Review article: the therapy of gastrointestinal infections associated with the acquired immunodeficiency syndrome

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SUMMARY

Although there have been dramatic strides in the therapy of human immunodeficiency virus infection over the last few years, the number of infected people world-wide is tremendous and, at least in developing countries, continues to expand. Complications which involve the gastrointestinal tract are common in these patients, because the gut is a major site for involvement by opportunistic infections and neoplasms in patients with the acquired immunodeficiency syndrome. It is important to recognize the clinical spectrum of gastrointestinal diseases, as well as the appropriate and most cost-effective diagnostic strategies, as therapies for a number of these disorders are both widely available and highly effective. This review summarizes the major gastrointestinal infections which are seen in patients with the acquired immunodeficiency syndrome, and their treatment.

INTRODUCTION

Human immunodeficiency virus (HIV) infection remains a common world-wide infectious disease. Diseases of the gastrointestinal tract are among the most frequent complications of the acquired immunodeficiency syndrome (AIDS). Oesophageal disease occurs in 30–40% of patients, and the incidence of diarrhoea may be as high as 90%, particularly for patients with severe immunodeficiency.[1–4] The incidence of some disorders has been unfavourably altered by the widespread use of prophylaxis for *Pneumocystis carinii* pneumonia.[5–6] Over the last decade, greater experience with gastrointestinal disorders in these patients has resulted in a better appreciation of the spectrum of potential aetiologies, and an improved approach to evaluation and therapy. Fortunately, our therapeutic options have expanded due to the application of old drugs to new problems as well as through the development of newer agents. Nevertheless, truly effective therapy is still lacking for some opportunistic infections. This review will focus on the therapy and prophylaxis for the most common infections involving the gastrointestinal tract in HIV-infected patients (see Table 1).

CANDIDIASIS

Oropharyngeal and oesophageal candidiasis are common opportunistic infections in HIV-infected patients, and are frequently the initial manifestation of infection. Oropharyngeal candidiasis (thrush) is readily diagnosed by the characteristic white plaques which coat the buccal mucosa. Oropharyngeal candidiasis may occasionally present as diffuse erythaema without plaques or angular cheilitis.[7] It is important to differentiate oral hairy leukoplakia from thrush, given the different aetiology and therapy. Although *Candida albicans* is by far the most common cause of candidiasis, other non-*albicans* species cause the same disease including *C. krusei, C. tropicalis, C. parapsilosis* and *C. glabrata*.[8] In

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Table 1. Major gastrointestinal infections in patients with HIV

Diagnosis	CD4 count (/mm^3)	Clinical presentation	Diagnosis	Treatment	Prophylaxis
Candidiasis					
Oropharyngeal	any	Thrush (pseudomembranes), plaques (hyperplastic), erythaema	Clinical appearance Potassium hydroxide (KOH) preparation test Biopsy, culture	Nystatin* Clotrimazole* Fluconazole* Itraconazole Amphotericin B Ketoconazole	Primary: NR Secondary: R for severe, recurrent disease
Oesophageal	< 300	Dysphagia, odynophagia, patchy or circumferential white plaques	Endoscopy, biopsy, brushings	Fluconazole* Ketoconazole* Itraconazole* Amphotericin B	Primary: NR Secondary: R for recurrent disease
CMV oesophagitis	< 100	Odynophagia, dysphagia, oesophagospasm (chest pain), ulcers	Endoscopy, biopsy, immunohistochemistry, *in situ* hybridization, PCR	Ganciclovir* Foscarnet*	Primary: R for CD 4 < 50 and seropositive for CMV Secondary: R
CMV colitis	< 100	Abdominal pain, diarrhoea, fever, ulcers, submucosal petechiae, patchy colitis, ulcer	Endoscopy, biopsy, culture, immuno-histochemistry, PCR, *in situ* hybridization	Same as for oesophageal disease	Same as above
HSV stomatitis	< 200	Ulcers, vesicular lesions	Clinical appearance, cytologic smear ('giant cells'), culture, tissue biopsy	Acyclovir* Foscarnet Trifluoridine	Primary: NR Secondary: R only if recurrent
HSV oesophagitis	< 200	Odynophagia, dysphagia, chest pain, deep ulcers, diffuse mucosal erosions	Oesophagoscopy, biopsy, 'intranuclear Cowdry type A inclusions'	Acyclovir* Foscarnet Trifluoridine	Primary: NR Secondary: R
Recto-anal HSV	< 200	Proctalgia, tenesmus, mucopurulent discharge	Anoscopy, sigmoidoscopy see above	Acyclovir* Foscarnet	Primary: NR Secondary: R
Protozoa					
Cryptosporidia	< 180	Watery diarrhoea, weight loss, abdominal cramps	Stool: modified AF stain, biopsy, electron microscopy	Paromomycin Spiramycin, Azithromycin	Primary: NR Secondary: R if CD 4+ < 100
Microsporidia	< 200	Chronic watery diarrhoea, cholangitis, papillitis	Small intestinal biopsy (Giemsa, methylene blue) Stool: modified trichrome	Albendazole	Primary: NR Secondary: NR
Isospora	< 200	Weight loss followed by profuse diarrhoea, nausea, abdominal pain, dehydration	Stool: modified Kinyoun acid-fast stain	TMP-SMX* Sulphadione Pyrimethamine	Primary: NR Secondary: R
Cyclospora	any	Watery diarrhoea, fatigue, anorexia	Small bowel biopsy, acid-fast spasm	TMP-SMX	Not known

Giardia lamblia	any	Stool, duodenal aspirate	Watery diarrhoea, bloating	Metronidazole	No
Entamoeba	any	Stool	Dysentery	Metronidazole Iodoquinol	No
Bacteria					
MAC	< 100	Stool AFB stain Biopsy AFB stain	Fever, weight loss, diarrhoea	Clarithromycin* RFP, EMB, Cipro	Primary: R Yes, if CD4+ < 100 Secondary: more requiring lifelong treatment
C. dificile	any	Sigmoidoscopy, toxin	Bloody diarrhoea, abdominal pain	Metronidazole Vancomycin	No
Salmonella	any	stool, blood, urine cultures	Bloody diarrhoea	Ciprofloxacin TMP-SMX	No
Campylobacter	any	stool, blood culture	Bloody diarrhoea	Erythromycin	NO

Abbreviations: HIV, human immunodeficiency virus; CMV, cytomegalovirus; RFP, rifampicin; EMB, ethambutol; HSV, herpes simplex virus; NR, not recommended; R, recommended; AFB, acid-fast bacilli; PCR, polymerase chain reaction; AF, acid-fast TMPSMX (trimethoprimsulphamethoxazole); MAC, Mycobacterium avium complex. The drugs marked with * have been used for prophylaxis.

general, determining the aetiologic species is unnecessary since therapy is the same.

Clinically, oesophageal candidiasis may be strongly suspected in the patient with thrush, moderately severe immunodeficiency (CD4 lymphocyte count < 200/mm^3), and oesophageal symptoms.[9] However, thrush may be absent in one-third of patients with oesophageal candidiasis.[9] A definitive diagnosis rests on the identification of typical yeast forms in endoscopic mucosal biopsies or oesophageal brushings. The detection of *Candida* does not exclude other disorders, as *Candida* may coexist with other oesophageal processes in 14–25% of symptomatic patients.[1, 10–12]

Therapy

Topical non-systemic therapy has been the mainstay of treatment for oropharyngeal candidiasis. Although nystatin is effective, clotrimazole troches have now largely replaced nystatin as the principal non-systemic agent used due to its ease of administration, palatability, negligible side-effects and drug interactions, and effectiveness. Clinical cure is seen in 65–94% of patients following 14 days of clotrimazole therapy.[13, 14]

The first oral systemic antifungal agent available for widespread clinical use was ketoconazole. This agent has a broad spectrum of antifungal activity which includes *Coccidioides immitis*, *Histoplasma capsulatum* and *Blastomyces*, has minimal efficacy for *Cryptococcus* and lacks activity against *Mucormycosis* and *Sporothrix*.[15] It requires an acid milieu for absorption. Fluconazole, released in 1990, has a broader spectrum of antifungal activity than ketoconazole, including *Cryptococcus*. Excellent absorption, regardless of gastric pH, and long half-life ($\approx$30 h), make this an ideal oral antifungal agent. Importantly, the pharmacokinetics of fluconazole are similar in HIV-infected patients as compared to other immunocompromised hosts.[16] Fluconazole is excreted solely in the urine; therefore, dose adjustments may be required in patients with renal insufficiency. Itraconazole is the newest oral systemic antifungal agent. Like fluconazole, it has a broad spectrum of antifungal activity, prolonged half-life and is well tolerated. Similar to ketoconazole, elevations in gastric pH retard absorption.[17] Contrasts and comparisons between these agents are listed in Table 2.

Although local non-systemic therapy is effective, a number of trials have demonstrated a therapeutic advantage of systemic therapy for oropharyngeal

Table 2. Comparisons of antifungal agents used to treat candidiasis

Antifungal	Presentation	Uses	Dose	Side-effects	Drug interaction
Nystatin	Oral suspension pastilles	Thrush Prophylaxis	500 000–1000 000 U 3–5 every day × 14 days same dose	Oral irritation, diarrhoea, nausea, vomiting, urticaria	None
Clotrimazole	Troches, oral suspension	Thrush Oesophagitis Prophylaxis	10 mg p.o. 5 × d × 14 days same dose	Nausea, vomiting, pruritus, rash	None
Fluconazole	Tablets, oral suspension, iv preparation	Thrush Oesophagitis (first line) Prophylaxis	200 mg p.o./followed by 100 mg p.o. until improvement (1–2 weeks) 50–100 mg p.o. q.day 150 mg p.o. q.week	Nausea, pruritus, headache, rash, seizures, hepatitis, alopecia, anaphylaxis, eosinophilia,	Sulphonylureas Coumadin Phenytoin Rifampin Theophylline Cyclosporin
Ketoconazole	Tablets (take with cranberry juice or carbonated beverage), oral suspension	Thrush Oesophagitis Prophylaxis	200–400 mg p.o. q.d.s. × 1–2 weeks 200 mg p.o. q.d.s.	nausea, vomiting, anorexia, impotency, adrenal suppression, hepatitis, pruritus, decreased libido, hypocholesterolemia, rash, gynecomastia	Coumadin Rifampin Prednisone Contraceptives Terfenadine Astemizole Cisapride Didanosine Theophylline Midazolam H_2 blocker Antacids Cyclosporin Phenytoin Oral hypoglycemics
Itraconazole	Capsules, oral suspension	Oesophagitis non-responsive to fluconazole	200 mg p.o. q.d.s. × 14 days	Nausea, vomiting, pruritus, rash, hypokalemia, oedema, hypertension, SGOT elevation	Digoxin Same drugs as ketoconazole
Amphotericin B	Lozenges, i.v. preparation, oral suspension	Thrush Oesophagitis Disseminated candidiasis	0.3–0.5 mg/kg q.d.s. × 7 days following 1 mg test dose	Nausea, vomiting, anaemia, hypomagnesemia, renal failure, thrombophlebitis, hypokalemia, Nephrotoxic agents	Pentamidine Aminoglycosides Cyclosporin Digitalis Corticosteroids Antineoplastics

candidiasis in HIV-infected patients. Fluconazole has been shown to be superior to clotrimazole troches for oropharyngeal candidiasis.[13, 14] The largest comparative trial[14] suggested overall equivalency, although fluconazole-treated patients were more likely to have mycologic cure (65% vs. 48%) and had a lower rate of relapse at 2 weeks (82% vs. 50%); this relapse difference was equal at 1 month follow-up. Single-dose therapy with fluconazole 150 mg is as effective as a 7-day treatment course.[18]

Unlike oropharyngeal disease, non-systemic therapy (e.g. nystatin) is largely ineffective for oesophageal candidiasis. At most centres, fluconazole has become the drug of choice for oesophageal candidiasis in AIDS. Randomized trials have shown fluconazole to be superior to ketoconazole for both oropharyngeal[19, 20] and oesophageal candidiasis.[21] In a prospective randomized trial, Laine and colleagues[21] compared ketoconazole 200 mg/day to fluconazole 100 mg/day in 143 patients with AIDS and oesophageal candidiasis.

Endoscopic cure and symptom resolution were found in 91% and 85%, respectively, of fluconazole-treated patients, compared to 52% and 65%, respectively, for patients randomized to ketoconazole. Clinical cure paralleled endoscopic cure. Both drugs were well tolerated with very few side-effects. The response rate of oesophageal candidiasis with fluconazole tends to be very rapid, with most patients experiencing significant clinical improvement by 3–5 days.[12, 22] Itraconazole 200 mg/day was found to be equivalent to ketoconazole 200 mg b.d. for oropharyngeal and oesophageal candidiasis.[23] Another study[24] found greater endoscopic cure at 3 weeks (75% vs. 38%) with fluconazole 100 mg b.d. compared to itraconazole 100 mg b.d., although no differences in short-term clinical remission (78% vs. 73%) were demonstrated. In the largest study reported to date, Barbaro et al.[25] randomized 2213 AIDS patients with a first episode of Candida oesophagitis to fluconazole or itraconazole. Clinical cure was achieved in 81% of fluconazole-treated patients compared to 75% of itraconazole-treated patients ($P < 0.001$), although there was no difference at the end of the follow-up period (96%). Approximately 25% of patients in both groups required an increase in dosage at 2 weeks.

Oral suspension forms of both fluconazole and itraconazole have recently been developed, and their efficacy appears similar to pill forms.[26] Preliminary results of comparative trials between fluconazole pills and itraconazole suspension suggest equivalency.[27] The suspension form is an attractive alternative to pills for patients with severe oesophageal symptoms, as well as for use in children. The additional cost of fluconazole and itraconazole over ketoconazole ($\approx$2–3 times more expensive) may be a consideration, especially when the disease is mild and non-life-threatening (e.g. mild thrush). Monotherapy with flucytosine at 100 mg/kg/day orally was found to be inferior to fluconazole for the treatment of oesophageal candidiasis.[28]

Amphotericin B is highly effective against all Candida species. Because of its toxicity, this drug is used almost exclusively in patients with thrush and/or oesophageal candidiasis with clinical and/or microbiologically resistant Candida. Although large studies evaluating the efficacy of amphotericin B for oesophageal candidasis in AIDS have not been conducted, clinical experience suggests this agent is highly effective. The use of intralipid with amphotericin B infusion may reduce some of the side-effects.[29, 30] Low doses of amphotericin B (0.5 mg/kg/day for 7–10 days) are usually adequate therapy for oropharyngeal and oesophageal candidiasis. The availability of a new lipid formulation (liposomal amphotericin B) reduces the side-effects and toxicity and maintains efficacy, although at a markedly increased cost.[31] A suspension form of amphotericin B for oral use is now commercially available, and may find its greatest utility in patients with resistant thrush.[32]

Resistance

An emerging problem of significant concern is the development of azole resistance. A number of studies of both oropharyngeal and oesophageal candidiasis have now documented clinical and microbiological resistance to these azole agents, most notably fluconazole.[33, 34] Testing of Candida isolates from patients with AIDS have found resistance in up to 33%.[35–37] The mechanism(s) for drug resistance are incompletely understood. Risk factors for resistance include prior use of azole drugs including total dosage, severe immunodeficiency (CD4 lymphocyte count < 100/mm^3), and recurrent episodes of candidiasis.[27–39] Some patients may harbour resistant strains without any prior azole therapy.[35] In vitro resistance correlates with clinical resistance.[38, 40–43] With prolonged azole use, there may be selection of a single resistant strain[44–46] as well as an increase in non-albicans strains,[8] which are inherently more resistant to these drugs.[46] Despite an increase in MIC, clinical response to fluconazole is usually maintained regardless of high-level resistance.[37] With fluconazole resistance, the MIC to other azoles, such as itraconazole, may also increase;[36] resistance to one azole therefore suggests cross-resistance to others.[47] Although most fluconazole-resistant strains remain susceptible to itraconazole, there is an upward shift of the MIC to itraconazole,[48] which may result in a poor clinical response. Return of sensitivity to fluconazole has been noted following drug discontinuation.[34] It is unclear whether intermittent azole use leads to greater resistance than continued drug administration.[49]

Mild drug resistance can often be overcome with increases in the dosage of the antifungal agent; up to 800 mg/day of fluconazole have been used. If higher doses are clinically ineffective or cause side-effects, switching to another azole can be tried; if there is no response, amphotericin B is effective. Microbiological and clinical resistance to amphotericin B is very rare. Nystatin or clotrimazole may occasionally be effective in

patients with oropharyngeal candidiasis and clinical resistance to systemic azole agents. Combination therapy of flucytosine with azoles for drug resistance has not been well studied.[50] Until further studies are available which clarify the mechanisms of drug resistance, it appears prudent to limit the use of azoles where possible.

Prophylaxis

Despite the frequency of oropharyngeal and oesophageal candidiasis in HIV-infected patients, primary prophylaxis is not widely administered, because these disorders are non-life-threatening, therapy is very effective, and there is concern that widespread use of primary prophylaxis will exacerbate the problem of drug resistance.[51] Both non-systemic[52] and systemic therapies provide effective prophylaxis.[53, 54] Whereas primary prophylaxis for *Candida* is rarely provided, secondary prophylaxis is commonly given, especially for patients with multiple recurrences. Fluconazole 50–100 mg/day or 150 mg once weekly are effective prophylaxis against recurrent oropharyngeal and oesophageal candidiasis.[55, 56] The use of fluconazole as prophylaxis has not shown a survival benefit. An additional benefit of chronic azole therapy is a reduction in the incidence of systemic cryptococcosis.[6, 57]

VIRAL DISEASES

Cytomegalovirus

Cytomegalovirus (CMV) is one of the most common opportunistic infections in patients with AIDS. Clinical and/or autopsy evidence of CMV disease may be observed in up to 90% of these patients,[58] and antibody positivity to CMV is present in 90% of homosexual men and 70% of intravenous drug users.[59] In fact, recent studies have shown an increasing incidence of CMV disease paralleling the widespread use of prophylaxis for *Pneumocystis carinii* pneumonia.[5, 6] CMV disease typically occurs when immunodeficiency is severe (CD4 lymphocyte count $< 100/mm^3$); in these patients, the incidence of disease may approach 21% at 2 years.[60] Although the retina is the most common target for CMV, gastrointestinal involvement remains important because of its frequency and morbidity. The diagnosis of CMV disease is best established by identification of viral cytopathic effects (inclusions) in gastrointestinal muco-

sal biopsies; viral culture of biopsy specimens is less sensitive and specific.[61]

Therapy. Treatment for gastrointestinal CMV disease is limited to intravenous therapy with ganciclovir, foscarnet, and more recently, cidofovir (Table 3). These drugs have similar mechanisms of antiviral action, including inhibition of viral DNA polymerases.[62] In addition to the anti-CMV effects, foscarnet, and possibly ganciclovir, also have an inhibitory effect on HIV.[63, 64] A number of open-label trials of ganciclovir for HIV-infected patients with gastrointestinal CMV disease have demonstrated clinical improvement in ≈75% of patients.[65–68] Open-label trials of foscarnet have yielded comparable results.[69, 70] The only placebo-controlled trial of ganciclovir, which evaluated colitis, found no clinically significant differences, probably because the treatment period was only 2 weeks.[71] A randomized trial comparing ganciclovir to foscarnet in 48 AIDS patients with gastrointestinal CMV disease found similar clinical efficacy (73%) regardless of the location of disease (oesophagus vs. colon), with endoscopic improvement documented in over 80%.[72] Time to progression of disease was similar (13–16 weeks) regardless of the use of maintenance therapy. Side-effects occurred in half the patients in each group.

Ganciclovir has a significant inhibitory effect on haematopoiesis; leukopenia occurs in up to 40% with long-term use[62] and is more severe when concomitant drugs which affect the bone marrow are given, such as azidothymidine (AZT).[73] The use of growth-stimulating factors will usually restore cell counts toward normal, permitting continued drug administration. In contrast to ganciclovir, foscarnet has no myelosuppressive effects, but causes renal insufficiency and disturbances in calcium, phosphorus and magnesium homeostasis.[74] Foscarnet is an anionic compound that binds divalent cations, such as calcium and phosphorus, which accounts for the metabolic effects on these cations. Adjustments in dosage based on creatinine clearance, and the intravenous administration of isotonic saline prior to and during foscarnet infusion help prevent renal insufficiency.[74] When symptomatic, electrolyte disturbances may be treated by oral supplementation. Coadministration of foscarnet with intravenous pentamidine should be avoided given the similar effects on calcium homeostasis. Similarly, drugs which cause renal insufficiency such as amphotericin B and aminoglycosides should be used cautiously when administering

Table 3. Comparisons between ganciclovir and foscarnet

Drug	Mechanism of action	Presentation	Dose	Adverse effects	Drug interactions
Ganciclovir (or Cytovene)	Prodrug, phosphory-lated intracellularly to triphosphate by viral enzymes. Inhibits viral DNA polymerase	i.v. preparation: 10 mL sterile vial (500 mg each)[a] p.o. tablets[b]	(i) Induction: 5 mg/ kg q.d.s. 12 h × 14–21 days (ii) maintenance 5 mg/ kg q.d.s. or 6 mg/ kg q.d.s. × 5 days every week	Myelosuppression Thrombocytopenia Granulocytopenia[c] Anaemia Seizures[d] Abnormal LFTs Headache Confusion Raises Creatinine Renal tubular acidosis	Probenecid Zidovudine Imipenem Dapsone Pentamidine Flucytosine Amphotericin Vincristine Adriamycin
Foscarnet (Foscavir)	Inhibits viral DNA polymerases and transcriptase	i.v. preparation 250 and 500 mg bottles	(i) Induction 90 mg/ kg 12 h or 60 mg/ kg q.d.s. 8 h × 2–3 weeks[e] (ii) maintenance 90–120 mg/kg/day	Renal failure[g] Hypophosphatemia Hypocalcemia Hypokalemia Hypomagnesemia Hyperphosphatemia Anaemia[f] Seizures Genital ulcers	Aminoglycosides Amphotericin Drugs that induce hypocalcemia

[a] Do not refrigerate after reconstitution (may precipitate).
[b] Store capsules at 15–30 °C.
[c] G-CSF administered subcutaneously, 1–8 μg/kg/day, for ganciclovir-induced neutropenia.
[d] Especially if combined with imipenem.
[e] Response may be evident in up to 6 weeks.
[f] Leukopenia and thrombocytopenia are uncommon.
[g] Administer one litre of normal saline prior to the infusion.

foscarnet. Genital ulceration in both males and females has been reported, and appears to be due to exposure of these tissues to high urinary concentrations of foscarnet.[74] The newest agent released for the treatment of CMV disease is cidofovir. This drug is a nucleotide analogue with activity against all herpes viruses; it has a very long half-life and can be given once weekly. It must be given with probenecid to prevent renal insufficiency.[75] To date this drug has been tested exclusively in patients with retinal disease, but future studies assessing efficacy for gastrointestinal CMV disease are anticipated.

The efficacy, tolerability and cost of ganciclovir have established it as first line therapy for gastrointestinal CMV disease in AIDS. Our current policy for the therapy of gastrointestinal CMV disease is to administer intravenous ganciclovir, assuming there are no major contraindications to this agent such as pancytopenia. We treat with induction doses for 2–4 weeks, depending on the clinical and endoscopic response. In our experience, oesophageal disease tends to respond more

rapidly than does colonic disease. Endoscopic re-examination following therapy is important for those patients with persistent symptoms. Ophthalmological examination is mandatory at the time of diagnosis in all patients to exclude retinal disease; long-term drug administration will be necessary in these patients. Failure to respond to ganciclovir may be the result of low serum levels[76] or drug resistance.[62] For patients with major contraindications to ganciclovir or in whom bone marrow stimulating factors are ineffective, foscarnet should be given. If a patient does not respond to ganciclovir (and the diagnosis is well established), foscarnet is usually effective.[68, 77] Combination therapy of foscarnet and ganciclovir appears to be effective for ganciclovir failures and has been used as primary therapy.[78, 79] (See Table 3 for comparisons between ganciclovir and foscarnet.)

If retinal disease is absent and a complete symptomatic and endoscopic response is documented following induction therapy, we stop therapy and look for recurrent symptoms. The relapse rate for oesophageal and colonic

disease is similar (30–50%).[68, 72] For those patients with frequent relapses of gastrointestinal disease, long-term once-daily maintenance intravenous administration is appropriate. There are no data regarding the efficacy of oral ganciclovir for either maintenance therapy or treatment of acute gastrointestinal disease.

Prophylaxis. Oral ganciclovir has been recommended for primary prophylaxis when immunodeficiency is severe (CD4 count < 100/mm^3), given the incidence of disease in this setting. The oral absorption of ganciclovir is poor, with a bioavailabilty of 6–9%.[62] The half-life of oral ganciclovir (3–7.3 h) is similar to intravenous administration (5 mg/kg); however, serum drug levels are much less (0.5 μ g/mL) than those achieved with intravenous therapy (4.5–10 mg/mL).[62] Oral ganciclovir occasionally causes bone marrow suppression.

Randomized placebo-controlled studies of oral ganciclovir for primary prophylaxis have demonstrated a reduction in the incidence of retinal and gastrointestinal involvement. In one study,[80] the incidence of CMV disease at 1 year was 14% in the treated group compared to 26% in the placebo group. The number of patients developing gastrointestinal CMV was low in both groups. The development of resistance is a concern with long-term use of oral ganciclovir. Nevertheless, studies to date have shown resistance to be rare with either oral or intravenous administration.[62] Resistance to foscarnet has not been extensively studied.

Herpes simplex virus

Herpes simplex virus (HSV) is an uncommon gastrointestinal pathogen in HIV-infected patients, in contrast to other immunocompromised patients. Since HSV primarily infects squamous mucosa, oropharyngeal, oesophageal and perianal involvement are the most common sites of disease. Oropharyngeal disease may be isolated, or may occur in association with oesophageal disease. In a large prospective study of 100 HIV-infected patients with ulcerative oesophagitis, HSV oesophagitis was identified in only 5%, whereas the prevalence of CMV disease was almost 50%.[81] Like CMV, the incidence of HSV disease increases as immunodeficiency worsens, with the greatest frequency occurring when the CD4 count is < 100/mm^3.[82] Mucosal biopsy is the most specific diagnostic method; cytology and culture also appear to be reliable techniques.

For the patient with mild to moderate disease who is able to tolerate pills, oral administration of acyclovir 15–30 mg/kg/day is effective.[81, 83] Absorption of oral acyclovir is inconsistent and may be <30%;[84] thus for patients with more severe disease, a higher dose may be required. Intravenous administration should be used when severe odynophagia limits oral intake or when the patient has not responded to high-dose oral therapy. In general, resistance is defined clinically as progression of disease despite acyclovir therapy. Although uncommon, acyclovir resistance has been documented, and is usually caused by a mutation in the thymidine kinase gene.[85] The incidence of acyclovir resistance during long-term therapy is unknown. In patients who are not immunocompromised, *in vitro* resistance can usually be overcome by increasing doses, whereas immunocompromised patients usually require an alternative therapy.[86] Ganciclovir, foscarnet and famciclovir are also highly effective against HSV; foscarnet is the preferred therapy for acyclovir resistance.[87] Foscarnet resistance has also been reported following long-term therapy for HSV.[88] The relapse rate of gastrointestinal disease is not well defined, but is probably similar to CMV. Primary prophylaxis is not currently recommended; secondary prophylaxis is usually provided for patients with genital disease or those with frequent relapses of oropharyngeal or oesophageal disease.

Other viral diseases

A number of other viral pathogens have been reported to involve the gastrointestinal tract in patients with AIDS. Epstein–Barr virus has been described as a cause of oesophageal ulcer.[89] Rotavirus has been linked to both acute and chronic diarrhoea.[90] Adenovirus has been reported to cause diarrhoea and colitis.[90–92] Several unusual viruses have been identified in HIV-infected patients with chronic diarrhoea, including astrovirus and picobirna virus[93] and coronavirus.[94] Although the true incidence of these viruses as gastrointestinal pathogens is unknown, it is probably low, and therapy is not currently available.

PROTOZOA

The emergence of the AIDS epidemic has greatly expanded the spectrum of gastrointestinal protozoal infections. Unlike fungi and viruses, these pathogens primarily involve the small intestine. As such, they play

the greatest role as causative agents of diarrhoea. These pathogens may also infect biliary epithelium, resulting in the AIDS cholangiopathy syndrome.[95, 96]

Cryptosporidia

In most series, *Cryptosporidium parvum* is the most common protozoal infection causing diarrhoea, identified in up to 11% of symptomatic patients.[97] Although a cause of acute diarrhoea, cryptosporidiosis is most commonly found in HIV-infected patients with chronic diarrhoea. Outbreaks of cryptosporidiosis are well described in both immunocompetent and immunodeficient hosts and result from contamination of public water sources.[98, 99] In contrast to immunocompetent patients with cryptosporidiosis, where spontaneous cure is uniform, the natural history is much more variable in HIV-infected patients.[100] This variablity is due to the effect of immunodeficiency, as patients with CD4 lymphocyte counts $> 180/mm^3$ usually have a self-limited illness,[101] whereas in patients with a CD4 count $< 50/mm^3$, the disease is often devastating, resulting in severe malabsorption, electrolyte disturbances, dehydration and weight loss, with a median survival of <12 weeks.[100] The pathogenesis of mucosal injury is poorly understood, although the degree of architectural distortion (villous atrophy) and inflammation are related to the parasite burden.[102]

Therapy. Over 60 therapies have been used for the treatment of intestinal cryptosporidiosis, most without success.[103] Several case reports suggest that immune reconstitution, either through potent antiretroviral therapy[104] or improvements in nutritional status,[105] may result in a clinical remission. A novel therapy includes the use of bovine colostrum. This consists of a concentrate of immunoglobulin prepared from bovine colostrum following immunization with cryptosporidial antigens;[106, 107] case reports have demonstrated clinical improvement in 50% of patients following the use of bovine colostrum. The results of an open-label trial[108] found a reduction in stool frequency and weight in patients receiving the powder (but not pill) formulation of bovine immunoglobulin, although less than half of the patients had a 50% reduction in stool weight or clearance of the pathogen from the stool.[108] Letrazuril, a drug with activity against coccidia, was found to have some efficacy in two studies.[109, 110]

The most effective agent currently available for the treatment of cryptosporidiosis is paromomycin. This non-absorbable[111] oral aminoglycoside agent has previously been used for the treatment of other parasitic diseases, but its mechanism of action for cryptosporidiosis is unknown. *In vitro* models using a human enterocyte cell line suggest an antimicrobial effect,[112] whereas a study using cryptosporidia in culture did not demonstrate sensitivity with this agent.[113] Case reports and small open-label trials of paromomycin have documented response rates up to 100%.[103, 114–116] In a study of 35 patients, a complete response was seen in 20% of patients, with a partial response observed in an additional 43%;[116] responders had higher preserved immune function as assessed by CD4 count. In a prospective open-label trial of 24 patients, 22 (92%) had a clinical response, with a complete remission observed in 18.[115] In the 22 responders, clearance of the organisms was noted on follow-up stool studies and/or small bowel biopsy. Other studies, however, have found persistent oocyst excretion, despite clinical improvement.[114] The efficacy of paromomycin was best shown in a randomized double-blind placebo-controlled cross-over trial of 10 patients, where both stool frequency and oocyst excretion were significantly reduced with paromomycin as compared to placebo.[117] Although the available literature supports the use of this agent, in our experience and others,[99] those patients with the most severe disease (and most severe immunodeficiency) are the least likely to respond. If the CD4 count is $>200/mm^3$, drug discontinuation after clinical cure is appropriate with close follow-up. For those patients with a CD4 count $< 100/mm^3$ in whom therapy is clinically effective, long-term administration is required to prevent relapse. Nevertheless, despite continued therapy, relapse may still occur.[115]

Microsporidia

Over the last decade, microsporidia have gained global attention as gastrointestinal pathogens in both immunodeficient and immunocompetent patients. Intense investigation has demonstrated that these parasites are common intestinal and biliary pathogens in patients with AIDS.[118–120] Microsporidia are a heterogeneous group of obligate intracellular spore-forming (coccidian) protozoa which may involve a variety of organ systems causing either localized or disseminated disease.[121, 122] The environmental source and mode of transmission of

these pathogens are unknown. Six microsporidial genera have been linked to human disease; gastrointestinal disease has been reported from only two of these, *Enterocytozoon bienusi* and *Encephalitozoon intestinalis; E. bienusi* is the cause of most cases of gastrointestinal disease.[121] Coinfection with these two microsporidia or with other pathogens has been reported.[123] In some studies of HIV-infected patients, microsporidia are the most commonly identified pathogen. Kotler and Orenstein[119] found microsporidia in 39% of AIDS patients undergoing gastrointestinal evaluation for diarrhoea. This high prevalence is probably not related to an increasing incidence of disease, but rather to greater recognition and improved diagnostic testing. Although electron microscopy of small bowel biopsies is considered the gold standard for diagnosis, recent studies have shown haematoxylin and eosin, brown-brenn, Giemsa, or modified trichrome staining of small bowel biopsies to have sensitivities of 77–83% with specificities approaching 100%;[121, 124] large comparative trials of stool testing with small bowel biopsy are lacking.[125] Immunofluorescent stains are being developed and are likely to provide additional sensitivity over current stool testing methods.

Therapy. Treatments for microsporidia are variably effective. Initial studies of metronidazole demonstrated some efficacy,[126] although our experience, as well as others,[127] has shown this agent to be largely ineffective. Atovaquone showed some efficacy in a small open-label trial.[128] Albendazole, an anti-helminthic drug, has shown promise in open-label trials,[129–131] with response rates of ≈50%. Despite clinical improvement, the organisms persist in the stool and on small bowel biopsy.[130] In contrast, studies of patients with *E. intestinalis* show response rates to albendazole of 66–100%, with some patients having clearance of the organism,[127, 130] and no relapse.[130] With the recognition that two microsporidial species involve the bowel, it has become clear that albendazole is highly effective for *E. intestinalis* but largely ineffective for *E. bienusi*. This response difference emphasizes the importance of a species-specific diagnosis of intestinal microsporidiosis. Currently, albendazole is only available on a compassionate basis from SmithKline. Prophylactic studies for microsporidia have not been performed and are unlikely to be initiated given the variable geographical prevalence and lack of a widely available effective therapy for *E. bienusi*.

Isospora

Isospora belli is a rare gastrointestinal pathogen in HIV-infected patients in the US, whereas it is endemic in many developing countries such as Haiti,[122] and is a major cause of chronic diarrhoea. As with other protozoa, it is primarily a small bowel pathogen. The diagnosis is best established by modified acid-fast stool staining;[122] small bowel biopsy may also be diagnostic. In contrast to cryptosporidia and microsporidia, effective therapy is available. Trimethoprim–sulphamethoxazole results in a cure in most patients. The relapse rate is unknown. The widespread use of trimethoprim–sulphamethoxazole prophylaxis for *Pneumocystis carinii* may be one explanation for the low incidence of this infection in developed countries.

Cyclospora

Cyclospora, another coccidian protozoa, have recently been recognized throughout the world as gastrointestinal pathogens both in immunocompetent patients and patients with AIDS.[131, 132] The prevalence of cyclospora in both developed and developing countries is unknown. A number of similarities exist in the microbiology, epidemiology and clinical expression of cyclospora and cryptosporidia. Cyclospora have a similar morphological appearance to cryptosporidia, although larger in size (8–10 μm vs. 4–6 μm, respectively).[131] These pathogens are difficult to appreciate on routine microscopy of small bowel biopsies, although electron microscopy is often diagnostic. Since trimethoprim–sulphamethoxazole is a highly effective therapy,[132] the frequency of cyclospora in developed countries is likely to be low.

Giardia

Giardia species, including *Giardia lamblia,* have no increased prevalence in HIV-infected patients, and the clinical presentation and diagnostic methods are also similar to HIV-seronegative patients. It is well recognized that multiple stool tests obtained on different days may be required for diagnosis as intestinal shedding is sporadic.[133] Light microscopic detection of giardia cysts and, less frequently, trophozoites, continues to be the mainstay of diagnosis. Fresh stool specimens should be examined or fixed with polyvinyl alcohol formalin and then stained with trichrome or iron haematoxylin. Cyst detection can be improved by the use of immunofluores-

cent antibody to cyst protein. Although still not widely used in routine diagnostic laboratories, faecal immuno-fluorescent tests have shown promising results. Small bowel aspiration and biopsy may be diagnostic when stool testing is negative. Therapy with metronidazole (500 mg b.d. for 5–7 days) is highly effective, resulting in clinical cure. In the patient with historical features and clinical findings compatible with giardiasis such as dyspepsia, crampy abdominal pain, borborygmi and watery diarrhoea, an empirical trial of metronidazole is appropriate particularly if initial stool testing is negative.

Amoeba

Like giardia, HIV-infected patients do not appear to have an increased suspectibility to amoeba.[134] Amoeba are frequently found in routine stool studies from asymp-tomatic and symptomatic homosexual men;[135–138] however, amoebic colitis is distinctly uncommon. In these patients, non-pathogenic amoeba (non-pathogenic zymodemes) including *Entamoeba dispar*, are likely, as they are indistingushable by light microscopy from pathogenic amoeba.[139] Other non-pathogenic amoeba such as *Entamoeba hartmanii* and *Entamoeba coli* have also been commonly identified on stool testing of homosexual HIV-infected men with diarrhoea.[136] It may be expected that colonization, even with non-pathogenic strains, might cause significant disease in immunocompromised patients. Instead, a benign clini-cal course has been found. A number of symptomatic patients in whom *Entamoeba* were identified had other potential pathogens, suggesting that a search for other causes is always appropriate in a symptomatic HIV-infected patient with diarrhoea and amoebic cysts. In addition, despite clearance of these protozoa from the stool, treatment has not been shown to reliably cure diarrhoea, suggesting that in most patients these do not represent pathogens (e.g. *Entamoeba dispar*). It is inter-esting to note that in the developing world, a higher percentage of asymptomatic infection may be due to pathogenic organisms. Metronidazole (750 mg t.d.s. for 10–14 days) is highly effective for *E. histolytica*, and relapse is rare. Because metronidazole is not an effective agent for cysts, use of a luminal acting agent to eradicate intestinal colonization is recommended for those with invasive amoebiasis. Three major luminal agents are available: iodoquinol, diloxanide furoate and paromomycin. All have efficacy rates of 85–95% for the eradication of cyst passage.

MYCOBACTERIA

With the widespread use of *Pneumocystis carinii* prophy-laxis, mycobacteria, have emerged as increasingly important pathogens in AIDS.[5, 6] Patients with a prior AIDS-defining illness have an incidence of *Mycobacteri-um avium complex* (MAC) of 23% at one year,[140] but 39% in those with a CD4 count $< 10/mm^3$.[141, 142] *Mycobac-terium tuberculosis* may complicate HIV disease at any stage of immunodeficiency, whereas MAC (formally termed *Mycobacterium avium intracellulare*) is only seen in patients with severe immunodeficiency. Indeed, the mean CD4 lymphocyte count in patients with MAC is $60/mm^2$.[140, 143] Although *Mycobacterium tuberculosis* can present in an atypical fashion in HIV-infected patients, gastrointestinal involvement remains rare, especially in developed countries.[144] MAC has rarely been reported to involve the oesophagus, biliary tree and colon; small intestinal disease is the most common site of luminal gastrointestinal involvement.[145] The pathogen-esis of MAC is believed to be ingestion of mycobacteria with subsequent small intestinal infection, followed by widespread dissemination.[146] Nevertheless, autopsy studies of AIDS patients with MAC bacteremia may fail to identify any foci of disease in up to 30% of patients.[147] The liver and spleen are the most common sites for dissemination.[148] Small bowel involvement is often diffuse. Massive infiltration of the small bowel, mimic-king Whipple's disease, has been described, and may account for the severe malabsorption seen in some patients.[149] Although diarrhoea is common, systemic symptoms and signs of fever and wasting often dominate the clinical presentation. Positive blood cultures estab-lish the diagnosis of disseminated MAC, but does not prove active gastrointestinal disease. In those with suspected disease, blood cultures may be negative, necessitating repetitive cultures, bone marrow biopsy or empirical therapy. The presence of a positive stool culture suggests, but does not prove, gastrointestinal involvement; stool culture positivity is a marker for subsequent disseminated disease.[150, 151]

Therapy. Therapy for MAC has improved substantially over the last decade. Previously used multi-drug regimens were poorly tolerated, associated with signi-ficant side-effects, and had low efficacy.[152] More recently, dual therapy with clarithromycin and et-hambutol has been shown to reduce bacterial load and provide clinical benefit.[153] In general, single-agent

therapy is insufficient and frequently leads to resistance.[154] Clarithromycin appears to be the most effective single agent; ethambutol is also effective.[154, 155] A combination of rifabutin, ethambutol and clarithromycin was shown to be superior to rifampin, ethambutol, clofazamine and ciprofloxacin;[155] bacteremia was cleared at 1 month in 78% of those receiving three drugs as compared to 40% in the four-drug regimen; survival was also significantly greater with the three-drug regimen (8.6 vs. 5.2 months, respectively). Relapse at 16 weeks was not seen in the three-drug group, suggesting the absence of resistance. Lifelong therapy is often given if a patient responds, because clearance of bacteria does not prove cure, as complete eradication is probably never achieved.

Depending on the clinical setting, there may be initial concern over the possibility of *Mycobacterium tuberculosis* in some patients. Multidrug regimens are effective for *M. tuberculosis* with microbiological and clinical cure observed at 9 months, provided drug resistance is not present;[156] long-term therapy is thus unnecessary.

Prophylaxis. Rifabutin was the first agent studied for MAC prophylaxis. Placebo-controlled trials of this agent found a reduction in incidence of bacteremia and improvement in some clinical parameters, but no differences in survival.[157] Based on this evidence, rifabutin was recommended for AIDS patients with CD4 count < 50/mm^3.[158] More recently, prophylaxis trials have compared clarithromycin to placebo,[159] and azithromycin to rifabutin vs. the combination of these two agents.[160] These studies show clarithromycin to be highly effective as monotherapy with a 6 month incidence of infection of 6% as compared to 16% for placebo.[159] Of the 19 patients developing infection, 11 (58%) had clarithromycin-resistant strains. In the other study,[160] azithromycin was found to be superior to rifabutin, with the combination regimen most effective. However, side-effects were significantly more common with the multidrug regimen (15.3% vs. 6% vs. 2.3%). As with the previous study,[159] patients developing clinical disease while on azithromycin had developed *in vitro* resistance. These studies in combination suggest that the preferred therapy for prophylaxis should consist of a macrolide antibiotic, probably clarithromycin 500 mg b.d. Because of side-effects and drug interactions with dual therapy including rifabutin, monotherapy is appropriate for prophylaxis. Nevertheless, resistance commonly develops.

BACTERIA

Unusual presentations of common bacterial diseases became apparent early in the AIDS epidemic where *Salmonella* sp.[161] or *Campylobacter* sp. bacteremia[162] were reported as initial manifestations of AIDS. Bacteria were frequently identified in earlier studies of diarrhoea in HIV-infected patients.[163, 164] Currently, the prevalence of these infections as causes of diarrhoea are not well known, although are probably lower than in the past given the use of trimethoprim–sulphamethoxazole for prophylaxis. The spectrum of bacterial causes of diarrhoea and clinical presentation in AIDS are similar to immunocompetent patients. Blood and/or stool cultures are usually diagnostic; blood cultures may be positive when stool cultures are negative.[165] Colitis may be identified by flexible sigmoidoscopy; mucosal biopsies should be performed in severely immunocompromised patients as CMV colitis may appear endoscopically similar. The role of enteroadherent *E. coli* as a cause of diarrhoea is unknown.[166]

Clostridium difficile colitis is an important cause of diarrhoea in HIV-infected patients. A high frequency of *C. difficile* colitis would be anticipated in these patients, given the prevalence of antibiotic use and frequent hospitalizations—both factors which have been linked to *C. difficile* disease.[167, 168] In the appropriate clinical setting, detection of *C. difficile* toxin is diagnostic. Faecal leucocytes are usually present (60%) and are an important clue to the diagnosis.[168] Flexible sigmoidoscopy is warranted in the patient in whom the disease is suspected but stool toxin is negative.

The clinical presentation and response to therapy of *C. difficile* colitis are no different in HIV-infected as compared to uninfected patients.[169] Metronidazole, which can be administered either orally or intravenously, represents first line therapy. Vancomycin should be reserved for those patients with contraindication to or failure with metronidazole or when the disease is life-threatening; this agent is only effective when administered orally. Clinical cure can be obtained in essentially all patients. The relapse rate appears to be similar in HIV-infected as compared to uninfected patients.[169]

IDIOPATHIC OESOPHAGEAL ULCER

An important entity not clearly linked to a specific infection is the HIV-associated idiopathic oesophageal ulcer (IEU). These lesions can present at the time of

seroconversion,[170] although typically occur when immunodeficiency is severe; the median CD4 count in these patients is <50/mm^3.[80] Several studies have identified HIV-infected inflammatory cells in the ulcer base of these lesions, suggesting an aetiological role for HIV.[171, 172] However, HIV has not been identified in oesophageal squamous mucosa but rather in inflammatory cells, and has been found in HIV-infected patients with oesophageal diseases other than IEU.[173, 174] These lesions present similarly to ulcerative oesophagitis from other causes; severe odynophagia is almost uniformly present. IEU are almost as common as CMV oesophagitis in patients with AIDS, comprising ≈40% of oesophageal ulcers in these patients.[81] The diagnosis is one of exclusion; CMV oesophagitis and IEU are indistinguishable clinically, radiographically and endoscopically.[175]

Therapy. Treatment of HIV-associated IEU is rewarding. Prospective studies have documented healing rates of over 90% with oral corticosteroids.[176] The regimen most commonly employed is prednisone 40 mg/day decreasing to 10 mg/week for a 1 month treatment course.[176] Shorter courses of therapy may be effective for smaller ulcers. Although beneficial, intralesional injection of corticosteroids should be considered as second line therapy.[172] The side-effects of corticosteroids are well recognized; patients with AIDS may be more likely to develop CMV disease while on therapy.[177] Because oropharyngeal and/or oesophageal candidiasis may complicate steroid use and confuse the therapeutic response, we routinely use short courses of azole therapy with prednisone. The response to corticosteroids is rapid, with most patients experiencing significant pain relief within days.[176] Although not as well studied, thalidomide also appears to be highly effective for IEU.[178, 179] Its mechanism of action is unknown, but it has been suggested that it is an inhibitor of tumour necrosis factor-α production.[180] In doses of 200–300 mg/day, thalidomide has been documented to result in a clinical response rate and endoscopic cure in over 90% of treated patients.[178, 179] Thalidomide is well tolerated, with the main side-effect being somnolence; administration of the drug at bedtime tends to overcome this. Peripheral neuropathy and skin rash have also been seen.[181] The major fear with thalidomide is the inadvertent use in the first trimester of pregnancy, which consistently results in severe birth defects. Thus, most would not use this agent in women of childbearing age, unless the patient is surgically sterile. Both prednisone and thalidomide are similarly effective for oropharyngeal apthous ulcerations. The relapse rate of IEU is ≈40–50% regardless of therapy.[81, 176]

SYMPTOMATIC THERAPY OF DIARRHOEA

For patients in whom antimicrobial therapy is ineffective or no specific cause for diarrhoea is found, symptomatic therapy will be necessary. When the diarrhoea is mild, bulking agents, bismuth or Kaopectate may provide relief. With more severe diarrhoea, medications to reduce intestinal transit are required. We routinely use diphenoxylate (Lomotil) in doses up to 10 tablets/day. Larger doses may cause anticholinergic side-effects, because diphenoxylate is combined with atropine in Lomotil.[182] Despite the potential for abuse, narcotic agents are also highly effective. In patients with severe diarrhoea, tincture of opium (paregoric) is very effective. It is usually provided with a dropper which provides a morphine concentration of 0.4 mg/mL. The normal dose is 5–10 mL/day in divided doses, and the dose can be titrated up to 20 mL/day. Some patients may experience somnolence or abdominal cramps; these tend to dissipate over time. Octreotide, a somatostatin analogue, is an antisecretory agent with a variety of inhibitory functions throughout the gastrointestinal tract. Initial studies in patients with AIDS found this drug to provide effective control of diarrhoea in ≈50%.[183–185] However, a large randomized placebo-controlled trial failed to demonstrate efficacy of this agent in patients with and without identifiable pathogens.[186] The drug is given subcutaneously in doses of 50–100 μg t.d.s. Side-effects include decreased biliary motility (gallstones), diabetes and steatorrhea, the latter of which may potentially exacerbate diarrhoea. Although the drug has not been clearly proved to be effective, its use may be attempted in patients with severe diarrhoea requiring hospitalization (e.g. cryptosporidia). We consider a clinical response to be a reduction in stool frequency/volume of at least 50%.

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