Chronic Enteropathy: Clinical Aspects

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Abstract

Diarrheal disease is a major cause of childhood morbidity and mortality worldwide. Chronic enteropathy with subsequent persistent diarrhea and associated vicious cycles of malnutrition, increased gut permeability and secondary immunodeficiency are particularly devastating in the childhood population. The major causes of chronic enteropathy differ significantly between developed countries and developing countries. In developed countries, infectious and postinfectious diarrhea as well as abnormalities in immune response including celiac disease, food-induced allergic enteropathy and idiopathic inflammatory bowel disease account for most cases of chronic enteropathy. In developing countries, syndromic persistent diarrhea associated with malnutrition and secondary immunodeficiency due to human immunodeficiency virus (HIV) infection predominate as the major causes of chronic enteropathy. These latter two causes account for a disproportionate share of the more than 2.5 million deaths of children under 5 years of age due to diarrhea each year worldwide. From a practical perspective, diagnostic evaluation of chronic enteropathy in developing countries is often limited to identifying potential causative enteropathogens and antimicrobial treatment. Proper management with an emphasis on fluid homeostasis and protocolized nutritional therapy and rehabilitation is essential to successful treatment of syndromic persistent diarrhea.

Introduction

Diarrheal disease remains a major cause of all childhood morbidity and mortality. Chronic enteropathy leading to persistent diarrhea is particularly damaging, although the major causes differ between developed and developing countries with socioeconomic and nutritional status being the main determinants. From a global perspective, chronic enteropathy manifested as syndromic persistent diarrhea accounts for a disproportionate share of the
more than 2.5 million deaths each year of children under 5 years of age due to all diarrheal illness.

**Defining Chronic Enteropathy**

For the present discussion, chronic enteropathy is defined as chronic functional derangement of the small bowel. The primary consequence of chronic enteropathy is persistent diarrhea which is loose or watery stools at least 3 times per day of more than 14 days' duration, with change in stool consistency more meaningful than stool frequency. Depending on the specific pathophysiology, other symptoms may dominate the clinical picture; for example, Crohn’s disease may present with bloody stool or the child with celiac disease (CD) who, able to partially compensate for reduced absorptive capacity by increasing dietary intake, may present with stunting.

**Infectious Enteropathy**

Postinfectious persistent diarrhea occurs in infants and young children associated with a variety of enteric viral and bacterial pathogens that cause acute infectious diarrheal disease including rotavirus, enteric adenovirus, astrovirus, *Shigella*, and *Salmonella*, among others. Postinfectious diarrhea may follow a single severe episode of acute diarrhea or more commonly repeated distinct episodes of acute diarrhea by different pathogens, persisting well after the inciting infectious agent is no longer detectable. Secondary disaccharidase deficiency and sensitization to food antigens due to small bowel mucosal damage leading to disaccharide malabsorption as central mechanisms of postinfectious persistent diarrhea, while operative in some children, has been shown to be less prevalent than initially thought. When postinfectious persistent diarrhea occurs in the context of malnutrition, it is often referred to as syndromic persistent diarrhea because of stereotypical pathophysiological derangements and treatment implications. In contrast, certain pathogens are associated with chronic enteric infection and chronic enteropathy resulting in prolonged watery diarrhea that is often profuse and with growth failure and malnutrition (table 1) [1]. *Giardia*, *Cryptosporidium*, and * Cyclospora* are common causes of persistent diarrhea and poor nutritional outcomes in both immunocompetent and immunocompromised children. Two diarrheagenic *Escherichia coli*, enteropathogenic *E. coli* (EPEC) and enteroaggregative *E. coli* (EaggEC), are the most important bacterial causes of persistent diarrhea in children. EPEC is a major pathogen in children less than 1 year and especially less than 6 months of age; compared to other pathogens, EPEC has been associated with more severe diarrhea and dehydration, cow’s milk intolerance, and progression to persistent diarrhea [2].
EaggEC is the most common cause of persistent diarrhea and its nutritional sequelae in many children in developing countries [3].

**Table 1.** Causes of chronic enteropathy in children

<table>
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<th>Causes</th>
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<tr>
<td>Enteric infection</td>
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<td><em>Giardia lamblia</em></td>
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<td><em>Cryptosporidium parvum</em></td>
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<td><em>Cyclospora cayetanensis</em></td>
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<td>EaggEC</td>
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<td>EPEC</td>
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<td><em>Mycobacterium avium-intracellulare</em> complex</td>
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<td><em>Isospora belli</em></td>
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<td><em>Microsporida</em></td>
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<td>Immune deficiency</td>
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<td>Primary immune deficiencies (enteric infection including small bowel overgrowth)</td>
<td>Primary immune deficiencies are uncommon causes; secondary immune deficiencies including due to HIV infection and malnutrition are major causes worldwide</td>
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<tr>
<td>Secondary immune deficiencies</td>
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<td>Protein energy and micronutrient malnutrition, HIV</td>
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<td>Abnormal immune response</td>
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<td>CD</td>
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<td>Food-allergic enteropathy</td>
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<td>Autoimmune disorders</td>
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<td>Autoimmune enteropathy</td>
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<td>Graft versus host disease</td>
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<td>Idiopathic inflammatory bowel disease</td>
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<td>Crohn's disease</td>
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<td>Congenital persistent diarrhea (structural defects?)</td>
<td>More common in developed countries</td>
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<td>Microvillus inclusion disease</td>
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<td>Tufting enteropathy</td>
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<td>Congenital chloride diarrhea</td>
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<td>Congenital disaccharidase (lactase, sucrase-isomaltase) deficiencies</td>
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<td>Congenital bile acid malabsorption</td>
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<td>Syndromic persistent diarrhea (associated with malnutrition)</td>
<td>Of greatest importance worldwide</td>
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Immune Deficiency Including Human Immunodeficiency Virus

The mucosal lining of the gastrointestinal tract is constantly exposed to an ever-changing environment rich in microbial pathogens, dietary antigens and
toxins. The immune system plays a pivotal role in ensuring homeostasis is maintained within the system. The immune-deficient child is susceptible to common gastrointestinal infections that can occur in the immune-competent host; however, chronic enteropathy in immunodeficiency is characterized by recurrent, persistent, severe unusual and opportunistic infections with subsequent secondary malabsorption and maldigestion states. The immune-deficient child with persistent diarrhea often rapidly spirals into a cycle of anorexia, inadequate dietary intake, catabolic losses to combat infection, and catabolic losses from the gastrointestinal tract (fig. 1). Micronutrient and general malnutrition are key risk factors for as well as consequences of many chronic enteropathies resulting in well-defined impairments of immunity. The combination of immunodeficiency, malnutrition, and chronic enteropathy and their mutually reinforcing properties is a major global cause of childhood morbidity and mortality (discussed in greater detail under the heading Syndromic Persistent Diarrhea below). Optimal management includes aggressive search and treatment of infectious etiologies for chronic enteropathy, fluid and electrolyte replacement, close monitoring of nutritional status, and nutritional rehabilitation.

Though generally rare, over 70 different primary immunodeficiencies have been described. Chronic enteropathy is commonly associated with many of these, although the precise abnormalities as well as risk for and type of enteric infection may differ depending on the specific aspect of the immune system that is abnormal. Treatment effects of primary immune deficiency can
have a role in the development of chronic enteropathy, such as graft versus host disease involving the bowel following bone marrow transplantation.

From a global prospective, chronic enteropathies associated with secondary immunodeficiency states are perhaps the most consequential in terms of total numbers of children affected and morbidity and mortality. Primary malnutrition and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) constitute the majority of cases of secondary immunodeficiency. The World Health Organization AIDS Epidemic Update in December 2005 estimates that 40.3 million people are infected with HIV worldwide, 90% of whom live in resource-poor settings in Asia, Africa, and South America [4]. Secondary malnutrition and persistent diarrhea are the hallmarks of inadequately treated HIV. Children with HIV are susceptible to all of the pathogens causing persistent diarrhea in the immunocompetent child as well as to opportunistic pathogens that rarely make otherwise normal children ill. Chronic diarrhea and secondary malnutrition are nearly universal comorbidities in HIV-affected people living in developing countries [5]. Indeed, persistent diarrhea in HIV-infected children can be attributable to the HIV-induced malnutrition as an important associated risk factor [6]. Cryptosporidia, Giardia, and the opportunistic pathogens Mycobacterium avium-intracellulare, Isospora, and Microsporidia are associated with immune deficiency states and especially inadequately treated, advanced HIV infection and AIDS. Individuals with HIV/AIDS are not uncommonly infected with multiple pathogens. Immune recovery related to highly active antiretroviral therapy has led to resolution of persistent diarrhea due to opportunistic infections previously considered untreatable. However, since highly active antiretroviral therapy is not accessible by the great majority of HIV-infected children in developing countries, these pathogens remain important causes of morbidity and mortality in this population [7]. Not all cases of persistent diarrhea in advanced HIV/AIDS have an infectious etiology and in up to 45% of patients no enteric pathogen can be identified [8]. The enteropathy is characterized by reduced villous height and increased crypt depth, with severity of enteropathy often independent of infection but related to nutritional status and immune dysregulation [9, 10]. Other important causes of persistent diarrhea include side effects of protease inhibitors in up to 50% of patients, gastrointestinal malignancies of Kaposi sarcoma and lymphoma, and ‘HIV enteropathy’ [11, 12].

Abnormal Immune Response

Celiac Disease

CD is complex autoimmune enteropathy caused by a permanent sensitivity to gluten in genetically predisposed individuals. European and US studies indicate the prevalence of CD in children between 2.5 and 15 years is approximately 3–13 per 1,000 children [13]. Previously considered rare in children in developing
countries, more recent evidence challenges this view [14]. In some ways, CD also represents an important form of food-allergic enteropathy. Small bowel damage occurs following mucosal exposure to ingested wheat gluten and similar grains, most notably rye and barely. Unlike other food-allergic enteropathies, CD susceptibility is determined in part by a common HLA association, namely the major histocompatibility complex class II antigens HLA-DQ2 (86–100% patients) and HLA-DQ8 (5% patients) haplotypes. Gliadin, the main wheat protein, presented by HLA-DQ2 and/or HLA-DQ8 molecules to T cells stimulates production of proinflammatory cytokines that damage intestinal mucosa and activate plasma cells to produce antibodies to gliadin, tissue transglutaminase (TTG), and endomysium.

While symptoms can be protean and nongastrointestinal, the classical clinical expression of CD in children is a persistent malabsorptive enteropathy and diarrhea, malnutrition, abdominal pain, vomiting and abdominal distention. Nongastrointestinal symptoms may predominate and occur in the apparent absence or subtle gastrointestinal symptoms and include proximal muscle wasting, dermatitis herpetiformis, dental enamel hypoplasia of permanent teeth, osteoporosis, short stature, delayed puberty, iron deficiency anemia resistant to oral iron, among others. The risk of CD is much higher among first-degree than second-degree relatives and in children with certain chronic disease such as type-1 diabetes mellitus (2–5%) and autoimmune disorders, IgA deficiency (10%), Down’s syndrome (10%), Turner’s syndrome, and Williams syndrome.

Diagnosis of CD is defined by characteristic changes seen on small intestinal histology: villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes. With the advent of accurate serologic markers and in cases where there is full clinical remission with gluten withdrawal from diet, it is no longer considered necessary to confirm the diagnosis by gluten challenge and repeat biopsy. Of available serological tests, neither IgG nor IgA antigliadin antibody test is routinely recommended due to variable sensitivity and specificity. Measurement of IgA antibody to human recombinant TTG is recommended and is highly sensitive and specific; IgA antibody to endomysium is as accurate as TTG but observer dependent and hence subject to error. In patients with features suggestive of CD concomitant assessment for IgA deficiency is helpful since IgA deficiency is associated with CD and a low TTG IgA in this context is not reassuring. In such a case, TTG IgG levels should be determined. Once the diagnosis is confirmed, the only treatment is lifelong use of a gluten-free diet. Compliance in children and especially the adolescent is always a problem. TTG level may be used to monitor dietary adherence.

Food-Induced Allergic Enteropathy

There are three clinically distinct food protein-induced gastrointestinal disorders that can involve the small bowel and cause persistent diarrhea: enterocolitis syndrome, enteropathy, and eosinophilic gastroenteritis. Food
protein enterocolitis syndrome is a cell-mediated hypersensitivity disorder that typically occurs in infants within the first 3 months of life, most commonly in reaction to ingested dairy or soy protein [15]. The disease process is often restricted to the distal colon and is the most common cause of bloody stool in infants in developed countries following enteric \textit{Salmonella} infection. Involvement of the small bowel as well as colon typically manifests as watery or bloody diarrhea, vomiting, and failure to thrive if diagnosis is delayed. Food protein-induced enteropathy (excluding CD) is an uncommon condition that occurs within the first several months of life and is manifested by persistent diarrhea and malabsorption; clinical presentation is the same as classical CD but usually with vomiting. Histological changes can be very similar to that found in CD, but less severe [16]. There is patchy distribution of mucosal damage, some degree of villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes. As with dietary protein enterocolitis, dairy and soy protein are the typical offending antigens. The underlying immune dysregulation shares many of the features of CD; its relationship, if any, to the dietary protein enterocolitis syndrome is unknown. Eosinophilic gastroenteritis is a rare, incompletely understood disorder that at times but not always is associated with an identifiable dietary antigen. It is IgE and/or cell-mediated and can occur at any age. Clinical presentation depends on the anatomic site of gastrointestinal involvement and depth of eosinophilic infiltration; when manifested as an enteropathy, diarrhea, iron deficiency anemia, and protein-losing enteropathy are characteristic. In contrast to food protein-induced enteropathy, eosinophilic inflammation is the distinguishing histological finding. The double-blind, placebo-controlled oral food challenge remains the gold standard for diagnosis of food-induced allergic disorders especially for cell-mediated sensitivities, but there are often practical limitations to its use. Diagnosis therefore often depends heavily on the medical history, attempting to determine if a food reaction is a possible cause, the specific food implicated, and whether the condition likely represents a cell-mediated or IgE reaction. Skin prick tests are useful in screening for IgE-mediated food sensitivity, with a larger size wheal increasing the specificity. The greatest value of skin testing is a negative test, which confirms the absence of an IgE-mediated dietary allergy. However a positive skin test combined with an unequivocal history implicating a specific food is considered diagnostic by many. RAST testing provides similar qualitative diagnostic information but is increasingly being replaced by quantitative food-specific serum IgE which has greater positive predictive value. Intestinal biopsy has a particular complementary role in diagnosis of food allergic enteropathy.

\textit{Autoimmune Enteropathy}

Autoimmune enteropathy is a rare disorder that usually results in death in early infancy or childhood. Its hallmarks are severe, protracted diarrhea and antienterocyte antibodies along the apex and basolateral enterocyte border.
It is frequently associated with extraintestinal disease including diabetes mellitus, glomerulopathy, and hemolytic disease as well as immunodeficiency such as IPEX (immunodysregulation, polyendocrinopathy and enteropathy, X-linked) syndrome.

**Idiopathic Inflammatory Bowel Disease: Crohn’s Disease**

Crohn’s disease is a chronic inflammatory disorder that can affect any part of the gastrointestinal tract; involvement of the small bowel may be referred to as Crohn’s enteritis. Crohn’s disease is comparatively more common in North America and Europe which have the highest incidence; the disease is relatively rare elsewhere, particularly in developing countries. To put it in context of all causes of enteropathy, recent data suggests the incidence of all childhood and adolescent Crohn’s disease in northern hemisphere countries is estimated to be 2–3.7 cases per 100,000. The cause of Crohn’s disease has not been defined, although the pathogenesis is complex involving an interrelation between genetic predisposition and environmental factors (fig. 2). The intestinal manifestations reflect the anatomic site of involvement, with Crohn’s enteritis manifested in various combinations as diarrhea, fever, occult or gross blood in the stool, abdominal pain, aphthous ulcers, weight loss and malnutrition. Numerous extraintestinal manifestations can be associated including joint involvement (arthritis, ankylosing spondylitis and arthralgia), eye involvement (uveitis, episcleritis and orbital myositis), liver (primary
sclerosing cholangitis) and skin (erythema nodosum and pyoderma gangrenosum). Management is focused on treating acute presenting disease or exacerbation and, once controlled, maintaining remission while ensuring adequate nutritional status. A variety of anti-inflammatory and immune-modulating agents are used depending on severity and site of disease activity. The more recent introduction of biological agents targeting specific host immune components such as tumor necrosis factor-α represents a new class of agents that improve the ability to reach treatment goals; however, there are no long-term studies of the use of these drugs in the pediatric population.

**Congenital Persistent Diarrhea**

These quite rare, severe chronic enteropathies include microvillus inclusion disease, tufting enteropathy, congenital chloride diarrhea, and congenital disaccharidase deficiencies [18]. These are conditions of defects in epithelial structure or gut transport mechanisms and present within hours to days of birth (table 1). Except for the disaccharidase deficiencies, the diarrhea is predominantly secretory and may lead to life-threatening electrolyte abnormalities and malnutrition. In the case of congenital diarrhea due to ultrastructural abnormalities, total parental nutrition with subsequent intestinal transplant is the likely route of management. A subset of early onset protracted diarrhea involves the primary maldigestion and malabsorption disorders. Though quite rare, secondary maldigestion and malabsorption form an integral part of almost all chronic enteropathies. Primary maldigestion arising from the intestinal tract is rare and includes congenital enterokinase deficiency which results in abnormal stool and failure to thrive from birth. The diagnosis is suspected when exogenous enterokinase restores proteolytic activity in duodenal juice and can be confirmed by direct measurement of enterokinase activity in the duodenal mucosa. Congenital sucrase-isomaltase deficiency and the extremely rare congenital lactase deficiency with corresponding disaccharide malabsorption are characterized by loose or liquid stool often with low stool pH due to fermentation. Congenital disaccharidase deficiency may be determined by a breath hydrogen test using the suspected sugar; however, intestinal biopsy with quantification of disaccharidase activity is the reference standard diagnostic test.

**Syndromic Persistent Diarrhea**

Syndromic persistent diarrhea in context of the current discussion refers to a condition of chronic enteropathy and diarrhea in infants and young children in developing countries, typically associated with malnutrition often in a vicious cycle, downward spiral relationship (fig. 3). While persistent diarrhea constitutes less than 10% of all diarrheal episodes in developing countries, it
accounts for 30–50% of all diarrheal deaths. Risk factors include antecedent general malnutrition, vitamin A or zinc micronutrient deficiency, and non-exclusive breastfeeding in early infancy. The pathogenesis is undeniably complex and multifactorial; however, prolonged small bowel damage is a final common pathway [19]. Infectious and food-sensitive enteropathies have been proposed as distinct and sometimes concomitant mechanisms contributing to development of syndromic persistent diarrhea, although their relative importance is not fully defined. Persistence of diarrhea may follow a single episode of infectious diarrhea in a malnourished child or repeated distinct episodes of acute diarrhea by different pathogens leading to malnutrition and persisting well after the inciting enteropathogen is no longer detectable. This is discussed in more detail in a preceding section, Infectious Enteropathy. Evidence also implicates dietary antigen sensitization due to increased intestinal permeability caused by acute or chronic diarrhea and that leads to allergic enteropathy, usually dairy soy, in the vulnerable patient.

Protein energy as well as micronutrient malnutrition promote persistent diarrhea by structural and functional abnormalities including alterations in host defense, immune dysfunction, mucosal injury, and impaired intestinal repair [20]. Gastric acid output is decreased in malnourished children, leading to a compromised gastric barrier against oral bacteria and important

**Fig. 3.** Conceptual framework of the pathogenesis of syndromic persistent diarrhea. CHO = Carbohydrate.
pH-sensitive enteropathogens, notably *Shigella* and *Vibrio cholerae*. Abnormalities of the small intestine are variable, but typically include chronic cell-mediated enteropathy with crypt hyperplasia, villous atrophy, and marked increase in intraepithelial lymphocytes. Mucosal profile indicates an imbalance that favors proinflammatory overregulatory cytokines and a poorly controlled Th1 cell-mediated proinflammatory response that accounts for many of the histological changes. Several factors in combination explain the observed pathology in syndromic persistent diarrhea including small bowel bacterial overgrowth and subsequent bile acid deconjugation, impaired motility, reduced pancreatic and biliary secretions, and abnormal intestinal immunity and especially reduced secretory IgA. Protein energy malnutrition and/or micronutrient deficiencies such as zinc, copper, selenium, iron, vitamin A, vitamin C, and vitamin E result in consequential immune dysfunction. Disruption of mucosal surfaces and increased intestinal permeability integrity lead to nutrient and bile acid malabsorption, fluid and electrolyte losses, and translocation of endotoxin and dietary allergen with pathologic sequelae including sepsis [21]. Even the ‘healthy undernourished’ child has increased intestinal permeability and mucosal cellular immune changes that can affect long-term growth and may be the underlying cause of tropical enteropathy in malnutrition [22].

From a practical clinical perspective, diagnostic studies are limited to testing of stool for enteric pathogens amenable to specific antimicrobial therapy. Because certain fundamental abnormalities are stereotypical while others vary at any given point in time, costly testing to document abnormalities such as small bowel overgrowth, disaccharide or fat malabsorption, among others does not lead to a change in management and therefore are not routinely necessary. In resource-constrained developing countries, this is especially important. Proper management, essential to achieve recovery and reduce mortality, is focused on fluid and electrolyte homeostasis and systematic enteral nutritional rehabilitation. Fluid and electrolyte replacement is best achieved using a reduced osmolarity oral rehydration solution [23]. The addition of soluble fiber to the oral rehydration solution promotes rehydration and recovery through its property as a short chain fatty acid precursor that uniquely promotes colonic as well as small bowel recovery [24, 25]. Algorithmic dietary management using locally available foods and simple clinical guidelines is effective in most children [26]. Breast milk feeding should be continued for children who are not weaned in addition to the therapeutic diets described in the algorithm. Lactose malabsorption, previously considered a common limiting factor in recovery, is problematic in a relatively small proportion of children; lactose-free diets therefore are reserved for the few children who fail diets containing modest amounts of lactose. Micronutrients have a key role in the treatment and prevention of persistent diarrhea; zinc supplementation of children with persistent diarrhea promotes earlier recovery and may prevent death while combined zinc and vitamin A supplementation synergistically
prevent persistent diarrhea [27, 28]. Severe malnutrition, common in children with persistent diarrhea, treated using a malnutrition management protocol significantly increases the likelihood of survival and includes diets described above but with additional nutritional interventions, avoidance of intravenous fluids, anticipatory antibiotic therapy, and prevention or prompt management of hypothermia and hypoglycemia [29].

**Approach to Defining Cause of Chronic Enteropathy**

There are numerous causes for chronic enteropathy in children and all methods of categorizing have their advantages and deficiencies. The majority of the worldwide burden of chronic enteropathy is due to malnutrition and secondary immune deficiency and should be readily diagnosed if in the associated context; most other forms of chronic enteropathy are rare. Regardless, a detailed and careful history is of primary importance in determining the potential causes of chronic enteropathy in the individual child and avoiding unnecessary and costly investigations. Clues to early onset enteropathy may be contained in the prenatal history such as a mother’s infectious status including exposure to HIV. In environments where antenatal ultrasonography is routine, fetal fluid-filled dilated loops of intestine and polyhydramnios may be an early indication of congenital enteropathy syndrome such as congenital chloride-losing diarrhea. A careful history of the age and time of onset of symptoms should be obtained. An association with feeding type, feeding modifications including early introduction of complementary feeding, and extraintestinal manifestations such as recurrent pneumonias, neutropenia, arthritis, mouth ulcers and a family history of similar illness may all provide clues to the underlying pathology.

**References**


Discussion

Dr. Chubarova: Could you please tell us the distinguishing criteria between hypertrophy of the mucosa, normal mucosa and atrophy, I mean villus-crypt relation or maybe the height of the villus?

Dr. Fuchs: I am not sure I fully understand your question but typically what happens is that crypt cell hypertrophy is relative to the villus, which reflects increased secretion by the crypt cell and decreased absorption by the apical cell.

Dr. Chubarova: It seems absolutely clear in your figures and when we take a biopsy we want to know the figures. How many micrometers is normal?

Dr. Fuchs: I have to apologize; I don't know the specific cutoff value.

Dr. Chubarova: Maybe for LH that we are talking about?

Dr. Fuchs: Does anybody else want to comment on that?

Dr. Milla: Most of us used to look at the villus-crypt ratio as a means of determining the normality of the mucosa and it varies at different ages. In adults you would expect the villus to be at least 3 maybe 4 times as long as a crypt; this is a simple way of determining whether the mucosa is normal or not. In younger children you would probably use a range of 2.5–3 as the villus-crypt ratio. The thing that you look at rather than measuring the length of the villus in micrometers is the relationship of the villus to the crypt. When the crypt becomes longer than the villus you start talking about crypt hypertrophy. But there are other signs of crypt hypertrophy as well insofar as you have to have an increased turnover of cells before looking to see if there is increased mitosis in the crypt; in other words the crypt contains too many dividing cells.

Dr. Balanag: Do you have any data showing what would happen in a patient with chronic diarrhea treated with probiotics, and then it is found that the patient has HIV?

Dr. Fuchs: The data on probiotics which I am familiar with are not convincing. There are some encouraging data but I have not seen anything that suggests that we should routinely recommend probiotics. Of course there are great differences in types of probiotic bacteria and dose amount. But of course the concern in any immune-deficient individual given probiotics is the potential for infection by these organisms that, based on a few case reports coupled with the lack of defined efficacy, make it hard to recommend them at this point.

Dr. Saavedra: You showed a couple slides relative to the frequency of pathogens in different geographic areas, and in one of them it is obvious that in many developing countries there is a very low percentage of rotavirus diarrhea. Is the percentage low because there are so many other pathogens and not because there is little rotavirus diarrhea? The point being that rotavirus diarrhea is probably there, it is just overwhelmed by the frequency of other bacterial pathogens. I do think rotavirus has a practical relevance to this vicious cycle of diarrhea and malnutrition in developing countries. Ultimately we need to rehabilitate the patient nutritionally because that is how they will recover from whatever the original pathogen was. What should we do for prevention? Would therapies that might prevent rotavirus diarrhea in developing countries make a difference?

Dr. Fuchs: I was showing the prevalence of pathogens associated with persistent diarrhea and, in this regard, we think of rotavirus as generally being associated with acute diarrhea. I know you have done quite a bit of work with probiotics in the prevention of rotavirus. The encouraging data are primarily from developed countries where use may be more feasible. I don’t know if developing countries are in a position to apply probiotics for no other reason than cost. Expenditure on health care in developing countries averages USD 12–15 or less per child per year for all health care including immunizations, micronutrient supplementation, etc. So one has to prioritize which interventions to implement. You are right that we must consider not only the
type of bacteria but the dose of the bacteria as well. I and my colleagues have studied different probiotic preparations of the same bacteria from different manufacturers and have seen positive effects by some but not others; the dosing and concentration of organisms were different not the type.

Dr. Rivera: I have to disagree with the data presented on rotavirus and persistent diarrhea. In the *New England Journal of Medicine* we published a paper on the efficacy of a new rotavirus vaccine [1]. Our epidemiological data showed that 63% of acute diarrhea was due to rotavirus vaccine. Furthermore we found that up to 10% of those cases of rotavirus had persistent diarrhea rather than the 5% that you reported.

Dr. Fuchs: Again this was persistent diarrhea, and you are absolutely right there are all sorts of explanations for the variation in rates. For example, it might reflect a different time in the year of the study, seasonality of an epidemic. There is no question that if the same study is done in different areas the rates may be different. In fact my slide showed that in the studies in Peru and Bangladesh the rates are not exactly the same. There is variation, so I suggest it is not a reason to be unsettled if it is 10% in that particular series and 5% in another.

Dr. Kamewa: We have started a program on rotavirus surveillance in my country and we will be able to answer some of the questions that have been asked here in the next 1 or 2 years. How long do you recommend zinc supplementation for a child who has recurrent episodes of diarrhea given that when supplemented during a diarrheal episode it is probably protective for about 2–3 months? What is the pathophysiology of constipation and food allergy because you alluded to constipation being a phenotype of food allergy?

Dr. Fuchs: The recommendation for acute diarrhea is to supplement zinc at approximately twice the RDA for about 2 weeks (20 mg/day for children and 10 mg/day for infants <6 months for 10–14 days) [2]. The question of periodic supplementation of zinc analogous to periodic vitamin A supplementation programs is a very interesting one. Periodic zinc supplementation in otherwise normal children at high risk of diarrheal disease would be expected to be beneficial, but to my knowledge periodic zinc supplementation on an ongoing basis over several years has not been studied. It is a very interesting question to which we still don’t have an answer.

Dr. Sorensen: When you talked about immunity, you mentioned T cells, neutrophils, complement. The only immunological intervention that I know of that has reversed chronic infectious diarrhea is the use of oral Ig preparations. I have used them in chronic rotavirus infection, in clostridium infection and in microsporidia. All those patients have T cell deficiencies; we cure them basically with IgG. We have to reevaluate the role of IgG-mediated immunity in these diseases too.

Dr. Fuchs: There is evidence that the immune system is more broadly involved and may differ for different specific infections. Good correlation has been shown for skin test reactivity to standard antigens and the risk of diarrhea and infection; quite clearly T cell immunity is involved. But the primary focus in an international health context regarding reconstitution of immune function has been on the particularly important role of micronutrients. There has been a lot of work on zinc and its positive effects on a variety of aspects of immune function and persistent diarrhea outcome. This and other micronutrients such as vitamin A also affect epithelial cell repair, for example. If you concentrate too much on one area of host defense you run the risk of overfocusing when it has a broader spectrum.

Dr. Imanzadeh: How long do you give the diet? As you mentioned chronic infection and bile acid conjugation may induce or activate persistent diarrhea. Oral gentamicin and cholestyramine can be used in the treatment of persistent diarrhea.
**Dr. Fuchs:** I don't recall the duration of the studies, but the diet should be given for 3 or 4 days and concern should arise if there is no effect in a positive direction. At this point you start having trouble maintaining electrolyte status. There are some reports from South Africa using gentamicin for persistent diarrhea, and cholestyramine can bind bile acids. On a case by case basis there may be a role in specific situations, but there are problems in broadly administering those agents. With regard to antibiotic therapy, if you look at all the data, it does not really have a consistent impact on recovery from persistent diarrhea. Cholestyramine again is treating the symptom rather than the cause, so it may have a cosmetic effect but it is not going to actually lead to recovery very quickly.

**References**