Gastrointestinal problems in the immunosuppressed patient

The gastrointestinal tract is a major component of the human immune system with a total lymphoid mass which is comparable with bone marrow.[1] The Peyer's patches are the principal sites of interaction among luminal antigens and lymphocytes, while the scattered lymphocytes in the lamina propria and epithelium are the effector cells that mediate immune response.[2] The gut is also a site of synthesis and release of a specialised form of immunoglobulin A (secretory IgA) which is resistant to digestion. These immunological mechanisms are important because the gut has a huge surface area which interacts with the numerous potentially noxious agents including micro-organisms and dietary antigens.[2 3] The intestinal tract is also one of the most metabolically active tissues in the body, with mucosal renewal taking place every three to five days, it is not surprising therefore that the gut is often the target organ for pathological processes in the immunosuppressed patients.[4 5] The deleterious effects of immunosuppression on the integral functioning of the gut are assuming greater importance now that the use of potent long term immunosuppression has become widespread, for example in autoimmune diseases and organ transplantation.

Pathophysiology of immunosuppression on gastrointestinal function

The effects of immunosuppression on the gastrointestinal tract are multiple and include loss of gastric acidity, impaired immune response, reduced mucosal integrity, and compromised mucosal regeneration.

THE SUPPRESSION OF GASTRIC ACID SECRETION

This may be induced by treatment with H_2 blockers or be secondary to malnutrition or immaturity (as in neonates), and the number of viable organisms surviving passage through the stomach can therefore increase by a 1000-fold causing gastroenteritis.

THE IMMUNE RESPONSE

The immune response may be globally attenuated by drugs such as steroids (reduction in chemotaxis and kinin production), or more specifically by cyclosporin A and tacrolimus, which inhibit T lymphocyte proliferation by inhibiting expression of interleukin 2.[6] Such immunosuppression may cause persistence of normally mild infections such as cytomegalovirus or cryptosporidium, and permit an increase in commensal organisms. Epstein-Barr virus which infects B lymphocytes can induce B cell proliferation and ultimately B cell lymphoma in the presence of altered immune response.[7] In transplantation, intestinal graft-versus-host disease (GVHD) is a risk when the mass of donor lymphocytes received is comparable with that of the recipient's, as is the case in allogenic bone marrow transplantation or even small bowel transplantation. This risk is increased when the immune system is further suppressed with potent treatments such as OKT3 and antithymocyte globulin.

MUCOSAL INJURY

Mucosal injury is well documented in patients with chronic intestinal inflammatory states. Loss of intestinal integrity is a recognised sign of rejection in small bowel transplantation.[8] Mucosal damage (mucositis) frequently occurs after tumour chemotherapy and after conditioning treatment before allogenic bone marrow transplantation in adults, but probably occurs less commonly in children.[4] Radiation has been shown to cause inflammatory changes in the lamina propria in human adults.[9] A protein losing enteropathy was reported to occur in up to 90% of paediatric bone marrow transplants,[4] and this is associated with hypoalbuminaemia which may contribute to impaired regeneration of the villi.

Aetiologies of intestinal dysfunction

INFECTIONS

The gastrointestinal tract is a portal of entry for numerous pathogens, and infections are a major cause of morbidity and mortality in immunosuppressed patients. Common viral agents include rotavirus, cytomegalovirus, adenovirus, and coxsackie A virus,[4 5] all of which may cause devastating diarrhoea in these patients. Bacterial infections include *Campylobacter jejuni* and salmonella,[3–5] which are normally sensitive to gastric acid, and so are a particular risk in patients receiving H_2 blockers.[10] *Clostridium difficile* infection, which is associated with the use of broad spectrum antibiotics as is common in immunosuppressed patients, may sometimes lead to pseudomembranous colitis. Fungal infections are extremely common ranging from superficial candidiasis to severe systemic infections with candida or aspergillosis involving the intestine and closely related organs such as the liver and spleen.[11] Infection by protozoa may also be a problem, and *Pneumocystis carinii* and cryptosporidium are the most frequently identified commensal organisms.[5] *Strongyloides stercoralis* is a nematode which may cause a fulminating infection in immunosuppressed patients from the tropical countries.[11]

DRUG TOXICITY

Immunosuppressive drugs can cause a variety of gastrointestinal lesions including mucosal erosions, bleeding, and viscous perforation (for example, steroids); hepatitis, cholestasis, and pancreatitis (for example, azathioprine); impaired enterocyte function causing malabsorption (for example, mycophenolate and tacrolimus).[12] Cytotoxic drugs (for example, cyclophosphamide and busulphan), and irradiation used as primary or adjunctive treatments with immunosuppressive agents cause an enteritis associated with gut mucosal ulceration and bleeding. Idarubicin has been associated with more diarrhoea than cyclophosphamide after allogenic bone marrow transplantation, necessitating support with parenteral nutrition.[4] The use of isolated parenteral nutrition itself, however, may worsen gastrointestinal function because enteral feeding is an important stimulus to pancreatic function, villus growth, and mucosal integrity.[13 14]

IMMUNOLOGICAL REACTIONS

GVHD may cause inflammation in the gut stroma and degeneration and necrosis of crypt cells in which apoptotic bodies are characteristically seen. A severe form of diarrhoea, often containing blood and albumin, may ensue.[15] Acute GVHD is a systemic disorder typically involving skin and liver in addition to the gastrointestinal tract; other organs such as the lungs and pancreas may also be involved. It usually occurs seven to 50 days after bone marrow transplantation (and occasionally after liver or small bowel transplantation). The damage GVHD causes to the liver is focused in the portal tracts with loss of bile

ducts and cholestasis, while the parenchyma is relatively spared. Lymphoproliferative disease that develops after transplantation may be considered as an "opportunistic cancer" in which the immunodeficiency state of the host has a key role in fostering the environment necessary for abnormal lymphoproliferation.[16] The development of lymphoproliferative disease after transplantation (usually leading to undifferentiated B cell lymphoma) may be related to exposure to Epstein-Barr virus, chronic antigenic stimulation from the allograft, or a direct oncogenic effect of immunosuppression.[7 17] After a heart transplant, approximately 10% of patients develop lymphoproliferative disease, and 10–15% of small bowel transplant recipients may develop this disease also. The gut is a common site for the lymphoma to occur and may cause symptoms of obstruction, perforation, bleeding, and diarrhoea as well as chronic anaemia.

VENO-OCCLUSIVE DISEASE

The peripheral branches of the hepatic veins are susceptible to occlusion by microthrombi, especially after bone marrow transplantation. The mortality rate is up to 30%, with a higher risk for patients who have a history of pretransplant viral hepatitis, radiotherapy, and busulphan conditioning. The increased hepatic venous pressure produces a Budd-Chiari like syndrome with unexpected weight gain and ascites.[18]

Patterns of gastrointestinal disorders

FEED INTOLERANCE

Feed intolerance is common in immunosuppressed patients and is usually manifested by vomiting and diarrhoea, which may contain frank blood. These symptoms may be related to infections such as bacterial overgrowth and to mucosal inflammation, GVHD, or enterocyte dysfunction. The presentation of infectious diarrhoea may be atypical in that an agent which usually produces superficial lesions in the mucosa may mimic another disorder such as Crohn's disease.[19] Mucositis induced by chemotherapy and total body irradiation is common in allogenic bone marrow transplantation, and up to half the transplant recipients in one paediatric study required two to four weeks of parenteral nutrition.[4] Intestinal GVHD occurs in 30–70% allogenic bone marrow transplant recipients and may provoke a severe diarrhoea.[20]

SECRETORY DIARRHOEA

This takes the form of a watery stool containing >60 mmol/l of sodium and may occur in isolation as a result of GVHD, cytomegalovirus, or rotavirus. In patients with chronic immune suppression, secondary to human immunodeficiency virus octreotide has been tried to control the secretory diarrhoea.[21] A secretory state may also develop after small bowel transplantation.

ABDOMINAL PAIN

Abdominal pain may occur in severe GVHD, but other causes such as gastritis, typhlitis, or paralytic ileus are more common. Veno-occlusive disease causes a tender hepatomegaly.[15 18]

JAUNDICE

Jaundice may be secondary to GVHD, veno-occlusive disease, sepsis (especially fungal), viral hepatitis such as cytomegalovirus, lymphoproliferative disease, or biliary sludge, which is common in patients who are receiving parenteral nutrition because of feed intolerance.

MALABSORPTION

Malabsorption is manifested by copious watery diarrhoea in which stools test positive for reducing substances and may contain fat if cholestasis or pancreatic dysfunction is present. Villus atrophy and mucositis result in a reduction in absorptive surface and marked carbohydrate malabsorption.[22]

BLEEDING

Bleeding presenting as haematemesis, melaena, and rectal bleeding is common after major surgery and bone marrow transplantation.[23] It may be related to the direct mucosal damaging effects of the drugs (steroids), poor anastomotic healing, anastomotic ulceration, or to haemorrhagic colitis/enteritis related to the infectious agents (for example, cytomegalovirus). Impaired platelet function and prolonged clotting times may also contribute to intestinal bleeding.

PERFORATION AND OBSTRUCTION

Perforation or obstruction, or both, are uncommon but may occur after cytomegalovirus enteritis, or steroid induced peptic ulceration. Silent perforation may sometimes occur in some of the patients (especially those with previous abdominal surgeries or underlying pathologies such as duodenal ulcers) who are receiving high dose corticosteroids, especially in the immediate period after the transplant.[24] Transmural lymphoproliferative disease may perforate or obstruct the intestinal lumen.

Diagnosis

The patterns of symptoms and signs vary in severity, and overlap despite different aetiologies, so investigation is crucial in order to make a specific diagnosis. The most useful tests screen for infection, malabsorption, and histological evidence of tissue damage mediated either by the immune system, chemotherapy, or infectious agents.

First line screening investigations

STOOL CULTURE AND ELECTRON MICROSCOPY

These processes can identify up to three quarters of the infectious agents.[5 20] Semiquantitative polymerase chain reaction (PCR) on circulating white cells reliably identifies cytomegalovirus infection and is soon likely to be applied to other tissues for other antigens (Epstein-Barr virus, for example).

FAECAL STEATOCRIT

Faecal steatocrit (greater than 2% fat in a 2 ml stool sample),[25] faecal chymotrypsin (a marker of pancreatic enzyme function), and faecal reducing substances all suggest malabsorption. Protein malabsorption suggests a submucosal injury is present (for example, GVHD) and was shown to be present in 47% of children after bone marrow transplantation in a study by Papadopoulou *et al*.[4] A protein losing enteropathy also occurs when the portal pressure is raised as in veno-occlusive disease. A faecal α_1-antitrypsin of more than 2.2 mg/g of stool is indicative of a protein losing enteropathy.[4]

ENDOSCOPY

Endoscopy provides direct visualisation for biopsy of mucosal lesions and can localise the site of blood loss. Light microscopic examination of the tissue biopsy specimens can provide conclusive evidence for GVHD, lymphoproliferative disease, cytomegalovirus, villous atrophy, inflammation, and rejection (in the case of small bowel transplant).[26]

RADIOLOGY

Radiology, including plain abdominal *x* ray and abdominal ultrasound, can detect obstruction and perforation, anastomotic leak, toxic megacolon, features of acute pancreatitis, mucosal oedema, ascites or fluid collections, and visceral candidiasis.[27]

Second line investigations

ABNORMAL LIVER FUNCTION

When abnormal liver function tests develop, is extremely useful to take a biopsy specimen from the liver for identifying microabscesses, GVHD, veno-occlusive disease, and drug toxicity. The risks of bleeding, however, are high in allogenic bone marrow transplantation because of marrow aplasia resulting in thrombocytopenia, and the recipients may have coagulopathy from other problems such as sepsis and GVHD. Therefore, blood product support and ultrasound guidance of the biopsy needle is recommended. Transjugular liver biopsy may be a safer option in older children after allogenic bone marrow transplantation, where necessary.

RADIONUCLIDE IMAGING

Radionuclide imaging using white cell labelling may be helpful in delineating the site of gut inflammation/abscesses, but steroid administration (leading to impaired neutrophil function) and reduced white cell counts are common in immunosuppressed patients and limit the usefulness of this test.[28] In brisk gastrointestinal bleeding, technetium-99m labelled red blood cells scan localise the site with diagnostic yield comparable with angiography.

INTESTINAL PERMEABILITY

Intestinal permeability is increased whenever the tight junctions between enterocytes are impaired by oedema, as in surgery to the intestinal tract, during gastrointestinal infections, after bone marrow transplant, and during acute cellular rejection after small bowel transplantation.[29] Intestinal permeability can be simply measured by analysing the differential absorption of two non-metabolised carbohydrates, but it is more useful in research than clinical practice.

Management

The non-specificity of gastrointestinal symptoms and the great diversity of potential pathologies affecting immunosuppressed patients mean that it is essential to make a precise diagnosis. Opportunistic infections or bacterial overgrowth may require specific treatment (for example, ganciclovir for cytomegalovirus, enteral immunoglobulin for adenovirus infection,[30] metronidazole for bacterial overgrowth, and co-trimoxazole for pneumocystis) and reduction in immune suppression if possible. Granulocyte colony stimulating factor may be helpful in patients with severe neutropenia. In small bowel transplant recipients, infection or altered permeability is a manifestation of graft rejection and, paradoxically, the dose of the immunosuppressants may need to be increased at the same time as instituting broad spectrum antibiotics. Acute GVHD is managed using a combination of high dose corticosteroids and cyclosporin, with antithymocyte or antilymphocyte globulin used as a second line treatment. Azathioprine and thalidomide are useful in the treatment of chronic GVHD. Ursodeoxycholic acid may be valuable if the GVHD is damaging the bile ductules.[31] The use of irradiated blood is presently considered the most effective method of preventing GVHD after transfusion.[32] The management of veno-occlusive disease is supportive using diuretics and fluid restriction with thrombolytic agents such as alteplase (tissue type plasminogen activator) for severe and progressive cases.[18] Gastrointestinal bleeding may occasionally require surgery if medical treatment with H_2 blockers, proton pump inhibitors, and sucralfate fails. Nasogastric tube feeding with high energy feed is an important method of improving the nutritional status and gastrointestinal function of immunosuppressed children.[4]

Summary

Gastrointestinal dysfunction is common in immunosuppressed children. It is almost invariably multifactorial, and often presents a diagnostic dilemma. Systematic investigation should allow an accurate diagnosis to be made so that immunosuppressed children can benefit from effective and timely interventions and may return to normal health more quickly and completely.

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1 Dobbins WO. Gut immunophysiology: a gastroenterologist's view with emphasis on pathophysiology. *Am J Physiol* 1982;**242**:G1–8.
2 Udall J. Immunologic aspects of gut function. In: Walker WA, Watkins JB, eds. *Nutrition in pediatrics; basic science and clinical aspects*. Boston: Little, Brown, 1985:301.
3 Webster ADB. Immunodeficiency and gut. *Balliere's clinical gastroenterology* 1987;**1**:547–65.
4 Papadopoulou A, Lloyd DR, Williams MD, *et al*. Gastrointestinal and nutritional sequelae of bone marrow transplantation. *Arch Dis Child* 1996;**75**: 208–13.
5 Engelhard D, Marks MI, Good RA. Infections in bone marrow transplant recipients. *J Pediatr* 1986;**108**:335–43.
6 Hooks MA. Tacrolimus, a new immunosuppressant: a review of the literature. *Ann Pharmacother* 1994;**28**:501–11.
7 Sokal EM, Caragiozoglou T, Lamy M, *et al*. Epstein-Barr virus serology and Epstein-Barr virus-associated lympho-proliferative disorders in pediatric liver transplant recipients. *Transplantation* 1993;**56**:1394–8.
8 Teitelbaum DH, Sonnino RE, Harmel RP Jr. Loss of intestinal integrity following small bowel transplant rejection in the rat. *Transplant Proc* 1996;**28**: 2547–8.
9 Fernandez Banares F, Villa S, Esteve M, *et al*. Acute effects of abdominopelvic irradiation on the oro-cecal transit time, its relation to clinical symptoms, and bile salt and lactose malabsorption. *Am J Gastroenterol* 1991;**86**:1771–7.
10 Neal KR, Brij SO, Slack RCB, *et al*. Recent treatment with H_2 antagonists and antibiotics and gastric surgery as risk factors for salmonella infection. *BMJ* 1994;**308**:176.
11 Doe WF. Immunodeficiency and the gastrointestinal tract. *Clin Gastroenterol* 1983;**12**:839–53.
12 Madsen KL, Yanchar NL, Sigalet DL, *et al*. FK 506 increases permeability in rat intestine by inhibiting mitochondrial function. *Gastroenterology* 1995; **109**:107–14.
13 Mainous M, Dazhong X, Qi L, *et al*. Oral TPN induced bacterial translocation and impaired immune defenses are reversed by refeeding. *Surgery* 1991;**110**:277–84.
14 Stringer MD, Puntis JWL. Short bowel syndrome. *Arch Dis Child* 1995;**73**: 170–3.
15 Weisdorf SA, Salati JA, Longsdorf NKC, *et al*. Graft versus host disease of the intestine: a protein loosing enteropathy characterized by fecal alpha 1 antitrypsin. *Gastroenterology* 1983;**85**: 1076–81.
16 Nalesnik MA, Starzl TE. Epstein-Barr virus, infectious mononucleosis, and posttransplant lymphoproliferative disorders. *Trasplant Sci* 1994;**4**:61–79.
17 Opelz G, Henderson R. Incidence of non Hodgkin lymphoma in kidney and heart transplant recipients. *Lancet* 1993;**342**:1514–6.
18 Shulman HM, Fisher LB, Schoch HG, *et al*. Veno-occlusive disease after marrow transplantation: histological correlates of clinical signs and symptoms. *Hepatology* 1994;**19**:1171–81.
19 Green ES, Parker NE, Gellert AR, *et al*. Campylobacter infection mimicking Crohn's disease in an immunodeficient patient. *BMJ* 1984;**289**:159–60.
20 Cox GJ, Matsui SM, Lo RS, *et al*. Etiology and outcome of diarrhea after marrow transplantation: a prospective study. *Gastroenterology* 1994;**107**: 1398–1407.

21 Cello JP, Grendell JH, Bausk P, *et al*. Effect of octreotide on refractory AIDS associated diarrhea. A prospective, multicenter clinical trial. *Ann Intern Med* 1991;**115**:705–10.
22 Donaldson SS, Jundt S, Ricour C, *et al*. Radiation enteritis in children. *Cancer* 1975;**35**:1167–78.
23 Kaur S, Cooper G, Fakult S, *et al*. Incidence and outcome of overt gastrointestinal bleeding in patients undergoing bone marrow transplantation. *Dig Dis Sci* 1996;**41**:598–603.
24 Benoit G, Moukarzel M, Verdelli G, *et al*. Gastrointestinal complications in renal transplantation. *Transplant Int* 1993;**6**:45–9.
25 Ianco G, Carroccio A, Cavatgio F, *et al*. Steatocrit test: normal range and physiological variations in infants. *J Pediatr Gastroenterol Nutr* 1990;**11**:53–7.
26 Appleton AL, Sviland L, Pearson ADJ, *et al*. The need for endoscopic biopsy in diagnosis of upper gastrointestinal graft versus host disease. *J Pediatr Gastroenterol Nutr* 1993;**16**:183–5.
27 Haron E, Feld R, Tuffnell P, *et al*. Hepatic candidiasis: an increasing problem in immunocompromised patients. *Am J Med* 1987;**83**:17–26.
28 Ascher NL, Ahrenholtz RL, Simmons RL, *et al*. Indium 111 autologous tagged leukocytes in the diagnosis of intraperitoneal sepsis. *Arch Surg* 1979;**114**:386–92.
29 Pamilli G, Laffaroli RV, Capuarno G, *et al*. Changes in intestinal permeability to lactulose induced by cytotoxic chemotherapy. *Cancer Treat Rep* 1982;**66**:1435–6.
30 Losonsky GA, Johnson JP, Winkelstein JA, *et al*. Oral administration of human serum immunoglobulin in immunodeficient patients with viral gastroenteritis. A pharmacokinetic and functional analysis. *J Clin Invest* 1985;**76**:2362–7.
31 Balisteri WF. Bile acid therapy in pediatric hepatobiliary disease: the role of ursodeoxycholic acid. *J Pediatr Gastroenterol Nutr* 1997;24:573–89.
32 Tasaki T, Ohto H, Abe R. Prevention of post transfusion graft versus host disease. *Fukushima J Med Sci* 1993;**39**:109–11.