Immunodeficiency and the gut

Brian Gazzard

Abstract

Gastrointestinal diseases associated with impaired immunity are largely infectious, although an increased incidence of extranodal lymphoma is also found in the context of HIV infection. The range of such infections is related to the role of CD4+ T cells in their eradication. Infections tend to occur with organisms of limited virulence and to be recurrent, and are associated with disseminated infection. The symptoms they produce are usually pain on swallowing, weight loss or diarrhoea. Abdominal pain can be associated with *Mycobacterium avium-intracellulare* or sclerosis of the bile ducts secondary to infection.

Keywords CD4 cells; *Cryptosporidium*; cytomegalovirus infection; diarrhoea; HIV; *Isospora*; microsporidia; MRCP; *Mycobacterium avium-intracellulare*

Key points

- Highly active antiretroviral therapy is now effective in eradicating most previously untreatable opportunistic infections in HIV-seropositive patients
- Profound loss of CD4 cells in the lamina propria can be demonstrated within 7 days of infection with a retrovirus in monkeys; this is associated with loss of normal integrins on the surface of these lymphocytes
- Microsporidial infection is now recognized as a common cause of diarrhoea in the tropics, producing continuing symptoms in immunosuppressed individuals
- Recent advances in typing *Cryptosporidium* have shown that human–human transmission is common
- Ciprofloxacin remains the mainstay of treatment of *Salmonella* and *Campylobacter* infections, but the prevalence of organisms with reduced sensitivity is rapidly increasing
- Nitazoxanide is effective treatment for cryptosporidiosis
- A new much less toxic agent against cytomegalovirus, ((letermovir (indication under investigation)), is now available for prophylaxis and is probably also effective in treatment
- The new checkpoint inhibitors used in cancer therapy are associated with an increased risk of colitis.

Introduction

The gut constitutes part of the mucosa-associated lymphoid tissue. It has two important and conflicting immune functions — to produce specific immune tolerance to food antigens, and to provide immune protection against potential pathogens.

The gut's immune system comprises intraepithelial lymphocytes, which are predominantly CD8 effector cells, and lamina propria lymphocytes, which are mainly CD4 helper cells. Specialized areas of the gut epithelium contain dome cells, which allow antigen presentation to Peyer's patches. Immunocompetent cells generated by this process circulate through the lymphatics and to the mucosal immune system via specific integrins (particularly B7) that interact with addressins on venules in the gut wall. Both immunoglobulin (Ig) A and IgM are secreted into the gut lumen to produce humoral immunity. Production of secretory IgA is associated with eradication of *Cryptosporidium* in calves, and CD4 cells have been shown to have a pivotal role in eradicating this infection in knock-out mouse experiments.

Causes of immune deficiency

Defects in production of secretory IgA

Defects in production of secretory IgA are the most common cause of immune deficiency in developed countries (1 per 700 population). This is often asymptomatic but can be associated with gut infections, and affected individuals are at increased risk of developing Crohn's disease and coeliac disease. Occasionally, serum IgA concentration is normal. Common acquired hypogammaglobulinaemia, in which concentrations of all plasma gammaglobulins are reduced, is also associated with gut infection.

Genetic defects

There is a wide variety of genetic defects in the immune system. These are often fatal in early life because of overwhelming infection. Others produce less severe disease and are associated with various gastrointestinal infections and mucocutaneous candidiasis.

Iatrogenic cellular immune deficiency

Iatrogenic cellular immune deficiency can occur as a result of total body irradiation or chemotherapy.

HIV infection

HIV infection is the most common cause of immune deficiency worldwide. Destruction of CD4 cells leads to an inexorable decline in immune function. Disproportionate early loss of CD4 cells occurs in the lamina propria, leading to a wide variety of gut infections.

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Common infections of the small and large intestine associated with immune deficiency

Many virulent gut infections that cause diarrhoea in immunocompetent individuals also affect immunodeficient patients, producing a more prolonged illness that is often untreatable and more likely to recur. In those with HIV infection, use of highly active antiretroviral therapy (HAART) has reduced the incidence of many infections. Some previously untreatable infections are eradicated during the immune reconstitution that occurs after HAART; this is associated with an influx of CD4+ cells into the lamina propria.

Giardia lamblia

This organism is mainly acquired from water, but is more common in homosexual men as a result of sexual activity. It causes steatorrhoea and three or four loose bowel actions per day, often with flatus, bloating and weight loss. Treatment is with a single dose of tinidazole, 2 g, or metronidazole, 400 mg three times daily for 5 days. The diagnosis can be reliably made by small bowel biopsy (Figure 1); cysts are detected in the stools in only 30–60% of individuals, but detection of *Giardia* antigen is much more sensitive. Many cases are treated presumptively.

Cryptosporidiosis

This infection is associated with chronic diarrhoea, nutritional compromise in individuals with a CD4 count $<200/mm^3$. Recently, nitazoxanide, 100 mg twice daily for 3 days or longer, has been shown to reduce symptoms and be associated with more rapid parasite clearance. *Cryptosporidium* is acquired after exposure to contaminated water or by human contact. Drinking boiled water effectively prevents waterborne transmission.

Microsporidiosis

This infection is caused by a sporulating intracellular pathogen that infects either only the gut (*Enterocytozoon bieneusi*) or the gut and other tissues (*Septata intestinalis*). Infection is probably waterborne. The symptoms are chronic diarrhoea and wasting. Prolonged treatment with albendazole, 400 mg twice daily, eradicates *S. intestinalis* but not *E. bieneusi* (Figure 2).

Bacterial diarrhoea

Relatively avirulent species of *Shigella*, *Salmonella* and *Campylobacter* can cause prolonged diarrhoea. Recurrent attacks, septicaemic illness and prolonged disease are common. *Shigella* is waterborne and sexually transmitted. *Campylobacter* and *Salmonella* infection follows ingestion of poorly cooked food. Suspected cases should be treated with ciprofloxacin, 500 mg twice daily, while cultures of blood and stool are awaited. Response to treatment is usually prompt, but the incidence of antibiotic resistance is increasing. Prolonged secondary chemoprophylaxis is required in some patients.

Mycobacterium avium-intracellulare

Diarrhoea caused by this opportunist is a late manifestation of HIV infection. Colonization of the gut without disease is common, so the diagnosis must be confirmed by the typical appearances on small bowel biopsy taken at upper gastrointestinal endoscopy. Azithromycin, 1.2 g weekly, and rifabutin, 450 mg daily, are effective, but resistance rapidly emerges.

Cytomegalovirus

This infection in patients with severe immune suppression produces bloody diarrhoea, sometimes associated with toxic dilatation and colonic perforation. Infection most commonly involves the rectum, but the terminal ileum and caecum can be affected. The histological appearance can suggest the diagnosis, which is confirmed by finding viral inclusions. Treatment for colitis or oesophagitis (see below) is with foscarnet, 100 mg/kg/day intravenously, ganciclovir, 5 mg/kg twice daily for 3 weeks, valganciclovir, 900 mg twice daily orally, or letermovir, 480 mg daily intravenously or orally.

Other infections

Immune-deficient patients can suffer from infections with many different organisms of little or no intrinsic virulence that never cause disease in immunocompetent individuals. Adenovirus infection, recognized histologically, is common in immunosuppressed children but rare in adults. Diarrhoea is usually associated with co-infection with another pathogen. *Isospora* is endemic in South America and can be recognized by characteristic spores in stool. It is treated with one double-strength tablet (480 mg) of co-trimoxazole four times daily for 4 weeks, but recurrent disease is common.

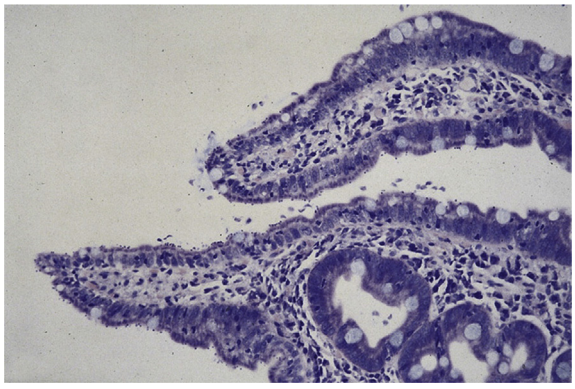

Figure 1 An oil immersion view of the tips of two villi, both showing numerous organisms attached to the surface (*Giardia*).

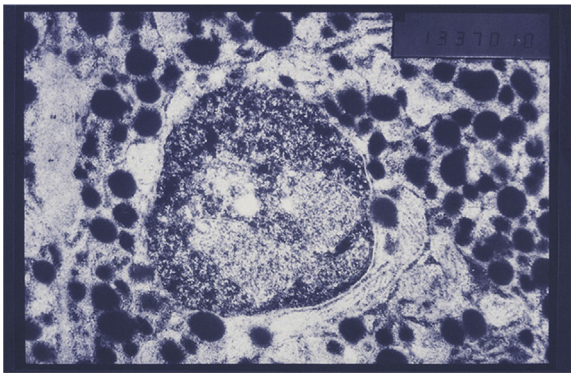

Figure 2 An electron micrograph showing developing microsporidia within a single cell surrounded by numerous mitochondria.

Common infections of the oesophagus associated with immune deficiency

Oesophageal candidiasis

This condition causes odynophagia (pain on swallowing) rather than true dysphagia and is usually associated with oral candidiasis. It is an important differential diagnosis, particularly in patients taking metered-dose inhaled corticosteroids. Treatment is usually expectant; fluconazole, 100 mg daily for 1 week, achieves a cure in most patients.

Cytomegalovirus

Cytomegalovirus of the oesophagus produces a haemorrhagic oesophagitis, which shows characteristic viral inclusions on histology.

Ulcers

Ulcers of unknown aetiology but which are thought to be infective are common in immunodeficient patients and are generally aphthous in appearance. They can be treated using intralesional injections of corticosteroids during endoscopy, or with thalidomide, 100–200 mg/day. Thalidomide is contraindicated in women who may become pregnant. It can also cause severe axonal peripheral neuropathy. ◆

FURTHER READING

Crump JA, Sjolund-Karlsson M, Gordon MA, Parry CM. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance and antimicrobial management of invasive *Salmonella* infections. *Clin Microbiol Rev* 2015 Oct; **28:** 901–37.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 26-year-old man presented with a recurrence of watery diarrhoea. He has had several similar episode in the past, most of which had settled spontaneously. Stool microscopy and culture in the past had usually been negative but on one occasion *Giardia* had been found and his symptoms had resolved with metronidazole, although he had needed a repeat course. He was otherwise well. Clinical examination was normal.

Investigations

Stool microscopy; cysts and trophozoites of Giardia intestinalis seen.

What further investigation should now be performed?

A Blood immunoglobulin (Ig)A levels
B Blood IgM levels
C Faecal elastase levels
D Blood vasoactive polypeptide levels
E Small bowel biopsy and culture

Question 2

A 32-year-old man presented with a 3-week history of severe watery diarrhoea, estimated up to 2 litres/day. He had also lost weight. He was known to have HIV infection. On clinical examination he appeared dehydrated with obvious weight loss, temperature 37.0°C, heart rate 96 beats/minute, blood pressure 105/72 mmHg.

What investigation would elucidate the most likely diagnosis?

A. Stool culture
B. Fresh stool microscopy looking for amoeba
C. Stools staying …. parasites
D. Colonoscopy
E. Measure the cytomegalovirus (CMV) viral load in the plasma

Question 3

A 27-year-old man presented with pain on swallowing. He had recently had a course of amoxicillin for a respiratory tract infection. On examination there were white patches on the tongue and palate which could only be scraped off with difficulty.

What is the next most appropriate action?

A. Advise a nystatin mouth wash
B. Perform a barium swallow
C. Perform a gastroscopy
D. Perform an HIV test
E. Start antiviral treatment