

# Gut

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## Leading article

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### Practical advice for the gastroenterologist dealing with symptomatic HIV disease

Government estimates for the likely scale of the HIV epidemic by the early 1990s have been revised downwards recently and the Cox Report<sup>1</sup> showed that 75% of all patients with HIV reside within the four Thames health regions. Nevertheless, patients with HIV related symptoms may present throughout the country.

#### Oesophageal symptoms

The commonest oesophageal symptom is pain on swallowing usually caused by candidiasis. About one third of patients have lesions caused by cytomegalovirus (CMV), herpes simplex, ulcerating leukoplakia, or aphthous-like ulcers similar to lesions present in the mouth. Superficial ulcers containing HIV negative like particles<sup>2</sup> have also been described at the time of seroconversion.

#### Diagnosis of oesophageal problems

Diagnosis is often possible from clinical signs and symptoms. Candidiasis and herpes simplex infection are associated with buccal involvement and CMV infection may be detected elsewhere. Symptoms of dysphagia and weight loss, which are rare when oesophageal candidiasis is the only finding, are commoner with dual or alternative pathology and indicate the need for early investigation.<sup>3</sup>

Although many American authors with large caseloads recommend the treatment of oesophageal symptoms with an antifungal agent, reserving further investigations for those who fail to respond, appropriate early investigation has many advantages. Thus most of these conditions satisfy the CDC criteria for the diagnosis of full-blown AIDS, which is an important milestone for the patient. In addition they may be the first indication for the use of anti-retroviral treatment, carry a poor prognosis,<sup>4</sup> and one third of patients who have more than one pathogen will not respond to empirical therapy.

#### Investigations

Radiology is not a satisfactory investigation for the oesophageal symptoms of HIV positive patients, it has a specificity of less than 50%, and often fails to detect candidiasis or superficial ulceration.<sup>3</sup> The specificity and sensitivity of diagnosis at endoscopy, however, is over 90%; thus CMV ulcers are usually linear with raised edges and are situated

just above the oesophago-gastric junction and although herpes infection may produce a generalised oesophagitis, fluid-filled vesicles which have not yet ruptured are also usually present.<sup>4</sup> Ulcerating hairy leukoplakia is usually found in the mid-oesophagus and has a characteristic appearance on histology.<sup>5</sup>

#### Treatment

Topical treatment is ineffective for oesophageal candida and systemic antifungal agents are required. Although a recent study comparing the new expensive triazole, fluconazole, with an imidazole, ketoconazole, showed the former was more effective,<sup>6</sup> the dose of the latter used was suboptimal<sup>7</sup> and in clinical practice there is little to choose between the two.

Foscarnet, given either by intravenous infusion continuously or three times a day, heals CMV ulceration of the gullet over a median period of eight days with longterm remission of symptoms for up to six months, and routine maintenance therapy is not recommended.<sup>4</sup> Home therapy, which may improve quality of life, is feasible. A major side effect of foscarnet is reversible renal failure and alternate day measurements of creatinine are needed.<sup>8</sup> Foscarnet also has complex effects on calcium metabolism with possible chelation of circulating ionised calcium and inhibition of renal phosphate reabsorption leading to hypo- or hypercalcaemia.<sup>9</sup> Intravenous pentamidine should not be used with foscarnet as the renal failure and hypocalcaemia are potentiated.<sup>9</sup> Ganciclovir is also an effective compound in the treatment of oesophageal CMV ulcers but may produce granulocytopenia leading to a higher rate of line sepsis.<sup>10</sup> Ulcerating leukoplakia of the oesophagus, probably caused by infection with Epstein-Barr virus or papilloma virus, may respond rapidly to acyclovir.<sup>5</sup> This drug is also used in the treatment of herpetic oesophagitis, although large doses may be required and intravenous therapy is often indicated.

#### Weight loss

The CDC now includes weight loss of greater than 10% of body weight without obvious cause in the diagnosis of AIDS.<sup>11</sup> The cause of this wasting syndrome remains unclear but it may be due to HIV infection of gut epithelial cells, leading to malabsorption.<sup>12</sup> Overt malabsorption, however, usually occurs in association with defined infection of the

gut.<sup>13</sup> The wasting syndrome of HIV disease sometimes associated with oedema resembles kwashiorkor, and both conditions are characterised by a raised serum IgA with a low secretory IgA<sup>14</sup> and a high serum ferritin.<sup>15</sup> Kwashiorkor may be caused by free radical excess generated by superinfection, particularly of the gut, and failure of the normal scavenging mechanisms because of lack of micronutrients such as selenium or vitamin E.<sup>16</sup> Malabsorption of similar vitamins and trace elements may be an important intermediary disease mechanism in HIV infected patients who have raised malonyldehydro (a marker of lipid peroxidation) values.<sup>17</sup> More needs to be learnt about these potential mechanisms before micronutrient or vitamin replacements are recommended.

An important cause of weight loss in HIV infected patients is poor dietary intake. The concept that widespread infection with candidiasis is an important intermediary disease mechanism for progression to AIDS is current in many of the alternative medicine approaches which encourage a low calorie sugar-free diet.

Other possible explanations for weight loss include an increased basal metabolic rate<sup>18</sup> and the production of cytokines such as tissue necrosis factor by HIV infected lymphocytes.<sup>19</sup>

In our experience extensive investigation of patients with weight loss but no diarrhoea is not fruitful.

### Diarrhoea

Diarrhoea is a common manifestation of HIV infection and may be caused by a number of opportunistic infections including cryptosporidium, CMV, and herpes simplex and less commonly *Salmonella* sp and *Mycobacterium avium intracellulare* (MAI).<sup>13</sup>

The possibility that *Microsporidium* sp are a major cause of diarrhoea is controversial. There are more than five hundred species of this organism but only two or three affect man, causing myositis, encephalitis, or diarrhoea. The form causing encephalitis is commoner in homosexuals, particularly those visiting the tropics.<sup>20</sup> Microsporidia have a unique spiral gland like a hypodermic needle which injects the oocytes into the small intestinal mucosa. Although the organisms were found in only two HIV positive patients with diarrhoea in the United Kingdom,<sup>21</sup> in a study of apparently pathogen-negative diarrhoea they were seen in up to a third of cases.<sup>22</sup> The organisms can only be identified by electron microscopy of jejunal biopsy specimens (not duodenal pinch biopsy specimens), although retrospectively subtle light microscopic abnormalities are often present on thin sections of jejunal mucosa.<sup>22</sup> Oocytes must be shed into the stools but they have not yet been identified.

The mainstay of diagnosis of diarrhoea is stool analyses, sigmoidoscopy, and biopsy. In a recent study the specificity and sensitivity of these techniques combined was over 90%.<sup>22a</sup> Additional information is rarely provided by total colonoscopy or barium enema.

### Stool analysis

In addition to the search for conventional stool pathogens and those responsible for the 'gay bowel syndrome', specific techniques are required to detect cryptosporidium.<sup>23</sup> There are no formal studies to compare the value of rectal histology and stool samples in the detection of this pathogen, although stools may be positive with no evidence seen on rectal biopsy specimens where the distribution of organisms is patchy.

*Mycobacterium avium intracellulare* may be grown from a number of body fluids, including the stool, without causing disease. Conventionally MAI confined to one site is relatively unimportant and is described as colonisation, whereas the presence of systemic symptoms such as fever or anaemia

associated with culture of the organism from more than one site is thought to indicate active infection.<sup>24</sup>

The other major pathogen causing diarrhoea, CMV, is only diagnosed on rectal histology. Sigmoidoscopy is macroscopically abnormal with a friable mucosa or discrete ulceration.<sup>13</sup>

### Apparently pathogen-negative diarrhoea

The variable frequency of apparently pathogen negative diarrhoeas<sup>13, 25</sup> is likely to depend upon the thoroughness with which primary care physicians screen for the common causes of diarrhoea in homosexual patients.

In our experience all patients with macroscopic changes at rigid sigmoidoscopy, which is always accompanied by histologically severe inflammation, have a defined cause for diarrhoea.<sup>22a</sup> The frequency of a positive diagnosis is considerably increased in patients who have lost more than 5 kg in weight or who have stool volumes of greater than 500 ml per day.

In addition tests of malabsorption, particularly the Schilling test, are most frequently abnormal with a defined cause of diarrhoea commonly cryptosporidial infection which often affects the terminal ileum producing malabsorption with only sporadic shedding of oocytes into the stool.<sup>26</sup>

No data exist as to the optimum number of stool samples that should be examined before a pathogenic cause of diarrhoea is excluded. We have previously found that up to six stool samples may be required to detect cryptosporidium, due to small numbers of oocytes and intermittent shedding.<sup>27</sup> The present advice is that with little weight loss, no sigmoidoscopic changes, and a normal Schilling test six stool samples and a rectal biopsy are sufficient investigation.

### Treatment

The mainstay of treatment for cryptosporidial diarrhoea is supportive, with oral rehydration treatment. Loss of autonomic neurones in the gut wall is a common feature in HIV infected patients with opportunistic infections<sup>21</sup> and this may exacerbate the diarrhoea and explain why anti-diarrhoeal agents have a strikingly beneficial effect.

Although macrolide antibiotics can reduce stool volumes transiently,<sup>27</sup> eradication of cryptosporidial infection has not been described, perhaps because of a reservoir of infection in the biliary tract which may not be affected by non-absorbable antibiotics. Thus there has been recent interest in using antibiotics such as spiramycin intravenously.

Although reports indicated that the use of zidovudine in patients with cryptosporidiosis improved the diarrhoea and sometimes eradicated the organism,<sup>27</sup> this is often not the case.

Diclazuril has been used in the treatment of various eimeria species of poultry.<sup>28</sup> Although there are some optimistic reports of its use in human cryptosporidiosis, it does not seem to eradicate infection or change the clinical course in seriously ill patients. This drug works better in poultry as a prophylactic agent and it may be that patients with small numbers of cryptosporidia will benefit.

Intravenous interleukin 2 eradicated cryptosporidial infection in about one third of patients in small studies.<sup>29</sup> The mechanism of action is unclear and it is a toxic drug. Further clinical controlled trials are underway.

Cytomegalovirus colitis responds to either ganciclovir or foscarnet, but less well than oesophageal disease, both because relapse is more rapid and coincident infection with cryptosporidiosis is common (submitted data).

Although MAI is often sensitive to a wide range of primary and secondary antituberculous agents in vitro, the response in vivo is disappointing.<sup>24</sup> Clinical trials are at present

underway of a new derivative of erythromycin, clarithromycin, which is highly effective in vitro.

### Prophylaxis against diarrhoea

Cryptosporidiosis is a zoonosis in rural communities<sup>30</sup> and nosocomial transmission is documented<sup>31</sup> but in the urban environment human to human transmission is probably the most important route of infection.<sup>32</sup> Nevertheless water supplies may be infected with cryptosporidium<sup>33</sup> and it would seem sensible advice that all HIV positive patients with evidence of immunosuppression should be advised to boil water before use.

Recent retrospective data indicate that high dose acyclovir (800 mg, five times daily) may prevent the development of CMV infection<sup>34</sup> and controlled trials of this treatment in patients with low OKT4 counts (less than 100 mm<sup>3</sup>) are underway.

### Abdominal pain

Cytomegalovirus infection is frequently associated with abdominal pain. Patients with colitis often have appreciable rebound tenderness and since a third of patients eventually die of perforation of the colon<sup>35</sup> they represent a difficult management problem. Infection of the upper gastrointestinal tract with CMV often presents with rather non-specific abdominal pain, and gastritis or ulceration is found at endoscopy.

Cholangitis related to cryptosporidial infection is an important cause of right upper quadrant pain, often with a raised alkaline phosphatase activity.<sup>35</sup> Cholangiography shows beading of the bile duct, which may be typical of sclerosing cholangitis, a dilated gall bladder, and papillary stenosis, although sphincterotomy may not help the pain.<sup>36</sup> In addition to cryptosporidial infection, CMV is often found at necropsy.<sup>35</sup> Consequently the pain may respond to interleukin 2 or to foscarnet.

Infection with MAI may cause non-specific abdominal pain with enlargement of abdominal lymph nodes, shown by computed tomography.<sup>37</sup> Alternative diagnoses to be considered include lymphoma and Kaposi's sarcoma.

### Decontamination of endoscopy equipment

This subject has been extensively reviewed recently.<sup>38</sup> Although contamination with cryptosporidial spores is probably greatly reduced by thorough washing, the potential problem of human to human transmission remains, particularly when immunosuppressed patients are sequentially endoscoped. Recently an excystation technique has shown that a chlorine dioxide based cold sterilant or 10% by volume hydrogen peroxide are effective against cryptosporidium<sup>39</sup> and may be suitable for use in units dealing with large number of HIV infected patients.

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