risk factor for developing disease. With
profound immunosuppression, there may be involve-
ment of the upper and lower GI tract, with the stomach,
duodenum, and colon sites affected (81). In a series of
patients with HIV and *Leishmania* infections, 11 of 91
patients had a diagnosis of visceral leishmaniasis (VL)
based on the detection of organisms in the GI tract (81).
More generally, VL in the non-HIV host is being more
frequently reported in the transplant population, pa-
tients with hematologic malignancies, rheumatologic
diseases, and a variety of other diseases with underlying
immunosuppression (82).

**DIAGNOSTIC APPROACHES**

Because of the numerous microbial agents causing GI
infections in the compromised patient, the diagnostic
workup can be both prolonged and costly (Table 1).
There are several approaches to differential diagnosis
of immunocompromised patients with GI infections.
Patients with uncomplicated acute gastroenteritis may
be classified as either having community-acquired, nos-
ocomial, or persistent infections as suggested by the
Infectious Diseases Society of America (IDSA) (83). Of
course, the immunocompromised host is at risk not only
for the common enteric pathogens seen in the competent
host, but also for a variety of infections not normally
seen in the competent host, particularly infection with
latent viruses, opportunistic mycobacterial and fungal
infections, and parasitic infections (Fig. 1). In the IDSA
algorithm, the differential diagnosis in the patient with
an acute community-acquired diarrheal illness should
first include the common community-acquired enteric
bacterial pathogens. Agents such as *Salmonella* spp.,
*Campylobacter jejuni*, *Shigella* spp., *Aeromonas* spp.,
*Plesiomonas shigelloides*, and other selected pathogens
should be considered depending upon the patient’s his-
tory. Additional bacterial agents such as *stx*-producing
*E. coli* and *Vibrio* spp. should be performed based on
history and relative prevalence of organisms in the
geographic region of the patient. Direct examination of
stool samples by Gram stain for *Campylobacter* spp.
may be a rapid, sensitive, and specific approach to di-
gnosing acute campylobacter infection, but has no
value for the diagnosis of other bacterial enteropatho-
gens (84). Other rapid methods such as detection of fecal
white cells have little to no value for the diagnosis of
bacterial GI pathogens (84). There are a number of
blood and fecal biomarkers that have been assessed as
screening tools for GI infections, including C-reactive
protein (blood), fecal lactoferrin, and fecal calprotectin
(85). It is unclear whether these tests have any clinical
utility as screening tools given a wide range of sensitiv-
ity, specificity, and predictive values (85). Stool culture
is the primary method used for detecting bacterial
enteropathogens and in acute bacterial gastroenteritis,
culture of up to two fecal samples has a high sensitivity
of 99%, although a single sample has a sensitivity of
96.9% (86). The detection of *L. monocytogenes* in stool
cultures is problematic for clinical microbiology labo-
ratories due to the lack of selective and differential me-
dium for this organism, but in high concentrations may
be detected on blood agar used as part of the routine
setup for stool cultures. The Centers for Disease Control
and Prevention (CDC) currently recommends that lab-
oratories both culture for *E. coli* O157 and simultaneous
detection of *stx*-producing *E. coli* (STEC) using non-
culture methods (87). Commercially available stool
toxin tests for STEC for detecting hemorrhagic *E. coli*
other than O157 are readily available (88). However,
the decision for routine laboratory testing versus selec-
tive testing for STECs may be based on local/regional
prevalence of STECs. Nosocomial infections with the
above enteric pathogens, other than with *C. difficile* and
norovirus, are extremely rare and should be considered
in the context of suspected outbreaks. Patients with a
history of antibiotic exposure who develop community-
acquired or nosocomial diarrhea may have *C. difficile*
disease and should be tested for fecal toxin. Importantly,
since *C. difficile* is commonly carried in asymptomatic
individuals, testing should only be performed on diar-
rheal stools (89). This is typically achieved either by
immunoassay testing for the toxin itself or molecular
testing for the toxin genes (*tcdA* and/or *tcdB*). Some
laboratories screen samples first using a combined *C. dif-
ficile* antigen/toxin immunoassay and then arbitrate
antigen-positive/toxin-negative samples via molecular
assay and this has been shown to be cost-effective (90).
Although outbreaks with norovirus have been recog-
nized, many institutions lack the capability of testing for
norovirus onsite. Studies have demonstrated that the
most common genotype associated with healthcare
outbreaks is GI.4 (91). The advent of new commercially
available molecular tests (either singly or as part of a
panel) to detect norovirus, will lead to the development
of monitoring strategies similar to those seen in *C. dif-
ficile*. Interestingly, recent data suggests that norovirus
can be detected in the air of healthcare facilities under-
going outbreaks, emphasizing the importance of being
able to detect and control this pathogen (92). The in-
testinal parasites generally cause persistent infections
and should also be considered in patients with unre-
mitting diarrheal illnesses.
A major change in how GI infections are identified in both the immunocompetent and immunocompromised patient is the advent of commercially available multiplex molecular assays for the detection of agents that cause gastroenteritis. While some single-target assays exist (e.g., norovirus and C. difficile), their utility is limited to looking for specific pathogens under specific indications. The multiplex panels, however, are widely applicable to any condition that is consistent with infectious gastroenteritis. These assays vary widely in their complexity as well as number and types of targets. Some assays, such as the enteric panel on the Verigene system (Nanosphere, Northbrook, IL), have fewer targets (n=9), only detecting bacterial or viral causes of gastroenteritis. Other assays, such as the FilmArray GI panel with 22 targets (Biofire, Salt Lake City, UT) or the Luminex GI-pathogen panel (GPP) with 14 targets (Luminex, Austin TX), detect parasites as well. There are a number of strengths associated with these assays, including the ability to test for multiple different targets from a single sample. Importantly, studies have shown that these tests can not only detect pathogens that are not recovered in culture due to low numbers, but also test for pathogens that the clinician may not have thought of or ordered otherwise (93). Additionally, these assays can provide results in a matter of hours as opposed to the 2–3 days that a traditional workup for GI infections would take. Significant challenges are also presented by these systems. Some of the systems include targets such as enteroaggregative E. coli (EAEC) or enteropathogenic E. coli (EPEC) whose clinical significance and disease course, especially in the immunocompromised patient, are poorly understood. Other targets, such as astrovirus or sapovirus, do not have other cleared assays to use as comparators, so their performance is unknown. Additionally, early studies have demonstrated a substantial increase in the positivity rate associated with the transition to molecular techniques. Clinical studies with the FilmArray panel have shown positivity rates in excess of 50% (94). No studies to date have been performed to look at whether this increase in positivity is due to an increase in detection of true disease or increased detection of colonization or shedding of nucleic acid. Further complicating the interpretation of these assays are the large numbers of mixed infections that are detected, which previously would have been attributed to a single agent. Finally, these assays may also adversely affect public health, as isolates may no longer be available for epidemiologic surveillance and outbreak investigation.

Fungal infections of the GI tract should be considered in patients with moderate to severe immunosuppression and may be detected through a combination of histopathologic analysis of tissue, culture of affected tissue, and immunoassays. There is limited data on the diagnosis of fungal infections in the GI tract and comparison of diagnostic methods. Recovery of mucorales from tissue may be negative in histopathologically positive tissues and may be due, in part, to poor preparation of tissues for culture, such as grinding the tissue (95). A recent study showed that recovery of Aspergillus spp. and mucorales from respiratory-tissue biopsies by culture was less sensitive than histopathology; ~78% sensitivity for detecting Aspergillus spp. and 33% sensitive for detecting mucorales, suggesting that similar results would be obtained with GI tissues (96). In recent years, the use of antigen detection for diagnosis of disseminated histoplasmosis has become an important tool for diagnosis (41). There is little data on the performance of the Histoplasma urinary-antigen test specifically in GI histoplasmosis; however, the sensitivity of urinary antigen is approximately 90% in disseminated disease (41). Aspergillus-antigen detection in serum is recently commercially available, and although the test is Food and Drug Administration (FDA)-cleared for routine use, the indications and optimal use of this test as an aid for invasive aspergillosis is still undergoing investigation (97). Practice guidelines for the diagnosis and management of invasive aspergillosis are forthcoming from the IDSA.

The diagnosis of viral infections of the GI tract may be accomplished by histopathologic analysis of tissue and immunologic and molecular methods for detection (see other chapters in this volume for specific viral agents). Diagnostic tests on stool have begun to implicate a large number of potential pathogens in transplant recipients. Detection of adenovirus and norovirus in stool is well established, but recent reports of BK virus as well as typical (Clostridium difficile) and atypical (Pseudomonas aeruginosa) bacterial GI pathogens have been identified as well (98–100). The value for utilization of stool to identify significant bacterial pathogens remains to be seen. However, for viral pathogens, it has been shown to add significant value as detection of adenovirus in stool by polymerase chain reaction (PCR) can predict invasive disease and viremia (101, 102). For definitive diagnosis, the approach to diagnosis of viral infection in a particular patient varies considerably. Histopathologic analysis of GI tissues, particularly in the lower GI tract, via PCR or histopathology remains the most common method. Among HIV patients with CMV GI disease, characteristic inclusions of CMV by histopathologic analysis of duodenal/rectal biopsies were detected in
33% to 54%, compared with 54% to 75% for culture and 100% detection using quantitative PCR (103). Recent studies looking at a number of different immunocompromised populations demonstrated 90% correlation between patients with positive histopathologic analysis and PCR positivity (104). In patients with lesions in the oral cavity or esophagitis, herpes simplex virus (HSV) is the most common viral agent involved and detection of HSV by direct immunofluorescent staining of smears, culture, or molecular testing of material from the lesions is an approach for rapid diagnosis. Importantly, these lesions may not be readily distinguished from those due to reactivation of varicella zoster virus (VZV) in an immunocompromised patient, suggesting that testing for both agents is a prudent approach. A comparison of cytologic and histopathologic examination with culture for detecting CMV and HSV esophageal ulceration in 15 HIV patients showed that cytopathology was very insensitive (0%), whereas culture detected 26.7% and histopathology (using immunohistochemical staining) was 100% sensitive (105). Tissue sampling may be an important issue for the diagnosis of viral esophagitis as multiple biopsies are needed to increase sensitivity for detection of CMV in HIV patients (106). At this time there are no FDA-cleared tests for the molecular detection of the herpesviruses in tissue, an issue that will need to be addressed going forward.

In patients receiving solid-organ transplants, the amount of time that has transpired posttransplant is helpful for considering potential viral agents of disease. For patients receiving transplants within one month of developing illness, HSV is the most common herpesvirus to be considered. CMV usually occurs after one month or longer, with Epstein-Barr virus (EBV) and VZV occurring several months following transplant (107). Temporal associations are more difficult in the HSCT population as varied prophylaxis regimens are utilized. In those without prophylaxis, HSV reactivation tends to occur within the first month and VZV between months 3–12 (108). Herpesvirus infections (CMV, EBV, HSV, VZV) are related to the degree of immunosuppression in patients with HIV infection. The temporal appearance of these viruses in HIV is related to low CD4+ T-cell counts (107). In the solid-organ and HSCT recipient, knowledge of the pretransplant serostatus for both the donor and recipient is helpful in estimating the risk of disease, particularly with CMV. Seronegative recipients (R-) who receive allografts from seropositive donors (D+) have a high risk for developing primary CMV disease. Seropositive recipients receiving seropositive or seronegative transplants are at risk for reactivation disease, thus, testing for CMV infection in this population is usually initiated at the first signs of GI infection. Viral load testing of plasma samples by molecular or antigenemia assays (described in more detail in Cytomegalovirus) are highly sensitive for detecting early CMV disease, especially in D+/R- cases, and can be used as indicators for preemptive antiviral therapy (109).

Testing for community-acquired viral infections, such as rotavirus and adenoviruses, can be performed using commercially available immunoassays for detection of viral antigen (110). Several commercial immunoassays for enteric adenovirus (Types 40/41) have sensitivities >90% compared with culture or electron microscopy, but the sensitivity of these assays may be reduced due to viral variants (111). More recent studies using reverse transcriptase (RT)-PCR show that immunoassays for both rotavirus and adenovirus substantially underestimate infections and molecular testing would appear to be preferred in antigen-negative cases to rule out infection (112). Importantly, in HSCT recipients, disease GI shedding of adenoviruses expand beyond the typical enteric 40/41 types. Norovirus detection is accomplished by RT-PCR assays and is usually available in commercial-reference laboratories or local/state public-health laboratories. The detection of norovirus in the hospital laboratory is becoming easier with the advent of multiplex panels that include norovirus as a target as well as sample to answer solutions such as the GeneXpert system (Cepheid, Sunnyvale CA). Several commercial immunoassays are available outside of the U.S.; however, these are inferior to current molecular methods for detecting norovirus (113, 114). Nosocomial transmission of rotavirus, adenovirus, astroviruses, and noroviruses may occur and should also be considered in the workup of nosocomial enteric infections in the compromised host (115, 116). Serologic tests for herpesviruses, other than for exposure status, are not useful for the diagnosis of viral infections in the compromised host. In patients suspected of having viral infections due to reactivation, such as with CMV, culturing CMV from a biopsy or cells from the colon or the esophagus may have low specificity for the diagnosis of CMV colitis or esophagitis because patients with low CD4+ T-cell counts might be viremic and have positive cultures for CMV in the absence of clinical disease (17). Similarly, detection of HHV-6 in blood samples may represent reactivation of the latent virus, without evidence of causation (63).

Patients with a persistent (>14 days) (117), community-acquired diarrheal illness with negative
bacterial-stool studies should be evaluated for the presence of parasitic agents, particularly giardia and cryptosporidium. *E. histolytica* and other intestinal helminths, nematodes, and trematodes should be considered in patients with relevant exposures and/or a history of travel to endemic areas. Patients with abdominal pain and unexplained eosinophilia or travel to endemic areas should be tested for the presence of *Strongyloides*, since there is an increased risk for *Strongyloides* hyperinfection syndrome in the immunosuppressed patient. In patients with severe immunosuppression, such as the patient with HIV and CD4+ T-cell count <200, microsporidium should also be considered. Parasitic agents affecting the GI tract are frequently diagnosed by examination of fecal samples by either conventional microscopic examination or immunoassay and may also be detected by histologic examination of tissue (73, 118). Examination of two to three fecal samples has high sensitivity for detecting common intestinal parasites (86). Antigen-detection-based immunoassays, particularly for detecting *E. histolytica*, *Giardia lamblia*, and *Cryptosporidium*, are widely used for diagnosis of these infections (119). Details about the performance characteristics of various parasitologic examinations can be found in Parasites.

**SUMMARY**

The approach to the diagnosis of GI infections, particularly diarrheal illnesses, in the compromised host is rather complex and there is no simple diagnostic algorithm to follow. The compromised host is susceptible to all of the common bacterial, viral, and parasitic agents that cause disease in immunocompetent hosts; thus, assessment of the patient for risk factors for specific infections will help narrow potential causative agents. An initial approach is shown in **Fig. 2.** In a patient presenting with acute lower-GI infection, consider whether this is a community- or healthcare-associated infection. It would be reasonable to perform bacterial stool cultures initially as well as tests for *C. difficile* (if risk factors are present). Viral studies for norovirus and enteric adenoviruses may also be warranted as part of the initial workup. For patients with recent travel within the U.S. or outside the U.S., with potential exposures putting the patient at risk for parasitic diseases, additional tests for relevant parasites should be ordered during the initial workup. Beyond the above studies, other agents, particularly viral, fungal, and mycobacterial agents, should be considered based on the patient’s degree of immunosuppression (Fig. 1), time transpired since initial solid-organ transplant or HSCT, risk for

**FIGURE 2** Algorithm for diagnostic approach to lower-gastrointestinal infections in the compromised host.
GVHD, and rejection. Consultation with the clinical microbiologist, infectious-disease specialist, and gastroenterologist should be strongly considered in difficult to diagnose patients.

REFERENCES


