Gastrointestinal manifestations 15

15.1 Approach to gastrointestinal symptoms

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Gastrointestinal symptoms and disease are common in people with HIV infection. They may be related to:

i) the epidemiological risk group; for example, enteric pathogens in men who have sex with men or hepatitis B virus in injecting drug users
ii) the degree of immunodeficiency; for example, cytomegalovirus (CMV) colitis and oropharyngeal candidiasis occurs at low CD4 cell counts whereas infection with bacterial enteric pathogens such as salmonella and shigella can occur at any CD4 cell count
iii) toxicity caused by therapy used to treat HIV or related disorders. Examples include diarrhoea associated with protease inhibitor treatment and nevirapine-induced liver injury. Many antiretroviral agents have side-effects and toxicities which affect the gastrointestinal system

The differential diagnoses of gastrointestinal symptoms in people with HIV are listed in Table 15.1. It should be noted that the frequency of clinical symptoms such as diarrhoea and opportunistic infections will differ with geographical region, as diarrhoeal illness and wasting disease are more common in

Table 15.1 Differential diagnosis of causes of gastrointestinal illness

Gastrointestinal illness	Causes	Gastrointestinal illness	Causes
Oesophageal symptoms	Common: Gastro-oesophageal reflux disease *Candida* spp. Cytomegalovirus Large idiopathic ulcers Herpes simplex virus Uncommon: Kaposi's sarcoma Non-Hodgkin's lymphoma *Mycobacterium tuberculosis*	Hepatic disorders	Drug toxicity: hepatitis, steatosis (many agents: antiretrovirals especially NNRTI and NRTIs, antifungals such as fluconazole and ketoconazole, co-trimoxazole, and antimycobacterial agents) Hepatotropic viruses: HBV, HCV: chronic hepatitis, cirrhosis, and HAV, HBV, HCV: acute hepatitis Syphilis *Mycobacterium avium* complex *Cryptococcus neoformans* Cytomegalovirus *Bartonella henselae* (peliosis hepatitis) *Mycobacterium tuberculosis* Non-Hodgkin's lymphoma Castleman's disease Kaposi's sarcoma
Diarrhoea	Common: Cytomegalovirus *Salmonella* spp. *Shigella* spp. *Campylobacter* spp. Idiopathic/HIV enteropathy *Clostridium difficile* *Giardia lamblia* Uncommon: *Cryptosporidia* spp. *Microsporidia* *Mycobacterium avium* complex Cyclospora Adenovirus Herpes simplex virus Rotavirus *Yersinia* spp. *Aeromonas* spp. *Entamoeba histolytica* Other viruses Kaposi's sarcoma	Biliary disorders	Processes: Sclerosing cholangitis Papillary stenosis Common bile duct strictures Acalculous cholecystitis Vanishing bile duct syndrome Causes: *Cryptosporidia* spp. Cytomegalovirus *Mycobacterium avium* complex *Microsporidia* Non-Hodgkin's lymphoma Kaposi's sarcoma
		Pancreatitis	Drug toxicity (e.g. didanosine, zalcitabine, stavudine, pentamidine) Opportunistic infections (rare) Tumours (rare)

NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside analogue reverse transcriptase inhibitors.
HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus.

developing countries. Conversely, opportunistic infections such as *Mycobacterium avium* complex (MAC) and CMV are more frequent in developed countries.

15.1.1 Odynophagia and dysphagia

The most common causes of odynophagia and dysphagia in people with HIV are oesophageal candidiasis, CMV ulcers, idiopathic ulcers and ulcers secondary to herpes simplex virus infection.[1] Of patients with dysphagia alone, 54% will have oesophageal candidiasis, and those with odynophagia alone are more likely to have CMV ulcers (42%) or idiopathic ulceration (35%).[1,2] Other causes of oesophageal pathology include Kaposi's sarcoma (KS), non-Hodgkin's lymphoma, reflux oesophagitis and mycobacterial disease.[1] Rarely, *Histoplasma capsulatum* can cause mucosal ulceration at any site in the gastrointestinal tract, and syphilis may present with odynophagia due to syphilitic ulceration.

Patients presenting with oral candidiasis have a high likelihood of concurrent oesophageal involvement. However, those with severe symptoms are more likely to have a cause other than candidiasis found at endoscopy, than are those who are mildly symptomatic.[2] The approach to odynophagia and dysphagia, where history and physical examination do not suggest an alternative diagnosis, is to treat empirically for oesophageal candidiasis with oral fluconazole 200 mg daily. Endoscopy should be performed if symptoms worsen or fail to respond to empirical therapy after several days.[2] If the patient has had extensive prior exposure to azole antifungal agents, the development of azole resistance should be considered and an alternative agent e.g. newer generation azoles, such as posaconazole and voriconazole or an echinocandin such as caspofungin prescribed. Culture and susceptibility testing of *Candida* spp. may assist in the management of patients who fail to respond to standard therapy.

There has been a significant decline in the incidence of oesophageal and oropharyngeal candidiasis since the widespread introduction of combination antiretroviral therapy (cART), but in the cART era, oesophageal candidiasis remains one of the most common AIDS defining illnesses.[3,4]

15.1.2 Gastro–oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) is common in the setting of HIV infection although specific incidence data are not available. Risk factors include smoking, oesophagitis, obesity and medications. In one survey, 56% of patients with HIV took non-prescription antacid drugs.[5] *Helicobacter pylori* infection occurs in approximately 70% of patients with HIV with dyspepsia, with no difference in the rates of associated gastric mucosal changes between patients treated with cART and those untreated.[6] Treatment of GORD with acid-suppressing therapy may have a significant impact on antiretroviral agents and other drugs used in the treatment of HIV. For example, exposure to atazanavir as measured by the area under the curve is reduced by 94% in normal volunteers treated with atazanavir and lansoprazole[7] and a similar finding has been documented in pharmacokinetic studies in a patient with HIV. [8] However, conflicting results have been published: two studies suggest that the concurrent administration of atazanavir and proton pump inhibitors does not affect virological suppression;[9,10] whereas Khanlou and Farthing found that, even with ritonavir boosting, adequate serum levels are not always achieved.[11] Therapeutic drug monitoring may be useful to help determine the significance of potential drug interactions.[12]

Gastric pH may also have an impact on absorption of other agents used in the management of HIV complications. For example itraconazole is poorly absorbed from a hypochlorhydric stomach resulting in potential treatment failure.

15.1.3 Diarrhoea

Since the introduction of cART, the frequency of opportunistic infection of the gastrointestinal tract as a cause of diarrhoea has fallen dramatically. In addition, the use of cART in immunosuppressed patients with chronic diarrhoea resulted in resolution of diarrhoea in 85% of affected individuals.[13] However despite the use of cART, people with HIV can still present with infectious diarrhoea. A recent study found 9% of patients receiving cART had an underlying opportunistic infection as the cause for diarrhoea and 40% of these patients were non-adherent to cART.[14]

Diarrhoea in patients receiving cART can result in a reduction in drug absorption, leading to viral resistance and treatment failure. It is therefore imperative to diagnose and, where possible, treat the cause of diarrhoea. If therapeutic drug monitoring is available to measure the serum levels of the antiretroviral agents, it should be considered as a guide to assess the adequacy of absorption in patients with chronic diarrhoea.

Acute diarrhoea

The causes of acute diarrhoea, defined as the new onset of more than three loose bowel motions in a 24-hour period and present for less than 14 days, in people with HIV without significant immunodeficiency are similar to causes of diarrhoea in the general population. A more extensive differential diagnosis should be considered in the immunodeficient patient where the CD4 cell count is <200 cells/μL. A history of travel, sexual contacts, contact with persons with diarrhoeal illness, medications associated with diarrhoea including recent exposure to antibiotic therapy, the presence of blood or mucous in the stool, fever, frequency, timing and nature of bowel motions, possible precipitating factors and abdominal pain should be elicited. Examination of faecal specimens should include microscopy for red and white blood cells, examination for ova, cysts and parasites including *Cryptosporidia, Cyclospora* and I*sospora,* and bacterial culture including *Clostridium difficile* toxin and culture. Bacterial blood cultures, including blood cultures specific for MAC if the CD4 cell count is <50 cells/μL, should be obtained if the symptoms and signs of a systemic illness are present. Antimotility agents are not recommended if bloody diarrhoea or fever is present. If a patient has fever and diarrhoea with blood and mucous, faecal samples should be obtained and empiric therapy commenced with oral ciprofloxacin 500 mg twice daily.

Chronic diarrhoea

Chronic diarrhoea, defined as diarrhoea present for more than one month, should be investigated thoroughly because many of the causative agents of chronic diarrhoea are treatable. A re-evaluation of the history, especially medication use, and an assessment of immune function are important. Although many cases of diarrhoea are infective, fat malabsorption is common in HIV infection and is independent of cART .[15] At least three faecal

specimens should be obtained to maximise the diagnostic yield, before proceeding to more invasive investigation.[16] There is a smaller incremental increase in diagnostic sensitivity when six faecal samples are analysed. It is important to speak with the staff of the microbiology laboratory to ensure that appropriate investigations have been performed on multiple specimens.

If the diarrhoea is watery and large volume, and therefore likely to be caused by small bowel pathology, the initial recommended investigations include gastroscopy and duodenoscopy with duodenal biopsy. If the diarrhoeal pattern is more consistent with a large intestinal localisation i.e. small volume, with cramping lower abdominal pain, mucous, blood, fever or rectal symptoms then sigmoidoscopy and/or colonoscopy with biopsy of macroscopically abnormal areas is recommended. Biopsy specimens should be examined with special stains such as Giemsa and Ziehl-Neelsen, and immunohistochemistry, viral and mycobacterial cultures and appropriate polymerase chain reaction (PCR) testing such as for lymphogranuloma venereum should be performed. In the event that no cause is identified from the initial biopsy, endoscopy and biopsy of the alternate part of the intestine should be undertaken.

Antiretroviral therapy is an important cause of chronic diarrhoea. All protease inhibitors can be associated with diarrhoea, although the incidence varies according to agent and concomitant therapy. Anecdotal reports of diarrhoea associated with efavirenz and new agents such as raltegravir indicate that most classes of antiretroviral therapy may be responsible for diarrhoea and should always be considered in the differential diagnosis.

In contrast, HIV itself may itself cause diarrhoea (see HIV enteropathy below). Kotler et al.[17] compared the influence of antiretroviral therapy on intestinal mucosa and peripheral blood immediately before, and seven days after starting cART. Treatment was associated with a marked reduction in gastrointestinal symptoms. Similar relative declines in HIV-RNA levels and increases in CD4 cell counts were found in blood and mucosa.

If a cause for chronic diarrhoea cannot be identified, symptom control with oral agents such as loperamide 4-32 mg daily by mouth in divided doses, diphenoxylate 2.5 mg plus atropine 25 µg taken as two tablets four times daily until the diarrhoea is controlled, followed by a maintenance dose, codeine phosphate 30-60 mg four times daily, or morphine may be of benefit. In general, once control of diarrhoea is achieved the medication dose should be reduced to the minimum needed to control symptoms. Other agents used for symptom control include octreotide 50-500 µg subcutaneously three times daily titrated to minimal effective dose and 20 mg hyoscine butylbromide orally four times daily or 20-40 mg subcutaneously four times daily.[18] Secondary lactose intolerance is relatively common after an episode of acute diarrhoea. A low lactose diet may be useful in improving diarrhoeal symptoms. Paradoxically, fibre supplements such as Metamucil may also improve diarrhoea associated with medications.

Inflammatory bowel diseases such as ulcerative colitis and Crohn's disease are rare in the setting of HIV infection but well documented and must always be considered in the differential diagnosis of chronic diarrhoea.

HIV enteropathy

The term HIV enteropathy is used to describe morphological changes in the intestinal mucosa of people with HIV infection who have unexplained diarrhoea.[17] These changes occur in 15-60% of patients with severe refractory diarrhoea.[19] Although HIV-infected cells can be detected in the intestinal lamina propria,[15] there is debate about whether HIV enteropathy represents direct mucosal damage by HIV, or whether the observed mucosal changes are secondary to the immunological or other disturbances induced by HIV infection.

Currently there are two major lines of investigation into the pathogenesis of diarrhoea related to mucosal HIV infection.[20] Studies of intestinal permeability demonstrate that alteration of transepithelial resistance and subsequent changes in ion and water flux occur *in vitro* and in people with HIV infection and diarrhoea[21] and may be mediated by cytokines.[22] An alternative explanation for HIV-associated enteropathy is mucosal cell damage which results in cytoskeletal changes in epithelial cells and may be the pathophysiological consequence of gp120 exposure rather than a direct consequence of epithelial cell HIV infection.[23]

The cardinal morphological changes of HIV enteropathy include inflammatory infiltrates, partial villous atrophy and crypt hyperplasia in the early stages of HIV,[24] and crypt hypoproliferative changes in the latter stages of HIV.[25] Dysfunction of brush-border enzymes accompanies these morphological changes.[26] Studies addressing the management of HIV enteropathy have not been conducted. However, improvements in brush-border-enzyme function[27] and reductions in adhesion-molecule expression, potentially normalising intestinal lymphocyte migration patterns,[28] have been associated with antiretroviral therapy.

15.1.4 Hepatitis

The diagnostic approach to hepatitis is not dramatically altered in the setting of HIV infection, although opportunistic infections and drug toxicities need particular consideration (Table 15.1). Both hepatitis A virus (HAV) and HBV can cause acute hepatitis in those with HIV who are non immune. Although acute hepatitis C virus (HCV) infection is commonly asymptomatic, it can also result in acute hepatitis.

Other causes of hepatitis in people with HIV include the recent introduction of antiretroviral therapy. The non-nucleoside reverse transcriptase inhibitors are the most likely class of antiretroviral agents to cause acute hepatitis, and tipranavir is also associated with greater rates of hepatitis than the other protease inhibitors. The syndrome of lactic acidosis with hepatic steatosis related to the nucleoside analogue reverse transcriptase inhibitors may occur years after the introduction of cART and is most commonly associated with didanosine or stavudine therapy. Imaging may indicate hepatomegaly with fatty liver, consistent with a diagnosis of hepatic steatosis and lactic acidosis, and liver biopsy is used to confirm suspected hepatitis or steatosis. People with HIV and chronic HCV or HBV co-infection are more likely to experience abnormalities of liver function when treated with cART than those with HIV infection alone.

Persons without a clear cause for abnormal liver function in the context of cART should be investigated for HBV and HCV infection. Molecular testing for hepatitis B DNA may be necessary to exclude precore mutant virus and hepatitis C

RNA should be measured as false negative antibody testing in the setting of HIV infection is well described.[29] Syphilis should be considered in the differential diagnosis of abnormal liver function tests in people with HIV infection as secondary syphilis may present with fever and hepatitis.

Liver biopsy may provide useful information in immunodeficient people with systemic disorders, and may be diagnostic in opportunistic infections such as mycobacterial disease or lymphoma.

15.1.5 Acalculous cholecystitis

Acalculous cholecystitis is an uncommon complication of late-stage HIV disease. HIV-associated acalculous cholecystitis presents with pain in the right upper quadrant, tenderness and fever. Non-specific ultrasonographic findings include thickening of the gallbladder wall and pericholecystic fluid in the absence of gallstones.[30] This condition may be complicated by gall bladder perforation. No precipitating factors for HIV-associated acalculous cholecystitis have been identified. In contrast, a range of factors including multisystem organ failure, burns and trauma precipitate non-HIV-associated acalculous cholecystitis. Several organisms have been associated with HIV-related acalculous cholecystitis including CMV, *Cryptosporidium parvum*, *Microsporidia* spp., *Campylobacter jejuni,*[31] *Pneumocystis jirovecii* and *Isopora* spp.[32] However, no single pathogen predominates. In up to 15% of patients with HIV-associated acalculous cholecystitis, no pathogen is isolated.[32] The treatment of choice is cholecystectomy or gall-bladder decompression. There are no data to suggest that antimicrobial therapy is beneficial. Acalculous cholecystitis remains a problem in the era of potent antiretroviral therapy.

15.1.6 Cholangiopathy

AIDS-associated cholangiopathy develops following post-inflammatory stricture formation associated with opportunistic infections of the biliary tree in very immunodeficient patients (CD4 cell count <50 cells/μL). Although the true incidence is unknown, AIDS-associated cholangiopathy is uncommon in the post-cART era. CMV, *C. parvum*, MAC, herpes simplex virus, and *Giardia duodenalis*[33] have been associated with this condition. Patients present with pain in the right upper quadrant, cholestatic liver function and morphological abnormalities of the biliary tree. Other symptoms include fever, nausea, vomiting and diarrhoea.[34] Alkaline phosphatase and gamma glutamyltransferase are commonly elevated at least ten times above normal, but bilirubin is rarely raised because biliary obstruction is seldom complete. Biliary dilatation is demonstrated by ultrasonography or endoscopic retrograde cholangiography (ERCP). ERCP may reveal papillary-duct stenosis and narrowing of the terminal common bile duct with proximal dilatation associated with intra- and/or extra-hepatic bile-duct narrowing. Papillary duct dilatation may also involve the pancreatic duct. ERCP is the preferred diagnostic investigation, as it will allow differentiation of the cholangiopathy from hepatic MAC infection (the predominant differential diagnosis) and it affords the opportunity for sphincterotomy and tissue sampling.

Sphincterotomy relieves the pain associated with papillary stenosis in up to 86% of cases.[34] However, serum biochemical abnormalities may not resolve following sphincterotomy. The benefit of treating identified pathogens has not been determined. Although there are case reports of improvement following specific antimicrobial therapy,[35] this is unusual. The one-year survival rate was 41% in the pre-cART era, and death was usually secondary to AIDS progression, as opposed to AIDS-related cholangiopathy.[34]

The vanishing bile duct syndrome is an infrequent cause of cholestasis due to progressive loss of small to medium sized bile ducts. Infection and drugs have been implicated and underlying malignancy, particularly lymphoma, is common. There is a single case report of vanishing bile duct syndrome associated with CMV infection in a patient with HIV and a CD4 cell count of 7 cells/μL.[36]

15.1.7 Kaposi's sarcoma

Involvement of the gastrointestinal tract is not uncommon and is frequently asymptomatic. Haemorrhage from KS lesions in the oral cavity, oesophagus, stomach and colon have all been reported. Other more unusual complications include perforation or obstruction of the bowel.[37]

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15.2 Gastrointestinal and oral infections

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15.2.1 Parasitic infections

Cryptosporidiosis

It should be noted that *Cryptosporidium parvum* is now a rare infection in people with HIV, including those not receiving combination antiretroviral therapy (cART). A major teaching hospital for HIV patients in Sydney has averaged less than one case per year for the last three years (Marriott D, St Vincent's Hospital; unpublished data) whereas it was the cause of AIDS-defining illness in up to 10% of Australian patients in the pre-cART era. (See also Chapter 13.8).

Microsporidiosis

Like cryptosporidiosis, microsporidiosis is now an uncommon opportunistic infection. Prior to the introduction of cART, the prevalence of acute or chronic microsporidial diarrhoea in HIV infected patients was estimated to be 14.1-34.8 %.[1] However a recent study from the USA indicated a prevalence of 0.16% in the post-cART era[2] and an Australian study found a reduction in incidence from 11% in 1995 to 0% from 2004 onwards.[3] (See also Chapter 13.10).

Cyclospora

Cyclospora cayetanensis is a coccidian protozoon which infects epithelial cells of the small intestine and induces secretory diarrhoea by an unknown mechanism. It causes profuse watery diarrhoea and biliary disease in both immunocompetent and immunosuppressed patients.[4,5] In people with HIV and CD4 cell counts <100 cells/μL, *C. cayetanensis* may cause a prolonged diarrhoeal illness. Cyclosporiasis is more common in tropical climates, where it causes 14% of infectious diarrhoea in patients with AIDS, compared with less than 1% of infectious diarrhoea in patients with AIDS living in non-tropical areas. The parasite is globally distributed and, although the epidemiology of cyclosporiasis has not been completely defined, water-borne

and food-borne transmission have both been documented, including contaminated imported raspberries used in fruit salads.[6,7] Faecal-oral transmission is also likely. Humans are the only known host for *Cyclospora* spp.

Clinical presentation

The spectrum of human illness caused by *C. cayetanensis* ranges from an asymptomatic illness to a febrile diarrhoeal illness, which may be self-limited, intermittent or persistent. Chronic cyclosporiasis is associated with anorexia, upper gastrointestinal symptoms, profound and prominent fatigue and weight loss. Abdominal pain is present in 10% of patients[7] and *Cyclospora* infection may also result in acalculous cholecystitis.[8]

Diagnosis

Diagnosis requires special stains such as modified acid-fast and auramine-rhodamine fluorescent stains[7,9] as *Cyclospora* oocytes are not reliably detected on routine faecal examination. *Cyclospora* are 8-9 µm in diameter and therefore larger than *Cryptosporidia*, with which they can be easily confused. Histopathological examination of jejunal biopsies from people with cyclosporiasis show mild-to-moderate acute inflammation of the lamina propria and surface epithelial disarray.

Management

Recommendations for the treatment of cyclosporiasis in patients with HIV disease are not based on controlled clinical trial data. Self-limiting illness requires supportive therapy only. Patients with chronic *Cyclospora* infection usually respond to trimethoprim/sulfamethoxazole 160/800 mg twice daily for seven to ten days. A second-line agent for patients with cotrimoxazole hypersensitivity is ciprofloxacin 500 mg twice daily for seven days[10] and nitazoxanide may be an effective alternative.[11] Long-term secondary prophylaxis with trimethoprim/sulfamethoxazole 80/400 mg daily or 160/800 mg three times weekly is necessary to prevent recurrence, which occurs in about 50% of patients.[4] It is not known whether secondary prophylaxis can be stopped with immune reconstitution, although relapse is unlikely in patients with CD4 cell counts >200 cells/µL.

Isospora

The coccidian parasite *Isospora belli* causes human intestinal disease. Infection is acquired by the consumption of oocytes, followed by invasion of the intestinal epithelial cells, where the parasite undergoes both sexual and asexual cycles of development. Oocytes excreted in stools are not immediately infectious, but require further maturation in the environment. Isosporosis is uncommon in non-tropical countries, but is endemic in Indochina, South America and the South Pacific. Disease usually occurs in patients with CD4 cell counts <100 cells/µL.

Clinical presentation

Typically, acute infections of *I. belli* present with the abrupt onset of fever, abdominal pain and watery, non-bloody diarrhoea. The illness may be self-limiting in immunocompetent hosts, but can last for months. In contrast, patients with CD4 cell counts <100 cells/µL usually develop a chronic diarrhoeal illness resembling chronic cryptosporidiosis.

Diagnosis

The diagnosis is usually made by detection of large (about 25 µm) elliptical oocytes in stool using modified, acid-fast staining. As oocyte excretion may be intermittent, repeated stool specimens are needed to reliably detect *Isospora* spp. Characteristically there is an absence of faecal white cells detected on microscopy. If the organism is not detected on faecal microscopy, endoscopic investigations with duodenal aspirate and small-bowel biopsy may be required. Peripheral eosinophilia is prominent. Eosinophilia is not a feature of other enteric protozoan infections, but occurs with helminth infections such as *Strongyloides* spp.

Management

First-line treatment for *Isospora* infection is trimethoprim/sulfamethoxazole 160/800 mg (one double-strength tablet) four times a day for ten days.[12] Ciprofloxacin 500 mg twice daily or pyrimethamine 50-75 mg daily are alternative agents for patients with cotrimoxazole hypersensitivity. Long-term maintenance therapy is required in patients who do not achieve immune recovery with cART. Drugs used for maintenance therapy include cotrimoxazole one double-strength tablet three times a week or one single-strength tablet daily, or combined sulfadoxine/pyrimethamine 500/25 mg once weekly.

Giardia

Giardia lamblia is a ubiquitous protozoan flagellate that inhabits the small intestine of humans and other mammals. It causes up to 5% of acute diarrhoeal illness in patients with HIV. Infection may occur following ingestion of as few as 10 cysts. Faecal-oral transmission is demonstrated by person-to-person spread (institutional or sexual), and food-borne and water-borne transmission.

Food-borne transmission occurs when food is contaminated after cooking. Humoral immune defences are important in *Giardia* infection, as demonstrated by the association of hypogammaglobulinaemia and severe giardiasis. The presentation and response to treatment is the same for patients with and without HIV.

Clinical presentation

Infections may be aborted, transient, recurrent or chronic. The incubation period is usually one to three weeks. Common symptoms include nausea, vomiting, abdominal pain, belching, bloating, flatus and non-bloody diarrhoea. Upper gastrointestinal tract symptoms may predominate and diarrhoea may be absent. Symptoms generally last for one week or more, distinguishing giardiasis from other common infectious causes of diarrhoea. Fever may rarely be present in the early stages of the infection, and blood is absent from faeces in giardiasis. Chronic giardiasis may present without a clear acute episode, in the absence of prominent diarrhoea, and with weight loss for investigation.

Diagnosis

Microscopy of faeces demonstrates *Giardia* cysts and trophozoites following standard trichome or haematoxylin staining. Multiple stool examinations are required, as cyst excretion is variable. Alternative diagnostic methods such as enzyme immunoassay and PCR are available. If faecal microscopy is negative then duodenal fluid aspiration or biopsy of the small intestine may be required for diagnosis.

Management

Giardiasis responds to 2 g of tinidazole taken orally as a single dose. Refractory cases can be treated with metronidazole (400 mg orally every eight hours) for one week. Oral albendazole (400 mg daily) for five days is equally as efficacious and associated with fewer side-effects.[13]

15.2.2 Bacterial infections

Salmonella

People with HIV have a 20 times higher risk of non-typhoidal salmonellosis than people without HIV.[14] HIV infection is a prominent risk factor for Salmonella bacteraemia and recurrent *Salmonella* bacteraemia is an AIDS-defining illness.[15,16] However it should be noted that the incidence of salmonellosis has fallen significantly in the cART era. A recent study from Taiwan indicated a fall of 96% in the incidence of *Salmonella* bacteraemia with the introduction of cART.[17]

Although *Salmonella* infection can occur at any CD4 cell count, recurrent Salmonella bacteraemia is an indicator of immune deficiency. *Salmonellae* cause 5-15% of acute infectious diarrhoea in patients with HIV, with non-typhoidal *Salmonellae* the most common causative agents of salmonellosis. Achlorhydria, which is relatively common in advanced HIV infection, may increase susceptibility to *Salmonella* infection.

Clinical presentation

In patients without HIV, *Salmonella enteritis* is classically a self-limited illness characterised by the abrupt onset of watery diarrhoea and fevers, six to 48 hours after the ingestion of contaminated food. Symptoms resolve over seven days. The presentation is more severe and complicated in people with HIV, in whom diarrhoea is accompanied by abdominal pain, abdominal distension, nausea and fever. Tenesmus and rectal pain are rare and, if present, suggest proctitis secondary to another pathogen.

Salmonella bacteraemia occurs in up to 50% of people with HIV compared with 9% of the general population.[14] Furthermore, 20-45% of people with HIV and *Salmonella* bacteraemia may have no accompanying colitis.[18] Metastatic infections may occur in almost every organ-system with the liver, spleen, cerebrum, meninges, lung, great vessels and kidneys the most commonly affected sites. It has been reported in 5% of patients with *Salmonella* bacteraemia without diarrhoea.[18]

Stool carriage and recurrence are more common in people with untreated HIV disease than in the general population. Recurrence of *Salmonella* bacteraemia occurs in up to 20% of patients with HIV disease. The mean time to recurrence is two months.[1] If no recurrence occurs within three months of treatment, the risk of future relapse is low. Patients with bacteraemia are more likely to experience recurrence than patients without bacteraemia. The risk of recurrence is not predicted by duration of symptoms prior to diagnosis, *Salmonella* serotype, duration of antimicrobial therapy or CD4 cell count at baseline.[18,19]

Diagnosis

The diagnosis is confirmed by isolation of *Salmonella* spp. from faecal culture. Faecal leukocytes may be present on smear, but are less common when compared with *Shigella* enteritis. Blood cultures should be performed for all patients.

Management

Oral ciprofloxacin 500 mg twice daily is the preferred treatment for *Salmonella* enteritis in people with HIV. It is the only agent shown to eradicate *Salmonella* in people with HIV and enteritis. Ciprofloxacin has also been demonstrated to shorten the duration of illness and reduce relapse rates of *Salmonella* disease in patients with advanced HIV disease.[20] However it should be noted that quinolone antibiotic resistance is increasing in many parts of the world and susceptibility can no longer be assumed.[17] Alternative agents include trimethoprim/sulfamethoxazole 160/800 mg twice daily or ceftriaxone 2 g per day. Sensitivity testing is essential to guide therapy as antibiotic resistance is increasingly reported. Duration of therapy is five days for uncomplicated infections. In patients with *Salmonella* bacteraemia, treatment with ciprofloxacin 500 mg orally twice daily should continue for a minimum of two months. If the patient is immunocompromised, consideration should be given to continuing secondary prophylaxis until there is a sustained rise in CD4 cells (over 200 cells/μL for six months). Patients who are severely unwell may require parenteral therapy. Patients who work as food handlers may pose a public health risk and require specific follow-up prior to returning to work.

Shigella

Shigella spp. are enteric pathogens that typically cause a self-limiting febrile diarrhoeal illness. *Shigella* enteritis is more common in patients with HIV than in the general population, and it has a more severe clinical course. It is the aetiological agent in 1% to 3% of diarrhoea in patients with HIV. The predominant mode of transmission is by oral-anal contact or by ingestion of contaminated food or water. An increased incidence of *Shigella* infection occurs in homosexual men, particularly those attending sex-on-premises venues because of sexual practices which expose them to this pathogen, and outbreaks have been reported.[21] In this setting, HIV is an important risk factor for acquisition of *Shigella*. A study of household contacts of patients with shigellosis suggests that host factors determine whether exposed people develop clinical disease.[22]

Clinical presentation

Shigella causes a spectrum of illness in people with HIV. Patients may present with fever and non-bloody, self-limiting, watery diarrhoea or an acute dysenteric illness. After an incubation period of one to seven days, patients develop acute-onset, bloody and watery diarrhoea accompanied by abdominal pain, distension, nausea and fever. In contrast to *Salmonella* enteritis, tenesmus is more often described. *Shigella* bacteraemia has been documented in patients with HIV although it is uncommon. Nevertheless, blood cultures are always indicated in people with HIV infection with fever and diarrhoea.[23] Relapses of *Shigella* are uncommon; about 15% of people with HIV experienced *Shigella* relapse in retrospective studies.[18] Extra-intestinal manifestations of shigellosis include headache, seizures and delirium, Reiter's syndrome and haemolytic uraemic syndrome.

Diagnosis

Shigella dysentery is diagnosed by faecal culture. Faecal microscopy demonstrates white cells and red blood cells.

Management

First-line therapy is ciprofloxacin 500 mg orally twice daily for three days. Second-line therapy is trimethoprim/sulfamethoxazole 160/800 mg twice daily for three days. Some authorities recommend that the duration of therapy should be extended to seven to ten days in immunocompromised patients (CD4 cell count<200cells/μL),[12] although controlled study data are lacking to support this recommendation. Alternative agents include norfloxacin, ceftriaxone or azithromycin. Antibiotic choice should be governed by local patterns of antibiotic sensitivity. Long-term maintenance therapy is not required for patients with HIV and shigellosis.

Campylobacter

Infection with *Campylobacter* spp., most commonly *Campylobacter jejun*i, is a common cause of diarrhoea worldwide. The frequency of *Campylobacter* infections is 40 times more common in the setting of HIV infection.[24] In one cross-sectional study, *Campylobacter* was isolated in 6% of cases of diarrhoea in patients with HIV and was the most frequent bacterial pathogen.[25] *Campylobacter* infections occur following ingestion of improperly cooked or prepared food, primarily poultry. Outbreaks have occurred following ingestion of contaminated milk or water. Sexual transmission in homosexual men is reported.[26] *C. jejuni, C. coli* and *C. upsaliensis*[27] are the most common *Campylobacter* species isolated from patients with HIV, although other species may also cause diarrhoeal illness.[28]

Clinical presentation

Following an incubation period of two to six days, patients develop diarrhoea, fever and abdominal pain. Less commonly, nausea and vomiting occur. The diarrhoea is usually watery and voluminous, especially early in the illness, but symptoms of proctocolitis, blood and mucous in the stool and tenesmus may become prominent later. The illness is usually self-limiting, especially in the immunocompetent patient. *Campylobacter* enteritis is more likely to be severe, persistent and recurrent in those with HIV.[18]

Bacteraemia occurs in up to 16% of people with HIV with *Campylobacter* enteritis and is more common in immunocompromised patients.[24] Bacteraemia may be the only manifestation of *Campylobacter* infection in people with HIV and should be considered in any febrile patient.[28,29] Metastatic infection, including pulmonary consolidation,[29] monoarthritis and a multifocal rash that resembles cellulitis have been reported, but are rare.[30]

Diagnosis

Diagnosis depends on the isolation of the organism from a faecal specimen. Faecal microscopy often reveals white and red blood cells. Specialised microbiological techniques are required to isolate *Campylobacter* spp. from faeces. Species identification can be performed by PCR amplification with species-specific primers and is more reliable than traditional biochemical techniques.[25] Blood cultures should also be obtained, as bacteraemic patients require a longer course of therapy.

Treatment

All people with HIV infection should receive antibiotic treatment for *Campylobacter* enteritis given the risk of severe, prolonged, recurrent and bacteraemic disease. Erythromycin 500 mg twice daily for five days remains the drug of choice. Ciprofloxacin 500 mg twice daily or norfloxacin 400 mg twice daily can successfully treat patients with recurrent *Campylobacter* diarrhoea that fails to respond to erythromycin.

Resistance of *Campylobacter* to both macrolide and quinolone antibiotics is increasing worldwide, and infection acquired in South-East Asia has a greater likelihood of drug-resistance than infection acquired elsewhere. In a Dutch cohort, 16% of isolates were resistant to quinoline antibiotics,[25] but up to 50% of isolates acquired in Thailand are expected to be resistant to these agents.[31] Multidrug-resistance has developed in people with HIV following multiple antibiotic courses for persistent and recurrent *Campylobacter* infection.[32,33] Alternative agents include tetracycline, clindamycin, amoxicillin and ticarcillin with clavulanic acid. Intravenous gentamicin may be required in severely ill patients with *Campylobacter* bacteraemia. Therapy should continue for up to three weeks in immunocompromised patients (CD4 cell count <100 cells/μL) or patients with bacteraemia or extra-intestinal foci of infection.

Clostridium difficile

Clostridium difficile is the major cause of antibiotic-associated diarrhoea and colitis. Interestingly, this organism is the only anaerobic bacterium which is transmissible between humans and there have been a number of recent outbreaks of infection both in medical institutions and the community that highlight the transmissibility of this organism.

C. difficile is an anaerobic, spore-forming, gram-positive rod which produces two toxins, toxin A and toxin B. Both are important in the pathogenesis of clinical disease. Transmission of *C. difficile* occurs by the faecal–oral route with spores colonising the colonic lumen. This colonisation is enhanced by the reduction of normal colonic flora following antibiotic therapy. A recent publication has highlighted the importance of skin contamination as a potential mode of transmission: *C. difficile* was isolated from the chest, hands and groin of patients even after resolution of diarrhoea, with ready transmission to health care workers.[34]

Clinical presentation

C. difficile produces a broad spectrum of disease ranging from asymptomatic carriage to fulminant pseudomembranous colitis. Disease is usually restricted to the colon and a protein–losing enteropathy is common. Fever and leucocytosis occur in approximately 50% of patients and nausea, malaise and anorexia are frequent. Recently the NAP1 strain, a new variety of *C. difficile* causing severe epidemic disease in North America with significant morbidity and mortality, has been reported. This organism produces high quantities of toxin, possibly due to deletion of the gene that down-regulates toxin production.[35]

In a study of bacterial diarrhoea in 44 768 people with HIV in the USA followed for a mean of 2.6 years, *C. difficile* accounted for 54% of culture-proven diarrhoea followed by *Shigella* spp. (14%), *C. jejuni* (14%) and *Salmonella* (7%).[36] *C. difficile* was therefore the major identifiable cause of bacterial diarrhoea. Similar data are not available in the Australian setting.

Host immunity, specifically antibody production against *C. difficile* toxins, is thought to be the most important factor in *C. difficile* disease presentation and progression. HIV infection impairs antigen–specific B cell responses, with immunoglobulin

production dependent on CD4 cell levels.[37] Therefore patients with low CD4 cell counts may be at greatest risk of symptomatic *C. difficile* infection due to inadequate antibody production to prevent toxin-mediated disease.

Diagnosis

Diagnosis of *C. difficile*–related diarrhoea is by means of culture of the organism and/or detection of *C. difficile* toxin production. Anaerobic culture is sensitive but expensive, time consuming and does not differentiate between toxigenic and non-toxigenic strains. Testing for production of toxin is now the most widely used means of diagnosing *C. difficile* infection. Tissue culture assays to determine toxin production are the gold standard but are expensive, slow and require a tissue culture facility. These have largely been replaced by commercial enzyme immunoassay kits; however these have a false-negative rate of up to 25%[38] so empirical therapy may be required in the appropriate clinical setting.

Treatment

Treatment of *C. difficile* infection is based on removal of antibiotic therapy where possible, supportive measures and specific therapy with metronidazole 400 mg three times daily for ten days or oral vancomycin 250 mg four times daily for ten days. Both regimens appear to be equally effective although vancomycin may be superior for patients with severe disease because it is not absorbed, resulting in high colonic concentrations of the drug. Metronidazole should be first-line therapy as it is less expensive than vancomycin and does not select resistant enteric gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. Alternative agents such as rifamixin, a poorly absorbable rifamycin, anion–exchange resins, probiotics and replacement of faecal flora by faecal transplant have also been investigated. Recurrences are common, occurring in approximately 20% of patients within 60 days.

15.2.3 Oral disease

Oral hairy leukoplakia

Oral hairy leukoplakia (OHL) was first described in 1984 in homosexual men, but has been rarely observed since the introduction of cART.[39] The prevalence of OHL is 20% in patients with untreated HIV infection.[40] Once considered pathognomonic for HIV, it has been described rarely in other immunosuppressed patients.[41] OHL is predominantly found in homosexual men with CD4 cell counts <200 cells/μL. Diagnosing OHL is important because of its strong association with HIV infection and its prognostic significance. Patients with OHL have a relative hazard for progression to AIDS of 1.8 compared to patients without OHL.[42] Furthermore, OHL predicts disease progression independently of CD4 cell count and predicts plasma viral load independently of CD4 cell count.[43,44]

OHL usually presents as asymptomatic white hyperkeratotic corrugations on the lateral border of the tongue, and may be confused with pseudomembranous candidiasis. However, unlike candidiasis, OHL does not rub off and does not respond to antifungal therapy. The diagnosis is usually made clinically, but can be confirmed by biopsy. This will demonstrate epithelial hyperplasia and the presence of Epstein Barr virus in the basal epithelial cells.[45] OHL is typically asymptomatic and does not require specific therapy. Occasionally the lesions may cause discomfort. Symptomatic OHL may respond to cART. Response has been documented to high-dose aciclovir (3200 mg daily in divided doses).[46] Podophyllum resin 25% has also been used.[47] Relapse is likely in the absence of cART-induced immune recovery.

Gingivitis

The prevalence of gingivitis in people with HIV has fallen from 15%[48] to 0.6% in patients treated with cART.[49] The most common form is linear gingival erythema, which is characterised by a 1-3 mm erythematous band along the gingival margin. It is usually asymptomatic, but may bleed and cause pain. There is no evidence to suggest that this form of gum disease will progress to more severe forms. Most patients with linear gingival erythema have oral candidiasis, but a causal relationship has not been established. Most cases respond to dental attention with scaling, root planning and chlorhexidine rinses.

More severe forms of gum disease seen in immunodeficient patients with HIV include necrotising ulcerative gingivitis and necrotising ulcerative periodontitis. Ten percent of people with HIV infection who are not receiving cART have necrotising ulcerative gingivitis. This condition is characterised by ulceration of the interdental papilla, pain and halitosis. Necrotising ulcerative periodontitis is more severe, with ulceration extending into the underlying alveolar bone. (Image 15.1.)The condition may be rapidly progressive.[50] Rapid loss of bone and soft tissue may occur, and teeth may loosen and fall out. Necrotising ulcerative periodontitis is usually associated with significant pain that leads to reduced oral intake. Patients with necrotising ulcerative periodontitis are typically profoundly immunodeficient with a mean CD4 cell count of 32 cells/μL.[48]

Image 15.1 Necrotising ulcerative periodontis

Source: Allworth AM, Bowden FJ. HIV and bacterial infections. In Stewart G, editor.. Managing HIV. Sydney: Australasian Medical Publishing Company; 1997:67.

Management includes topical anaesthetics, chlorhexidine washes (0.2% twice daily) and antibiotics (phenoxymethylpenicillin 500 mg four times daily for five days). In severe cases, oral metronidazole (400 mg twice daily) or parenteral penicillin may be required along with periodontal debridement. HIV disease may accelerate progression of chronic periodontitis. Patients with CD4 cell counts <400 cells/μL who are also smokers are particularly at risk. This patient group should be seen for regular dental prophylaxis every three months.[48]

Oral aphthous ulceration

Oral aphthous ulceration in patients with HIV has a prevalence of 2% and is associated with significant morbidity.[49] The lesions typically occur as multiple oval and shallow ulcers on the non-keratinised epithelium of the oral cavity. They can be extremely

painful and may interfere with eating. It is not known whether aphthous ulceration is more common in people with HIV, but in this setting it is generally associated with a greater number of lesions per episode, as well as more frequent episodes of longer duration than is seen in the absence of HIV. Major aphthous ulcers are associated with advanced HIV disease (CD4 cell counts <50 cells/µL).[50,51]

Oral thalidomide is the treatment of choice and has been shown to resolve acute and recurrent oral aphthous ulceration.[52,53] Somnolence, rash, neutropenia and peripheral neuropathy are recognised side-effects of thalidomide which occur commonly, often requiring a reduction in dose from 200 mg per day.[54] Prophylactic thalidomide therapy (100 mg three times weekly) is not effective.[55] Thalidomide is teratogenic; it should be used with great caution in women of childbearing potential and only after informed consent has been obtained. In severe cases, oral steroids may be required.

Oropharyngeal candidiasis

Candida species colonise the oral cavity in 30-60% of the general population. Colonisation increases with age, smoking and the use of antibiotics. *Candida albicans* is the most common *Candida* species that colonises the oral cavity and the most common cause of oropharyngeal candidiasis in patients with HIV. Approximately 80-90% of patients with advanced HIV will develop oropharyngeal candidiasis, which may be the first clinical manifestation of HIV infection. Oropharyngeal candidiasis is more common in smokers and patients with CD4 cell counts <200 cells/µL. Patients with oropharyngeal candidiasis have a relative hazard of HIV disease progression of 7.3 compared with patients with no oral pathology.[42]

There has been a significant increase in the rate of non-albicans *Candida* such as *C. glabrata* and *C. dubliniensis* isolated from patients with HIV. In the early 1980s, non-albicans *Candida* accounted for 3.4% of oral isolates from patients with HIV and increased to 17% in the 1990s.[56] Non-albicans *Candida* are more commonly isolated from patients receiving prolonged courses of fluconazole[57] and are often azole resistant.

Clinical presentation

Oropharyngeal candidiasis has four major presentations in patients with HIV infection. Pseudo-membranous candidiasis presents as white or yellow plaques, which may be located in any part of the oral cavity. This form is typically referred to as thrush. These lesions can be easily removed with a spatula.

Image 15.2 Extensive oral candidiasis

Source: Allworth AM, Bowden FJ. HIV and bacterial infections. In Stewart G, editor.. Managing HIV. Sydney: Australasian Medical Publishing Company; 1997:67.

The underlying mucosa appears erythematous and may bleed. These lesions may be painful, and limit eating and drinking. Erythematous candidiasis presents as red areas on the palate, the dorsum of the tongue, and occasionally on the buccal mucosa. It is usually asymptomatic. Hyperplastic candidiasis is characterised by white plaques that do not rub off and can be confused with OHL (Image 15.2). Angular cheilitis presents as fissuring at the corners of the mouth. Vitamin B12 deficiency, diabetes and indinavir-associated desquamative cheilitis should be considered as differential diagnoses for angular cheilitis.[58]

Diagnosis

The diagnosis is generally made on clinical appearance, but can be confirmed by cytological smear using a periodic acid Schiff stain which reveals *Candida*. Culture is useful as it allows species identification and therefore predicts antifungal susceptibility. Antifungal resistance testing is recommended when there is a poor response to therapy or frequent clinical relapse.

Management

First-line therapy

Topical therapies for the treatment of initial presentations of oropharyngeal candidiasis in patients with early HIV disease are appropriate (Table 15.2). Topical amphotericin B taken four times daily can be administered as a suspension, lozenge and tablet. Prospective studies comparing the efficacy of topical amphotericin B with other agents are limited. Clotrimazole 10 mg troches administered five times daily successfully treat mild-to-moderate oropharyngeal candidiasis during the early stages of HIV.[59] However, this therapy is less effective than fluconazole. Nystatin treatment for oral thrush is limited by the bitter taste, gastrointestinal toxicity and frequent administration. Compliance rates are low and the therapy is less effective than oral fluconazole.[60]

Oral therapy is recommended for patients with recurrent oropharyngeal candidiasis or advanced HIV disease. Fluconazole is the agent of choice. Complete clinical response occurs in up to 80% of people and a further 10-15% experience considerable improvement.[61] Clinical failure is rare. Response to fluconazole is characteristically rapid and dose-related. Median time to response in patients treated with 100-200 mg daily is five days compared with ten days in patients treated with 50 mg daily. Complete mycological cure is difficult to attain, and relapse is common. Itraconazole 200 mg twice daily has a similar spectrum of anti-*Candida* activity. Clinical response rates and relapse rates are similar in patients with oropharyngeal candidiasis treated with itraconazole solution compared with those patients treated with fluconazole.[62] However itraconazole solution is more expensive, has more drug-drug interactions and greater toxicity than fluconazole.

Second-line therapy

Up to 10% of patients with HIV who receive intermittent or continuous therapy for relapsing oropharyngeal candidiasis develop an infection that is clinically and microbiologically resistant to 100-200 mg of fluconazole.[63] The most effective strategy in the management of azole-refractory oropharyngeal candidiasis is to induce immune recovery with cART. Alternative strategies include: increased fluconazole dosage of 400-800 mg daily; use of the fluconazole suspension, which increases salivary levels of fluconazole following the 'swish-and-swallow' technique; and use of itraconazole cyclodextran solution 200

mg twice daily.[64,65] Patients treated with itraconazole achieve clinical cure or improvement in up to 70% of cases, but the rate of mycological cure is low (<30%) and relapses are common, occurring within 14 days.[66] Similarly, amphotericin B oral suspension has demonstrated clinical improvement rates in up to 75% of patients. However, the relapse rate is high, with relapse usually occurring within four weeks of ceasing therapy.[67] In severe cases intravenous amphotericin may be required.

New agents for the treatment of resistant candidiasis include extended-spectrum azoles such as voriconazole and posaconazole. A recent study evaluated the efficacy of oral posaconazole for people with HIV infection with oropharyngeal or oesophageal candidiasis who were clinically refractory to treatment with oral fluconazole or itraconazole. Overall, 75% achieved a clinical response with minimal toxicity reported.[68] Members of the echinocandin class of antifungal agents including caspofungin have also been demonstrated to have efficacy against *Candida* spp. and may be appropriate second-line therapy. Emergence of resistance to caspofungin in this setting has been described[69] but is uncommon.

If alternative agents are not available, fluconazole in combination with oral terbinafine has synergistic activity against resistant strains and may result in clinical improvement.

Antifungal prophylaxis

Although recurrences of oropharyngeal candidiasis are common and fluconazole therapy reduces recurrence rates,[70] the most appropriate long-term strategy to prevent fungal infection in patients with HIV is restoration of the immune system with cART. For antifungal prophylaxis, the drug, the dose and the duration (continuous versus intermittent) of therapy remain to be defined. One study found that fluconazole (200 mg per day) reduced the incidence of oesophageal candidiasis, superficial fungal infections and cryptococcal disease. The benefit was greatest in patients with CD4 cell counts <50 cells/μL, but there was no survival advantage.[71] Another study found that fluconazole (200 mg per week) decreases symptomatic oropharyngeal candidiasis and vaginal candidiasis in women with CD4 cell counts less than 300 cells/μL, and that the development of clinical and *in vitro* antifungal resistance was infrequent.[57]

15.2.4 Oesophageal disease

A large number of infectious and non-infectious causes lead to the development of oesophageal symptoms in patients with HIV (Table 15.3). These processes occur predominantly in patients with CD4 cell counts below 100 cells/μL. The most common causes are oesophageal candidiasis (see Section 13.3.), idiopathic ulceration and herpetic ulceration.

Idiopathic ulceration

Idiopathic oesophageal ulceration occurs during primary[72] and late-stage HIV disease.[73] In the latter setting, idiopathic oesophageal ulceration is reported in 4-8% of people with HIV presenting with oesophageal symptoms.[74] Odynophagia is the most common symptom, with weight loss and dysphagia being less common.[73] Endoscopic examination is required to make the diagnosis. Idiopathic oesophageal ulceration associated with acute primary HIV infection is characterised by multiple, small, superficial lesions with well demarcated borders. In contrast, the idiopathic oesophageal ulceration associated with later stages of HIV disease usually manifests as large, single lesions with overhanging margins located in the mid-to-distal oesophagus. Fistulae have been described and can be visualised using endoscopy.[74] The typical histological picture reveals acute and chronic inflammation with extension of ulceration into the muscle layer of the oesophagus.[74]

The diagnosis of idiopathic oesophageal ulceration is one of exclusion, and appropriate specimens must be taken for fungal, mycobacterial and viral staining and culture. Histopathological examination is needed to exclude associated malignancies. A thorough history is required to exclude zidovudine[75] and tetracycline antibiotics as possible causes of oesophageal ulceration, when the pill itself may induce ulceration by prolonged contact with the oesophageal mucosa.

The treatment of choice is thalidomide 200 mg daily for four weeks.[76,77] Thalidomide produces a complete response in more than 70% of patients. Rash, somnolence and peripheral

Table 15.2 Treatment of oral candidiasis in patients with HIV disease

Indication	Agent	Dose	Duration
Initial episode of oropharyngeal candidiasis	Amphotericin B lozenge	10 mg qid	1 week
Recurrent oropharyngeal candidiasis	Fluconazole	100-200 mg/day	1 week
Oropharyngeal candidiasis not responding to fluconazole 100-200 mg daily	Fluconazole	400-800 mg/day of suspension (8 mL of 50 mg/mL/day)	1-2 weeks
	Itraconazole (cyclodextran solution)	100-200 mg/day	1-2 weeks
	Voriconazole	300 mg bd on day 1 then 200 mg bd	1-2 weeks
	Posaconazole	200 mg tds	1-2 weeks
	Caspofungin	70 mg day 1 then 50 mg daily IV	1-2 weeks
	IV amphotericin B	0.3-0.5 mg/kg/day	1-2 weeks

bd= twice a day; tds = three times a day; qid= four times a day; IV= intravenous.

Table 15.3 Causes of oesophageal disease in patients with HIV infection

Cause	Common	Uncommon
Fungal	*Candida* spp.	*Histoplasma capsulatum* *Penicillium spp.* *Pneumocystis jirovecii*
Viral	Cytomegalovirus Herpes simplex virus	Human papilloma virus
Mycobacterial		*Mycobacterium tuberculosis* *Mycobacterium avium* complex
Parasitic		*Cryptosporidium* *Leishmania*
Neoplastic		Kaposi's sarcoma Non-Hodgkin's lymphoma Leiomyosarcoma
Miscellaneous	Idiopathic ulcer	Pill-induced ulceration Reflux oesophagitis

neuropathy occur in up to one-third of patients treated with thalidomide. Alternative agents include prednisone 40 mg daily, tapering to 10 mg daily over one month.[78] Local measures such as sucralfate slurries may have a palliative effect.

Herpetic ulceration

CMV infection is the most common herpetic infection of the oesophagus in people with HIV infection, in whom it accounts for 10-20% of oesophageal disease.[79] One-fifth of patients with oesophageal symptoms and HIV have both candidiasis and CMV, as defined by CMV culture or histopathological examination.[80] Treatment of candidiasis alone usually results in complete symptomatic resolution. Therefore, the diagnosis of CMV oesophagitis requires the presence of inflammation; histological or virological evidence of CMV and no evidence of other pathogens. Histopathological examination, direct immunofluorescence and viral culture confirm the diagnosis. The treatment of choice is intravenous ganciclovir 5 mg/kg twice daily for three weeks. Foscarnet 90 mg/kg twice daily intravenously is an alternative therapy.

Herpes simplex oesophagitis is the cause of oesophageal symptoms in 2-5% of cases.[79] Risk factors for the development of herpes simplex oesophagitis include treatment with corticosteroids, chemotherapy and recent nasogastric intubation. The absence of herpes labialis does not exclude the diagnosis of herpes simplex oesophagitis, as the two conditions occur simultaneously in 38% of cases.[80] Herpes simplex ulcers are usually shallow, small and coalescing lesions located in the distal half of the oesophagus. Characteristic intracytoplasmic inclusions and multinucleated giant cells are demonstrated on biopsy. Direct immunofluorescence and viral culture confirm the diagnosis. In up to 18% of patients who responded to a therapeutic trial of aciclovir, neither histology nor viral culture identified herpes simplex.[80] Herpes simplex oesophagitis responds to standard doses of aciclovir 200-800 mg orally five times daily or 5 mg/kg intravenously every eight hours for three weeks. Oral administration of aciclovir is adequate in the absence of vomiting.[80] Other orally administered anti-herpes agents may also be effective. Maintenance therapy is usually commenced only after the first relapse.

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