GASTROINTESTINAL AND NUTRITIONAL PROBLEMS IN CHILDREN WITH IMMUNODEFICIENCY AND AIDS

Harland Winter, MD, and Tien-lan Chang, MD

PATHOBIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS IN CHILDREN

Children acquire human immunodeficiency virus (HIV) either perinatally from an infected mother (*vertical transmission*) or from infected blood or blood products. The number of children infected following a blood transfusion has dropped markedly following the institution of rigorous screening protocols for blood donors in the mid-1980s. By the early 1990s, more than 95% of newly diagnosed HIV-infected children acquired the disease via vertical infection.[25] The World Health Organization estimates that more than 10 million people throughout the world are infected with HIV (Table 1). Three million of these individuals are women, most of whom are fewer than 40 years of age, whereas 500,000 of them are children.[37] Thus, heterosexual transmission of HIV is the most common means of acquiring the infection when viewed from a worldwide perspective.

HIV, a single-stranded RNA lentivirus, infects cells that express a receptor capable of binding to the envelope glycoprotein (gp), gp 120. T lymphocytes and monocytes or macrophages that are CD4-positive are the primary targets of the virus, but reports suggesting that other cells in the gastrointestinal tract can be infected have led investigators to

Table 1. GLOBAL DISTRIBUTION OF HIV-INFECTED PEOPLE

Region	Estimated Number
Sub-Saharan Africa	8 million
Latin America and Caribbean	1.5 million
South-East Asia	1.5 million
North America	1.5 million
Western Europe	500,000
North Africa and Middle East	75,000
Eastern Europe and Central Asia	50,000
East Asia and Pacific	25,000
Australia	25,000

Data from World Health Organization: The HIV-AIDS pandemic: 1993 overview. Geneva: WHO/GPA/GNP/93.1, 1993.

speculate that gastrointestinal symptoms may be related to epithelial cell infection with HIV-1. Fox and colleagues[9] reported that HIV-1 infection of the gastrointestinal tract was limited to the lymphoid elements of the lamina propria; other investigators believe that, because intestinal epithelial cell line cultures became infected in the laboratory,[19] epithelial cells were infected in vivo in HIV-infected adults.[10, 21] The characteristics of the mucosal immune system most likely have a significant role in the pathobiology of HIV-1 disease in children; however, mucosal immune function has not been studied specifically in HIV-infected children and, thus, pediatricians are left to speculate that observations made in the adult HIV-infected population are relevant to children. Table 2 summarizes gastrointestinal mucosal immunologic changes that occur in HIV-infected individuals.

Transmission

Vertical transmission occurs in approximately 30% of HIV-infected pregnant women who do not take antiretroviral therapy during pregnancy. The observations that transmission is increased in women who were symptomatic or who had more advanced AIDS[27] and that zidovudine therapy given during pregnancy reduces perinatal transmission[3] suggest that viral burden is an important factor in vertical transmission; however, the effects of maternal nutritional status, micronutrient deficiency, or acute infection on viral replication are difficult to evaluate. In addition, most HIV-infected women in Africa, Asia, and South America breast-feed their infants. This additional means by which infants can possibly become infected complicates assessment of factors contributing to transmission. In Africa, the percentage of postnatal transmission is approximately 50%.[36] Nevertheless, the morbidity and mortality caused by formula feeding in countries where potable water is a premium and safe infant formula is not readily available seem to be greater than the risk of acquiring HIV-1 from breast milk. The current recommendation is for the HIV-exposed infant to have formula feeding if and only if safe

Table 2. CLINICAL AND IMMUNOLOGIC ASPECTS OF HIV DISEASE

	Clinical Manifestations	Systemic Immune Function	Mucosal Immune Function
Early events	Acute febrile illness or asymptomatic infection	Infection of CD4 + lymphocytes with possible decrease in CD4 T-lymphocyte number	Infection of T cells and possibly macrophages in the lymphoid aggregates
Intermediate events	Altered body composition; lactase deficiency; bacterial overgrowth; malabsorption; *Candida* esophagitis; abnormal growth	Decreased CD4 + T-cell number, NK activity, cytotoxic T-cell activity, B-cell and macrophage number	Increased CD8 + and decreased CD4 + T lymphocytes in the lamina propria; decreased IgA secretion; extensive HIV-1 trapping in lymphoid aggregates
Late events	Malnutrition; enteric infection (cytomegalovirus, *Mycobacterium avium intracellulare*, cryptosporidium, adenovirus, and other opportunistic infections); malignancy	Decreased B-cell, T-cell, and monocyte/macrophage function	Decrease in lamina propria lymphoid elements; breakdown in mucosal lymphoid aggregate structure with release of HIV-1 from follicular dendritic cells

formula exists in the community. For most of the developing world, this is not a reality.

Pathogenesis ˙

The deterioration of the immune system and mucosal immune systems results in cellular and humoral immunoregulatory deficiencies. In the gastrointestinal tract, HIV-infected lymphocytes could migrate from the lymphoid aggregates through the mesenteric nodes, the thoracic duct, and into the circulation. Following selection by receptors on high endothelial venules, these infected cells then migrate home to the lamina propria, whereby in situ hybridization isolated HIV-infected cells can be identified (Fig. 1). Most evidence supports the hypothesis that deterioration of mucosal immune function results in bacterial overgrowth; increased production of bacterial products, such as endotoxin; activation of mucosal lymphocytes with increased cytokine production; and probable interaction between immunoregulatory elements and epithelial cell function (Fig. 2). Although the reasons for early development of lactose intolerance and malabsorption are not known, substances involved in immune regulation also may interact with intestinal epithe-

lial cells, resulting in dysfunction. HIV also may have a role in the genesis of intestinal dysfunction, but data are not available. Clearly, enteric infections begin to occur at the time when immune function is deteriorating (Fig. 3). The contribution of chronic intestinal infection to immune dysfunction, malabsorption, and malnutrition suggests that all of these factors are interrelated (Fig. 4).

One of the more important determinants of survival for the HIV-infected child is the health status of the mother. In studies from Africa, if an HIV-infected mother is symptomatic or dies, her HIV-infected infant is at increased risk for chronic diarrhea partially because of the resulting reliance on formula.[31] Chronic diarrhea in the HIV-infected child is an important prognostic variable for predicting malnutrition and death. Because of the availability of safe formula in North America and Europe, the relationship between maternal health and infant survival is not as obvious. Nevertheless, a chronically ill mother has an obvious negative impact on infant growth and development, particularly if no additional support is available, such as respite and day care programs designed to enrich infants' psychosocial development and nutritional status.

GASTROINTESTINAL PROBLEMS OF HIV-INFECTED CHILDREN

Nausea and Vomiting

In HIV-infected children, nausea and vomiting can be caused by infectious diseases, such as *Helicobacter pylori* or cytomegalovirus, medications, or central nervous system disorders. In a child with nausea, anorexia may be the presenting manifestation because she or he is not able to verbalize the sensation. In these individuals, refusal to chew or eat may be caused by gingival disease or painful lesions of Candida in the mouth. In many children, an identifiable agent or pathogen may not be found despite a thorough search. Some of the therapeutic agents that have been implicated as causes of nausea and vomiting are as follows:

> Zidovudine (azidothymidine, AZT)
> 2',3'-dideoxyinosine (ddI)
> Ganciclovir
> Pentamidine
> Spiramycin
> Amphotericin B
> Ketoconazole
> Nystatin

Altered mental status or developmental delay should alert the clinician to the possibility of central nervous system disease, such as encephalopathy caused by HIV, or pathogens, such as toxoplasmosis. Lymphoproliferative disorders in the central nervous system are rare in the pediatric population; however, lymphoma of the gastrointestinal tract
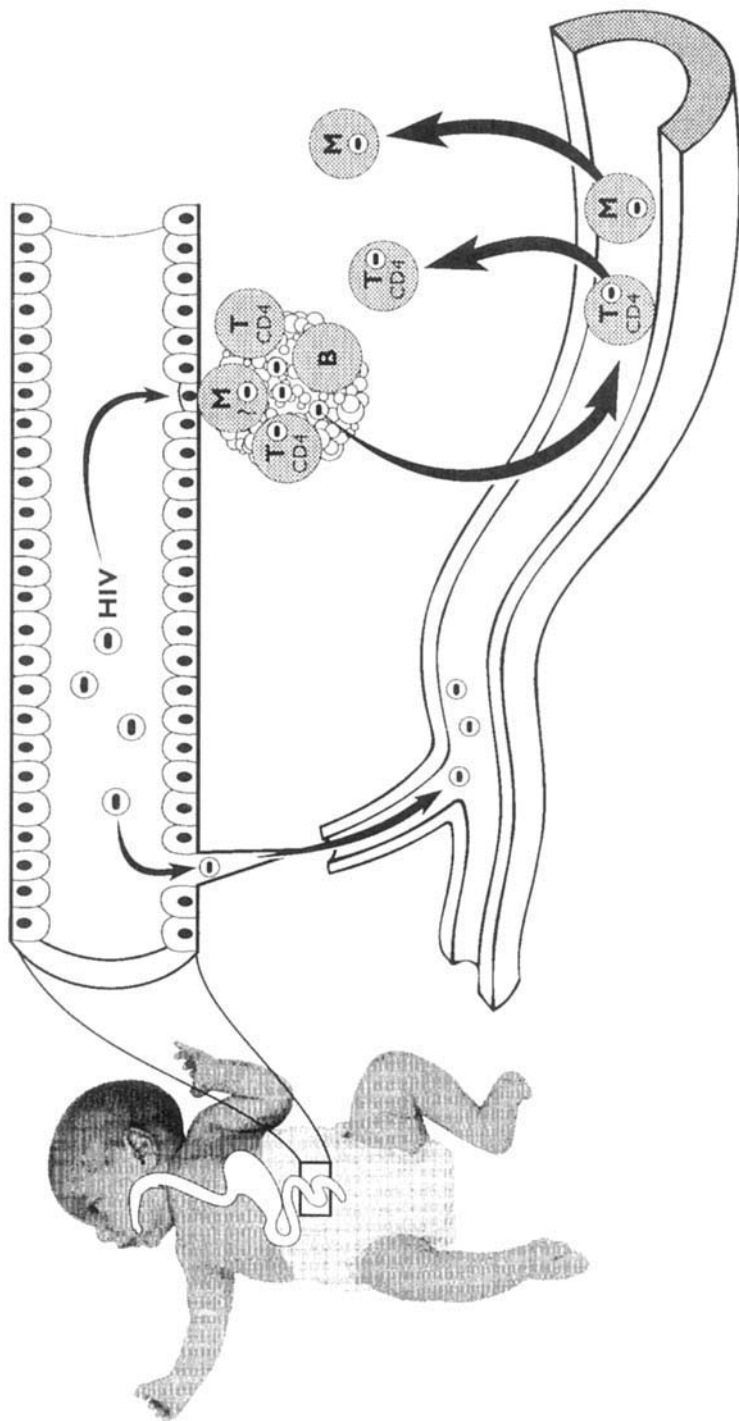
Figure 1. Early infection of HIV that may infect T cells and macrophages after crossing the intestinal mucosa. Infected cells then migrate through the circulation and home to the lamina propria of the intestine.

ASYMPTOMATIC
Altered body composition

SYMPTOMATIC
Abnormal growth

- Malabsorption
- Epithelial cell dysfunction
- Candida Esophagitis

Altered barrier function

Bacterial overgrowth

Bacterial products
(? endotoxin)

Cytokines

↓H+

Lactase deficiency

↓IgA

B IgA

T CD8

T CD4

Cytokines

M ⓞ

M

T CD4

T CD4

NK

CTL

T

B

M

Figure 2. *See legend on opposite page*

can cause splenomegaly resulting in compression of the stomach and early satiety.

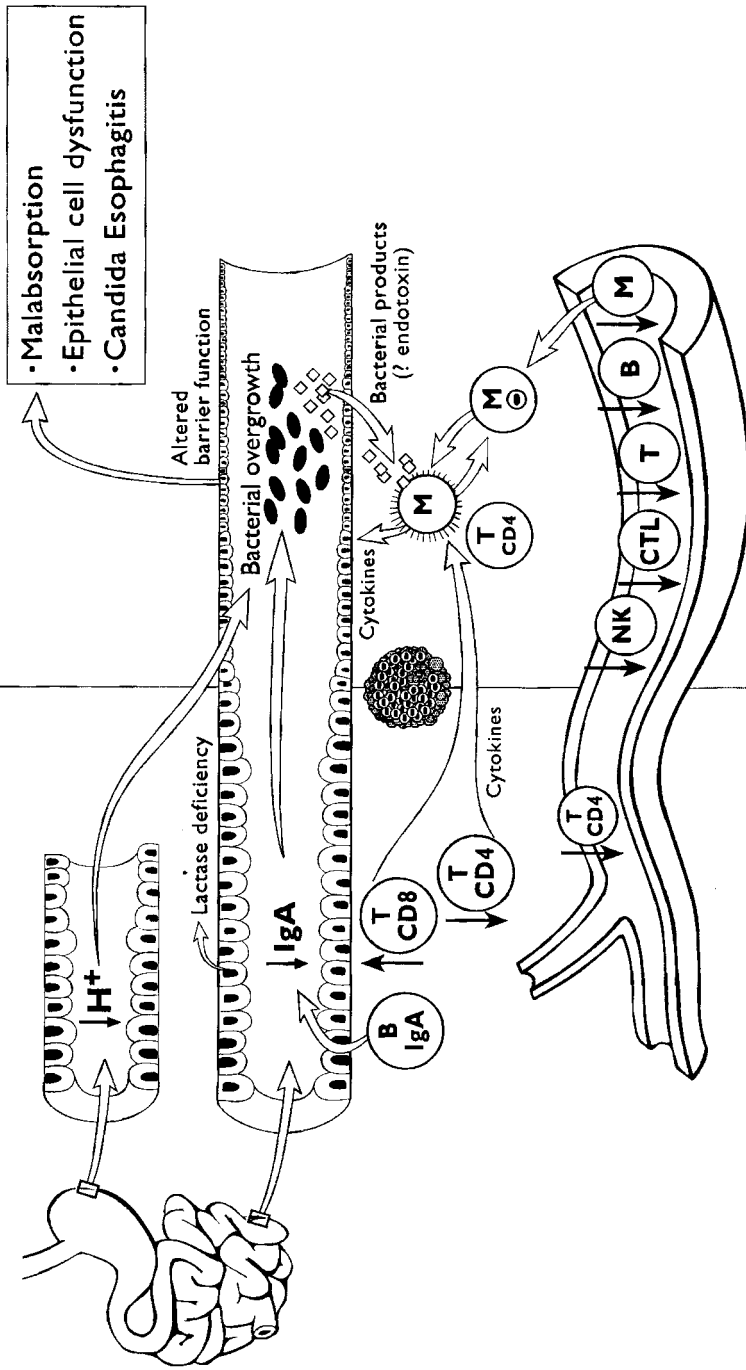Evaluation of HIV-infected children with anorexia, nausea, or vomiting should begin with a careful history, social history, physical examination, and neurologic evaluation. An upper gastrointestinal radiograph is not reliable enough to establish or rule out mucosal disease. For this reason, endoscopic evaluation is frequently necessary in children with persistent symptoms and normal hepatobiliary and pancreatic tests. Mucosal biopsies may identify an enteric pathogen or inflammation that can be treated with a specific agent. If no cause can be found, symptoms can be managed with phenothiazine derivatives, such as triethylperazine maleate (Torecan), prochlorperazine (Compazine), or promethazine (Phenergan). Other agents for which anecdotal treatment experience exists in children include: benzquinamide (Emete-con); trimethobenzamide hydrochloride (Tigan); hydroxyzine (Vistaril or Atarax); metoclopramide (Reglan); cisapride (Propulsid); and scopolamine (Transderm-scop); dronabinal (Marinol). If treatment fails to relieve the symptoms, re-evaluation should be considered.

Dysphagia

Difficulty in swallowing (dysphagia) or pain with swallowing (odynophagia) in children can be caused by oral lesions that can be identified by careful inspection of the mouth. Stomatitis caused by 2',3'-dideoxycytidine 5'-triphosphate (ddC), herpes simplex or Candida is treatable if the diagnosis is established. When oral lesions are present, coexistent esophagitis should be suspected. In contrast, if the mouth is free of lesions, esophagitis cannot be ruled out. Candida and cytomegalovirus are the most common infectious agents causing esophagitis. Dysphagia and odynophagia in HIV-infected children are more commonly associated with Candida than with cytomegalovirus. Children who are taking H_2 antagonists seem to be at increased risk for developing Candida esophagitis. Medications, such as zidovudine, have been reported to cause esophageal ulceration if, when swallowed, they do not reach the stomach.[6] Treatment for specific causes of oral or esophageal lesions is summarized in Table 3.

Figure 2. Asymptomatic phase of HIV infection in which virus is trapped within lymphoid aggregates. During this phase, speculation is that IgA decreases, acid secretion declines, and brush-border enzymes decrease in specific activity. As a child enters the symptomatic period, malabsorption, epithelial cell dysfunction, and infections such as Candida become more evident.
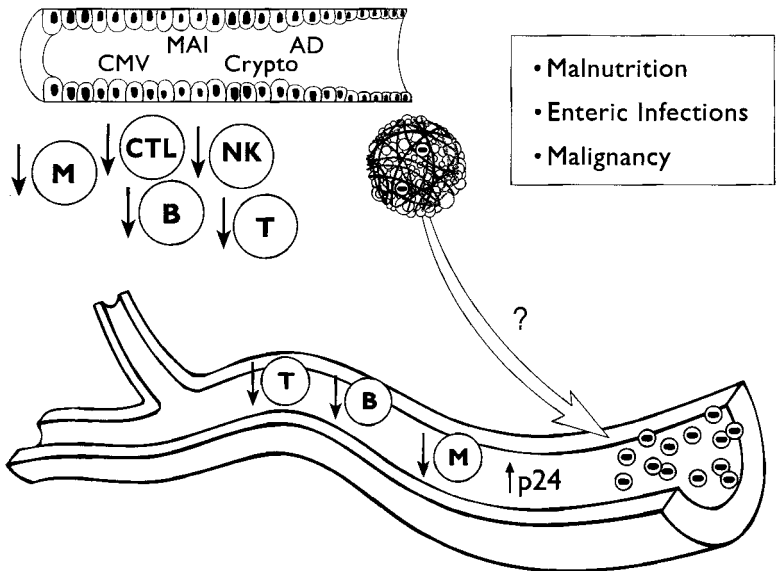
Figure 3. Late or end stage of HIV disease is characterized by loss of follicular dendritic cells and increased circulating virus. CD4 count declines, and opportunistic infection and malignancy are more prevalent.
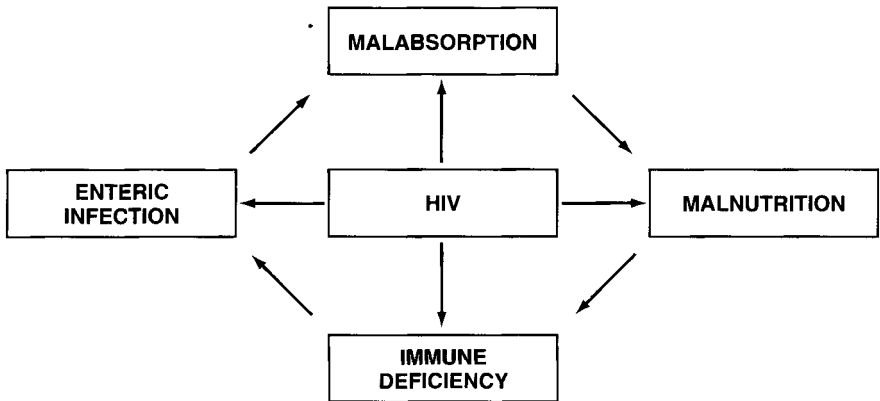

Figure 4. The relationship between malabsorption, malnutrition, enteric infection, immune deficiency, and HIV disease.

Table 3. TREATMENT OF ORAL OR ESOPHAGEAL LESIONS

Agent	Treatment
Candida	Fluconazole
	Ketoconazole
	Amphotericin B
Cytomegalovirus	Ganciclovir
Herpes simplex virus	Acyclovir
Acid-induced	H₂ antagonists
	Antacids
	Sucralfate
	Cisapride

Diarrhea and Gastrointestinal Bleeding

Most HIV-infected children experience diarrhea at some time during the course of their disease.[12] Opportunistic infections that can cause diarrhea are listed as follows (underscore = more common to the pediatric population):

Parasites
 Cryptosporidium sp.
 Giardia lamblia
 Isospora belli
 Entamoeba histolytica
 Microsporiduim sp.
Fungi
 Candida albicans
 Histoplasma capsulatum
Bacteria
 Salmonella sp.
 Shigella flexneri
 Escherichia coli
 Mycobacterium avium-intracellulare
 Campylobacter jejuni
 Clostridium difficile
Viruses
 Rotavirus
 Adenovirus
 Cytomegalovirus
 Herpes simplex virus
 Norwalk virus
 Caliciviruses
 Astroviruses
 Coronaviruses

Although enteric pathogens are frequently identified as the cause of diarrhea and weight loss in HIV-infected adults,[34] the incidence of

enteric infection in HIV-infected children seems to be lower,[40] and the relationship between diarrhea, enteric pathogens, and growth retardation is not as clearly understood. In Figure 4, the interrelationship between malabsorption, malnutrition, immune deficiency, and enteric infection is depicted. Enteric infection results in intestinal injury and malabsorption, which, if not compensated by additional nutrient support, results in nutritional deficiency. The development of malnutrition causes immune deficiency, which is characterized by a defect in T-cell function that is similar to the defect caused by HIV disease. Defective T-cell function results in increased susceptibility to enteric infection, and the circle is completed. HIV can interact at any of the stages of this cycle. In theory, intestinal absorption can be altered by modifying enterocyte function through immune modulators. By increasing apoptosis, HIV could cause premature senescence of enterocytes and decrease brush-border expression of disaccharidases and peptidases. Some of these same agents, such as the cytokine, tumor necrosis factor-α), are upregulated by HIV infection, affect intermediate metabolism, and cause malnutrition by increasing nutrient requirements. The effects of HIV on the immune system are well known and result in immunocompromise and increased susceptibility to opportunistic infection. Similar immunoregulatory abnormalities probably occur in the mucosal immune system, resulting in enteric infection. Thus, HIV interacts at many levels to potentiate the development of malabsorption, malnutrition, immune deficiency, and enteric infection.

Giardia lamblia causes watery diarrhea, abdominal distention, and crampy abdominal pain.[4, 22, 31] Metronidazole or furazolidone is effective therapy and eradicates the organism in more than 70% of infected individuals. Giardia lamblia does not occur more frequently in HIV-infected children than in the general population, but retreatment may be necessary in the immunocompromised host. Cryptosporidium parvum causes an acute, self-limited diarrheal illness in the immunocompetent host, but in the immunodeficient child with HIV disease, the infection causes a secretory diarrhea that is chronic and debilitating. The organism usually can be identified in the stool by immunofluorescent techniques or by Kinyoun carbolfuchsin stain.[7] In HIV-infected children in the United States, the incidence of cryptosporidiosis is lower than that reported in Africa and South America.[2, 4, 33] Cryptosporidium can infect the small intestine, colon, gallbladder, biliary tract, and pancreatic duct. No therapy is consistently effective in eradicating the organism, but octreotide is reported to decrease stool output.[26] Reports of the beneficial effects of hyperimmune bovine colostrum suggest that this form of passive immunotherapy may be effective in HIV-infected individuals.[35] Other enteric parasitic infections, including Isospora belli and Microsporidium, are rarely identified in HIV-infected children; however, Blastocystis hominis, a protozoan whose role as an enteric pathogen is still debated, may be more prevalent in HIV-infected children with diarrhea than in HIV-negative children.[3]

Bacteria are an important cause of diarrhea throughout the world

and for this reason contribute to the list of identifiable pathogens found in HIV-infected children. In Africa, pathogenic strains of *Escherichia coli* were identified in over three fourths of HIV-infected children.[22] The risk for other bacterial enteric infections is not known for HIV-infected children, but the incidence of *Salmonella, Shigella, Campylobacter, Yersinia,* and *Clostridium difficile* do not seem to be increased in HIV-infected children. The incidence of *Helicobacter pylori* may be decreased in HIV-infected children.[1] The most serious enteric bacterial infection is *Mycobacterium avium-intracellulare,* which causes a multisystemic infection involving the lungs, liver, mesenteric lymph nodes, gastrointestinal tract, and bone marrow in the most severely immunocompromised hosts with CD4 counts less than 50 cells/mm^3. Acidfast bacilli can be identified in the jejunal mucosa or grown from stool or blood. The most common gastrointestinal symptoms of *M avium-intracellulare* are abdominal pain and diarrhea, and neither responds dramatically to therapeutic intervention. Combinations of medications chosen from clarithromycin, ethambutol, ciprofloxacin, amikacin, rifampin, clofazamine, and azithromycin have been tried.[14]

Rotavirus is the viral agent that most frequently causes chronic diarrhea. In the immunocompromised child, rotaviral diarrhea can be severe, persistent, and difficult to distinguish from other agents causing secretory diarrhea. Diagnosis is established by identification of rotavirus in the stool using an enzyme-linked immunoassay. Enterally administered serum immunoglobulin is effective therapy,[15] but little published data exist on the treatment for rotavirus in HIV-infected children. Other viral pathogens, such as adenoviruses, can cause diarrhea but also are associated with systemic infection and fulminant hepatitis. Cytomegalovirus usually causes an asymptomatic enteric infection, but some individuals develop focal ulcerations in the colon or jejunum and present with bloody diarrhea and abdominal pain. Gastrointestinal bleeding is unusual in HIV-infected children, but, when present, it may be caused by focal ulcerations in the colon, stomach, small intestine, or esophagus from cytomegalovirus-induced disease. Merely culturing cytomegalovirus from the intestinal mucosa does not establish a link between diarrhea and the infection. Histologic evidence of mucosal injury is necessary. Ganciclovir and foscarnet are used to treat cytomegalovirus-induced intestinal disease in children with active symptoms. Bone marrow suppression is the main serious side effect.

Many children with HIV disease develop lactose intolerance earlier than predicted by genetic predisposition.[17] Nevertheless, these lactose-intolerant children do not seem to have an increased probability for growth retardation or diarrheal disease. The impact of lactose malabsorption on the nutritional health of HIV-infected children is unclear; however, children who have decreased absorption of the carbohydrate D-xylose have an increased incidence of harboring an enteric pathogen.[17]

To evaluate HIV-infected children with chronic, nonbloody diarrhea, stool analysis for bacterial, viral, and parasitic infection should be performed. Blood and polymorphonuclear leukocytes in the stool are

indicative of colitis and should prompt evaluation of the colonic mucosa. If no enteric pathogen is identified, functional tests, such as lactose breath hydrogen and D-xylose absorption, may be useful in guiding nutritional therapy. The most beneficial diagnostic test is an upper endoscopy with biopsy. In addition to routine histology, mucosal biopsies of any focal lesions should be tested for bacterial, fungal, and viral culture and analyzed via electron microscopy. Because mycobacterium and cytomegalovirus may not be detectable during endoscopic evaluation, surveillance biopsies of the jejunum should be evaluated by electron microscopy and culture. Despite these diagnostic studies, enteric pathogens frequently are not identified in many HIV-infected children with diarrhea.

Abdominal Pain

HIV-infected children with abdominal pain should be evaluated for enteric infection, especially if they have diarrhea. Fever and abdominal pain are symptoms that can indicate the presence of mycobacterium. Association of these symptoms with the ingestion of milk should alert the clinician to the possibility of lactose intolerance, but for many children with lactase deficiency, the relationship is not evident. In addition, pancreatitis in the HIV-infected child is a serious and debilitating illness. Not only do these children experience crampy abdominal pain, but the association with meals results in decreased caloric intake and increases the potential for malnutrition. Lipase seems to be an early and sensitive marker for pancreatitis in the pediatric population.[18] Medications such as ddI and ddC are associated with pancreatitis, which may develop following many months of therapy.[39] Other medications including pentamidine, trimethoprim-sulfamethoxazole, and dapsone have been implicated as causes of pancreatitis in children. The development of pancreatitis is an ominous event, and in one published study, the mean survival of children with pancreatitis was 8 months following the diagnosis.[18] Because of the guarded outcome, decisions to perform additional diagnostic tests should be made after much discussion with the health care team. If a dilated pancreatic duct is identified by ultrasonography, the indication for endoscopic retrograde cholangiopancreatography should be based on quality-of-life issues. Although strictures of the pancreatic duct could contribute to the symptoms, if therapeutic intervention is not feasible, invasive diagnostic studies should not be performed.

Hepatic Dysfunction

Although the majority of HIV-infected children have hepatomegaly, few experience severe hepatocellular dysfunction; fibrosis; or cirrhosis that results in coagulopathy, ascites, varices, or hepatic failure. Many of the medications used to treat complications of HIV disease cause

hepatocellular injury or cholestasis; however, infectious agents, such as hepatitis B, that cause hepatocellular injury by immune mechanisms have milder clinical courses in immunodeficient hosts.[24] Preservation of immune function in HIV-infected children could account for the apparent increase in chronic active hepatitis in the pediatric population compared with the incidence in adults.[32] Although abnormalities in liver function tests are not diagnostic, they are beneficial as screening procedures. Elevated transaminases are caused by infectious agents, medications, or nutritional deficiency and malnutrition. When the transaminases exceed four times normal, viral disease or a drug-induced hepatitis should be suspected. *M avium intracellulare*, hepatic *Pneumocystis carinii*, fungal-induced hepatitis, cytomegalovirus, or extrahepatic biliary tract obstruction cause elevation of alkaline phosphatase. Liver biopsy is necessary to identify hepatic pathogens and should be considered in a child presenting with either fever and elevated liver function tests or a focal hepatic lesion. Therapeutic intervention is available for some of the viral agents that cause hepatitis, but most infectious disorders in immunodeficient hosts do not respond favorably to treatment.

NUTRITIONAL PROBLEMS OF HIV-INFECTED CHILDREN

Failure to Thrive

Wasting of body mass is one of the more serious manifestations of HIV disease. In adults, the decline in lean body mass correlates with decreased quality of life and eventual death.[5, 13] In children with AIDS, growth failure and failure to thrive have been recognized symptoms from the beginning of the epidemic.[28] Infants born to HIV-infected mothers seem to weigh less by 3 months of life and to be shorter by 6 months of life when compared with HIV-exposed, but noninfected infants. In long-term survivors more than 8 years of age, lean body mass wasting and short stature are common clinical features. The etiology of these derangements in growth is multifactorial, possibly including deranged metabolism, malabsorption, or decreased nutrient intake. The mechanism for the catabolic process is not known, but futile cycling of energy substrates, protein wasting, or hypermetabolism mediated by cytokines such as TNF, interleukin (IL)-1, IL-6, and the interferons may contribute to the problem.

Nutritional Management

The initial assessment of HIV-infected children with failure to thrive is directed at determination of caloric intake, nutrient losses, and metabolic requirements. If caloric intake is diminished, the reason for anorexia should be determined. Nausea, abdominal pain, oral lesions,

depression, despair, or lack of access to food need to be evaluated by the health care team. Nutrient losses caused by diarrhea and malabsorption may contribute to increased nutrient requirements. Enhanced metabolic requirements from febrile illnesses, recurrent infection, or from HIV replication may result in weight loss. Anti-retroviral therapy can result in weight gain shortly after starting therapy.[23]

Counseling and oral supplements are the first steps in nutritional treatment for children with weight loss or decreased lean body mass. Providing increased calories and protein may reverse the loss, but most children require additional measures of support. Although nasogastric tube feeding is simple and effective for short-term management, the adverse effect on quality of life and the increased possibility of sinus disease are limiting factors. In children requiring nutritional supplementation lasting greater than 2 weeks, endoscopic placement of a gastrostomy tube button increases compliance and tolerance. As many as 150% recommended daily allowance for calories may be required to achieve weight gain in HIV-infected children. Newly developed one-step gastrostomy buttons permit endoscopic insertion of devices that do not limit activity and provide access for nutritional support. Despite providing sufficient nutrition to gain weight, enteral supplementation[16] and gastrostomy tube feedings[11] do not increase lean body mass in HIV-infected children. Similarly, appetite stimulants, such as megestrol acetate, a progesterone derivative, and dronabinol, a tetrahydrocannabinol derivative, do not increase lean body mass in adults infected with HIV. Promising data in adults suggest that mammalian cell-derived recombinant human growth hormone therapy results in weight gain and anabolism as measured by stool nitrogen, urine nitrogen, and potassium excretion.[20] If valid in the pediatric population, growth hormone could prove to be an effective treatment for failure to thrive by increasing lean body mass.   .

Anecdotal experience implicates specific vitamin deficiencies as contributing to the nutritional problems of HIV-infected children. In regions in which vitamin deficiency is endemic, it is not surprising to see the problem amplified in HIV-infected children. Decreased vitamin A causes diminished T-cell response to mitogens and antigens, atrophy of lymphoid tissue,[30] and is associated with increased maternal-child transmission.[29] Supplementation of vitamin A seems to increase CD4 + cells, boost antibody response, and decrease morbidity and mortality from other infectious diseases.[8] The effect of vitamin A supplementation on the health of HIV-infected children in the United States is not known. Other vitamins, including vitamins D, E, B_1 (thiamine), B_2 (riboflavin), niacin, B_6, B_{12}, folic acid, C, and carnitine, have been evaluated in various populations of HIV-infected individuals, and although abnormalities can be demonstrated for some vitamins, deficiencies related to the generalized state of malnutrition and not specifically to HIV-induced disease are difficult to prove beyond a reasonable doubt. Similarly, deficiencies of iron, zinc, and selenium have been described in HIV-infected individuals. Although these minerals have an important role in immunoregula-

Table 4. GASTROINTESTINAL MANIFESTATIONS OF PRIMARY IMMUNODEFICIENCY DISEASES

Immune Deficiency	Gastrointestinal Problems
Antibody defects	
IgA deficiency	Asymptomatic, chronic *Giardia lamblia* infection, nodular lymphoid hyperplasia, idiopathic enteropathy, gluten-sensitive enteropathy, pernicious anemia, idiopathic inflammatory bowel disease
X-linked agammaglobulinemia	Chronic *Giardia lamblia* or rotavirus, protein-losing enteropathy, idiopathic enteritis, colitis. Symptoms are usually less severe than those found in children with common variable immunodeficiency
Transient hypogammaglobulinemia of infancy	Chronic diarrhea, enteritis, colitis, regurgitation. Symptoms usually resolve by 1 year of age
Combined immunodeficiency	
Common variable immunodeficiency	Chronic *Giardia lamblia,* bacterial overgrowth, Salmonella (especially if achlorhydric), pernicious anemia, nodular lymphoid hyperplasia, gluten-sensitive enteropathy, idiopathic inflammatory bowel disease involving the small intestine, the colon, or both
Severe combined immunodeficiency: Adenosine deaminase deficiency Purine nucleoside phosphorylase deficiency	Chronic diarrhea, malabsorption, enteropathy, Candida esophagitis, bacterial enteritis/colitis, chronic rotavirus, or cytomegalovirus
Defects of phagocytic function	
Chronic granulomatous disease	Granulomatous enterocolitis, vitamin B_{12} malabsorption, hepatic and perirectal abscesses, antral narrowing, steatorrhea, dysphagia
CD11/CD18 Leukocyte glycoprotein deficiency	Stomatitis/pharyngitis, oral/esophageal candidiasis, perirectal abscess
Schwachman's disease	Pancreatic insufficiency
Complement disorders	
C2 deficiency	Colitis
Immunodeficiency syndromes	
Wiskott-Aldrich: T-cell dysfunction, eczema, thrombocytopenia	Enteric infections, bloody diarrhea, malabsorption (unusual)
Ataxia-telangiectasia: Cerebellar ataxia, oculocutaneous telangiectasia, sinopulmonary infections	Diarrhea if IgA-deficient, otherwise increased incidence of gastrointestinal malignancy
DiGeorge: Right-sided aortic arch, bifid uvula, congenital heart disease, dysmorphic facial features, hypoparathyroidism	Esophageal atresia, esophageal candidiasis, chronic diarrhea
Purtillo: Chronic Epstein-Barr viral infection, hypogammaglobulinemia, aplastic anemia	B-cell lymphoma, "septic" hepatitis

tion and host defense, their relevance to the immunocompromised host with HIV disease is unclear.

The redundancy of the immune system to provide protection against infection suggests that by the time the system begins to fail, no single cause can be found to correct the problem. For this reason, supplementation with a single therapeutic nutrient intervention can improve laboratory phenomena, but rarely impacts on a patient's quality of life or immunoregulatory defects.

GASTROINTESTINAL PROBLEMS OF CHILDREN WITH PRIMARY IMMUNODEFICIENCY

Patients with primary immunodeficiency disorders frequently experience gastrointestinal problems in association with other clinical manifestations of systemic disease. The respiratory and gastrointestinal tracts are exposed to the environment and, in response, have developed complex systems to protect their mucosal surfaces from pathogens. Antibody production, cell-mediated immune function, complement, and phagocytic function act together to prevent infection and uncontrolled inflammation. In the gastrointestinal tract, enteric pathogens and chronic inflammatory bowel disease are the two major clinical aspects of primary immune deficiency. Surprisingly, individuals with identical deficiencies may not experience similar gastrointestinal symptoms. For example, children with immunoglobulin A deficiency may be asymptomatic or may have chronic diarrhea associated with chronic intestinal inflammation disease. In general, children with T-cell defects seem to have a higher incidence of chronic gastrointestinal problems compared with children with antibody deficiency syndromes, complement defects, or disorders of phagocytic function. Table 4 lists the common primary immunodeficiencies together with the gastrointestinal manifestations commonly associated with each disorder.

SUMMARY

Immunodeficient children pose a challenge to clinicians because of the interrelationship between infectious disease, metabolism, gastrointestinal tract function, psychosocial problems, and immune function. The interplay between these factors is not always clear, and frequently the best course of therapy is obscured because of an inability to determine which factors have the greatest impact on child health. To optimize therapeutic intervention, a multidisciplinary health care team must be involved with the management of children and their families.

References

1. Blecker U, Keymolen K, Souayah H, et al: *Helicobacter pylori* in children with acquired immunodeficiency syndrome. Pediatrics 91:1217, 1993

2. Byers M, Feldman S, Edwards J: Disseminated histoplasmosis as the acquired immuno-deficiency syndrome-defining illness in an infant. Pediatr Infect Dis J 11:127, 1992
3. Cegielski JP, Msengi AE, Dukes CS, et al: Intestinal parasites and HIV infection in Tanzanian children with chronic diarrhea. AIDS 7:213, 1993
4. Centers for Disease Control: Zidovudine for the prevention of HIV transmission from mother to infant. MMWR 43:285, 1994
5. Chlebowski RT: Significance of altered nutritional status in acquired immune defi-ciency syndrome (AIDS). Nutr Cancer 7:85, 1985
6. Edward P, Turner J, Gold J, et al: Esophageal ulceration induced by zidovudine. Ann Intern Med 112:65, 1990
7. Fabris N, Mocchigiani E, Galli M, et al: AIDS, zinc deficiency and thymic hormone failure. JAMA 259:2850, 1988
8. Fawzi WW, Chalmers TC, Herrera MG, et al: Vitamin A supplementation and child mortality: A meta-analysis. JAMA 269:898-903, 1993
9. Fox CH, Kotler D, Tierney A, et al: Detection of HIV-1 RNA in the lamina propria of patients with AIDS and gastrointestinal disease. J Infect Dis 159:467, 1989
10. Heise C, Dandekar S, Kumar P, et al: Human Immunodeficiency Virus infection of enterocytes and mononuclear cells in human jejunal tissue. Gastroenterology 100:1521, 1991
11. Henderson RA, Saavedra JM, Perman JA, et al: Effect of enteral tube feeding on growth of children with symptomatic human immunodeficiency virus infection. J Pediatr Gastroenterol Nutr 18:429, 1994
12. Italian Multicentre Study: Epidemiology and clinical features of pediatric HIV infec-tion: Results from an Italian multicentric study on 544 children. Lancet 2:1046, 1988
13. Kotler D, Wang J, Pierson R: Bosy composition studies in patients with the acquired immunodeficiency syndrome. Am J Clin Nutr 42:1255, 1985
14. Masur H: Recommendations on prophylaxis and therapy for disseminated *Mycobacte-rium avium* complex disease in patients infected with the human immunodeficiency virus. N Engl J Med 329:898, 1993
15. Melamed I, Griffiths AM, Roifman CM: Benefit of oral immune globulin therapy in patients with immunodeficiency and chronic diarrhea. J Pediatr 119:486, 1991
16. Miller TL, Evans SJ, Orav EJ, et al: Growth and body composition in children infected with the human immunodeficiency virus-1. Am J Clin Nutr 57:588, 1993
17. Miller TL, Orav EJ, Martin SR, et al: Malnutrition and carbohydrate malabsorption in children with vertically transmitted human immunodeficiency virus 1 infection. Gastroenterology 100:1296, 1991
18. Miller TL, Winter HS, Luginbuhl LM, et al: Pancreatitis in pediatric human immunode-ficiency virus infection. J Pediatr 120:223, 1992
19. Moyer MP, Gendelmann HE: HIV replication and persistence in human gastrointesti-nal cells cultured in vitro. J Leukoc Biol 49:499, 1991
20. Mulligan K, Grunfeld C, Hellerstein MK, et al: Anabolic effects of recombinant human growth hormone in patients with wasting associated with human immunodeficiency virus infection. J Clin Endocrinol Metab 77:956, 1993
21. Nelson JA, Wiley CA, Reynolds-Kohler C, et al: Human immunodeficiency virus detection in bowel epithelium from patients with gastrointestinal symptoms. Lancet 1:259, 1988
22. Pavia AT, Long EG, Ryder RW, et al: Diarrhea among African children born to human immunodeficiency virus-infected mothers: Clinical, microbiologic and epidemiologic features. Pediatr Infect Dis J 11:996, 1992
23. Pizzo PA, Eddy J, Falloon J, et al: Effect of continuous intravenous infusion of zidovudine (AZT) in chldren with symptomatic HIV infection. N Engl J Med 319:889, 1988
24. Prufer-Kramer L, Kramer A, Weigel R, et al: Hepatic involvement in patients with human immunodeficiency virus infection: Discrepancies between AIDS patients and those with earlier stages of infection. J Infect Dis 163:866, 1991
25. Quinn TC, Ruff A, Halsey N: Pediatric acquired immunodeficiency syndrome: Special considerations for developing nations. Pediatr Infect Dis J 11:558, 1992

26. Romeu J, Miro JM, Sirera G, et al: Efficacy of octreotide in the management of chronic diarrhea in AIDS. AIDS 5:1495, 1991
27. Ryder RW, Nsa E, Hassig SE, et al: Perinatal transmission of the human immunodeficiency virus type 1 to infants of seropositive women in Zaire. N Engl J Med 320:1637, 1989
28. Scott GB, Hutto C, Makuch RW, et al: Survival in children with perinatally acquired human immunodeficiency virus type 1 infection. N Engl J Med 321:1791, 1989
29. Semba RD, Miotti PG, Chlehanaw JD: Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. Lancet 343:1593–1597, 1994
30. Semba RD, Muhilal, Ward BJ, et al: Altered T cell subset proportions in vitamin A deficient children. Lancet 341:5–8, 1993
31. Thea DM, St. Louis ME, Atido U, et al: A prospective study of diarrhea and HIV-1 infection among 429 Zairian infants. N Engl J Med 329:1696, 1993
32. Thung SN, Gerber MA, Benkov KJ, et al: Chronic active hepatitis in a child with human immunodeficiency virus infection. Arch Pathol Lab Med 112:914, 1988
33. Turner BJ, Denison M, Eppes SC, et al: Survival experience of 789 children with acquired immunodeficiency syndrome. Pediatr Infect Dis J 12:310, 1993
34. Ullrich R, Heise W, Bergs C, et al: Gastrointestinal symptoms in patients infected with human immunodeficiency virus: Relevance of infective agents isolated from gastrointestinal tract. Gut 33:1080, 1992
35. Ungar BLP, Ward DJ, Fayer R, et al: Cessation of Cryptosporidium-associated diarrhea in an acquired immunodeficiency syndrome patient after treatment with hyperimmune bovine colostrum. Gastroenterology 98:486, 1990
36. Van de Perre P, Simonon A, Msellati P, et al: Postnatal transmission of human immunodeficiency virus type 1 from mother to infant. A prospective cohort study in Kigali, Rwanda. N Engl J Med 325:593, 1991
37. World Health Organization/UNICEF: Statement on breast feeding and HIV. WHO/UNICEF consultative meeting of April 30-May 1. Wkly Epidemiol Rec 67:177, 1992
38. World Health Organization: The HIV/AIDS pandemic: 1993 overview. Geneva: WHO/GPA/CNP/93.1, 1993
39. Yarchoan R, Pluda JM, Thomas RV, et al: Long-term toxicity/activity profile of 2′,3′-dideoxyinosine in AIDS or AIDS-related complex. Lancet 336:526, 1990
40. Yolken RH, Hart W, Oung I, et al: Gastrointestinal dysfunction and disaccharide intolerance in children infected with human immunodeficiency virus. J Pediatr 118:359, 1991

Address reprint requests to

Harland Winter, MD
Division of Pediatric Gastroenterology and Nutrition
Boston University School of Medicine
801 Albany Street, S-117
Boston, MA 02118