

ENTEROPATHIES OF INFANCY

PIERRE RUSSO, MD

The Children's Hospital of Philadelphia and the University of Pennsylvania

INTRODUCTION

Acute diarrhea, in the industrialized world, is usually self-limited, infectious in nature, and rarely requires biopsy evaluation. *Chronic diarrhea* can cause failure to thrive, frequently results in intestinal biopsy and may require parenteral nutrition and other forms of therapy.

Protracted diarrhea has replaced the older term "intractable diarrhea" in the GI literature and denotes a syndrome of severe diarrhea, usually occurring in infants less than a year of age and requiring aggressive nutritional and sometimes immunosuppressive management. Though not strictly synonymous with chronic diarrhea, the two are frequently used interchangeably. Several recent reviews on the subject of protracted diarrhea in childhood are available[1-4].

Disorders resulting in chronic diarrhea of childhood can be grouped into several major pathophysiologic categories:

- I. Congenital transport disorders and disaccharidase deficiencies**
- II. Disorders of enterocyte development**
- III. Inflammatory and Immune-mediated disorders**
- IV. Systemic disorders and Tumors**
- V. Motility disorders**
- VI. Endocrine disorders – congenital adrenal hyperplasia**
- VII. Infections – “blind loop”, Giardia, HIV**
- VIII. Anatomic disorders – Malrotation, short gut, lymphangiectasia**
- IX. Pancreatic disorders – Cystic fibrosis, Shwachman disease**

During the past twenty years, enteric infections and food intolerance have been replaced by rarer congenital conditions, partly due to greater awareness of these entities as well as due to improvements in diagnosis and management

	1977-1993 (N=38)	1993-1996 (N=32)	1997-2001 (N=61)
ETIOLOGY	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Enteric infection	18 (48)	4 (12)	2 (3)
Food intolerance	8 (22)	3 (10)	10 (17)
Autoimmune enteropathy	2 (5)	8 (25)	7 (12)
Structural enterocyte defects	2 (5)	7 (22)	16 (26)
Celiac disease	1 (2.5)	0 (0)	0 (0)
Eosinophilic enteropathy	1 (2.5)	1 (3)	0 (0)
Lymphangiectasia	1 (2.5)	1 (3)	2 (3)
Motility disorders	2 (5)	3 (9)	16 (26)
Munchausen syndrome by proxy	0 (0)	0 (0)	1 (15)
Unknown	3 (7.5)	5 (16)	7 (11)

From: Guarino A and DeMarco G. Persistent Diarrhea, chapter 10, in Pediatric Gastrointestinal Disease, 4th edition (2004)

In evaluating intestinal biopsies, it is helpful to remember that disorders resulting in severe diarrhea tend to cluster in different age groups:

Infant

- Microvillus inclusion disease
- Autoimmune enteropathy
- Milk and soy protein intolerance
- Protracted infectious enteritis
- Hirschsprung's disease
- Congenital transport defects
- Munchausen syndrome by proxy

Toddler

- Irritable colon of childhood
- Protracted infectious enteritis
- Giardiasis
- Sucrase-isomaltase deficiency
- Tumors
- Celiac disease
- Inflammatory bowel disease

Modified from Vanderhoof J.A. p.32-42 ch 3 in Pediatric Gastrointestinal Disease, Wyllie R. And Hyams J.S., eds W.B. Saunders, 1999

The type of diarrhea can also offer clues: **Osmotic** diarrhea results from an increased osmotic load in the distal small bowel and colon, with an osmotic “gap” in stool electrolytes, and usually stops when oral feeding is discontinued. It is usually associated with disaccharidase deficiencies and transport disorders, decreased absorptive surface (microvillous inclusion disorder) and hypermotility disorders. On the other hand, **secretory** diarrhea is characterized by an exudate of mucous, protein or blood, and a variable response to withholding of oral feeds.

Disorders usually associated with secretory diarrhea include congenital fluid transport disorders, inflammatory disorders and increased secretion of gastrointestinal activating substances.

In evaluating intestinal biopsies, disorders that cause protracted diarrhea in early life can be broadly divided into those in which villus architecture is maintained, and those characterized by villus atrophy:

Normal villous morphology

- Congenital chloride diarrhea
- Congenital carbohydrate malabsorption
- Congenital sucrose isomaltase deficiency
- Congenital bile acid malabsorption

Lipid-filled enterocytes

- Abetalipoproteinemia
- Chylomicron retention disorder

Villous atrophy

Pauci-inflammatory

- Microvillous inclusion disease
- Epithelial dysplasia

Inflammatory

- Autoimmune enteropathy
- IPEX
- Enterocolitis with dysmorphic features
- Congenital immunodeficiency disorders
- Milk intolerance
- Gluten-sensitive enteropathy

Most transport disorders and disaccharidase deficiencies do not result in appreciable histologic changes on intestinal biopsies. In fact, normal findings on an intestinal biopsy should prompt the clinician to search for one of these entities.

Lipid transport disorders such as Abetalipoproteinemia, homozygous hypolipoproteinemia and chylomicron retention disease (Anderson disease) are characterized by accumulation of lipid within the enterocytes and clinical characteristics, such as fat malabsorption, low levels of serum lipids, failure to thrive in childhood, neurologic and visual problems resulting from malabsorption of fat-soluble vitamins. These conditions are associated with disorders of apolipoproteins, which reside on the surface of chylomicrons. Apolipoproteins native to the intestine are apolipoprotein (apo) A-I, apo A-IV, and apoB, which has two forms: apo B-100 and apo B-48, both encoded by the same gene located on chromosome 2[5].

Abetalipoproteinemia is an autosomal recessive disorder characterized by the absence of Microsomal Triglyceride Transfer protein (MTP), responsible for assembly of lipoprotein particles, and for the proper folding of ApoB, preventing its premature degradation[6]. Patients have diarrhea and fat malabsorption usually appearing within the first few months of life, with acanthocytosis, and deficiencies in fat-soluble vitamins resulting in retinitis pigmentosa and neurologic symptoms. Serum levels of cholesterol and triglycerides are typically low, and do not rise after a fatty meal. Fat-filled enterocytes are noted on intestinal biopsies of fasting patients, which on electron microscopy are irregular in size and generally non-membrane-bound. No lipid is noted in the extracellular space. *Chylomicron retention (Anderson) disease* is similar to abetalipoproteinemia in its gastrointestinal manifestations and impact on growth, though acanthocytosis is usually absent and neurologic and ocular abnormalities are much less severe. Also, in contrast to abetalipoproteinemia, serum fasting triglyceride levels are normal and hypocholesterolemia is less marked. The basis for the disorder appears to be an inability to export chylomicrons from the enterocyte into lacteals[7]. Fat-filled enterocytes are also seen in small bowel biopsies. On ultrastructure, lipid droplets are more uniform in size than the droplets

in abetalipoproteinemia, and some appear to be bounded by the membranes of the endoplasmic reticulum[8].

Microvillus Inclusion Disease (MVID)

Initially described by Davidson et al in 1978, and subsequently by investigators in other parts of the world, MVID is characterized by refractory secretory diarrhea occurring within the first week of life[9, 10]. There is a roughly equal sex incidence. Birth history is usually unremarkable, without evidence of polyhydramnios, as is seen in congenital chloride diarrhea. Tests of small intestinal function are diffusely abnormal[11]. The pattern of inheritance appears to be autosomal recessive[10].

Small bowel biopsies are characterized by severe villus atrophy, with little or no crypt hyperplasia, and without significant inflammation. The pathognomonic features are present on ultrastructural study and include absent or small stubby microvilli, vesicular structures located towards the apex of the enterocytes containing microvilli, and granules containing dense amorphous material. Even without an electron microscope, this disease can be strongly suspected on paraffin sections by the absence of a distinct brush border on the periodic-acid-Schiff (PAS) stain, and by the presence of PAS-positive diastase-resistant densities at the apex of the enterocytes. Similar observations are noted using immunohistochemical staining for alkaline phosphatase, CEA, and more recently, with anti-CD 10, a membrane-associated neutral peptidase[12]. Microvillus inclusions have also been reported in the colon, gallbladder and renal tubular epithelium in these patients[11]. These inclusions can sometimes be difficult to detect, and several biopsies may be required to identify them. It appears that *MVID* represents a spectrum of entities, ranging from cases with typical early presentation and diagnostic inclusions

on EM, to cases in which the clinical presentation is atypical, or cases in which inclusions either cannot be demonstrated (*microvillus dystrophy*), or the inclusions are “atypical”[13-16].

In a multicenter survey of 23 patients with MVID, the one-year survival was less than 25%[10]. Medical therapy in these patients has generally proven to be ineffective and small intestinal transplantation currently is the best treatment[10, 17, 18]. Instances of apparent resolution of the disease with improvement of the mucosal features on long-term TPN have been reported[19].

Tufting Enteropathy (Epithelial dysplasia)

First described by Reifen et al, then by Goulet and colleagues, patients with tufting enteropathy present in the neonatal period with a watery diarrhea. Prenatal history is uneventful and the disease appears to be inherited in an autosomal recessive fashion, as suggested by the finding of other affected siblings and frequent parental consanguinity[20, 21].

Its histological hallmarks are severe villus atrophy with the formation of “tufts” of rounded, tear-drop shaped enterocytes which appear to shed into the lumen. There may be a mild increase in the lamina propria inflammatory cells, but intraepithelial lymphocytes (IELs) do not appear to be significantly increased. Transmission electron microscopy has revealed a normal brush border. Abnormalities in immunohistochemical staining for basement membrane laminin and heparan sulfate proteoglycan, ultrastructural irregularities of desmosomes, and abnormal distribution of $\alpha 2\beta 1$ integrin have been observed in patients with this disorder, suggesting that the early onset of the disease and its characteristic histomorphological changes may result from abnormal cell-cell and cell-matrix interaction[22, 23]. Dietary manipulations, antibiotic and immunosuppression have proven ineffective in these patients, and long-term TPN and small-bowel transplantation are the current treatment options for these patients[11].

A probably related disorder resulting from the absence of intestinal epithelial $\alpha6\beta4$ integrin has been described. The salient features are severe watery diarrhea in the first two weeks of life in association with pyloric atresia, with extensive sloughing of the epithelium observed on biopsies[24].

Autoimmune Enteropathy

The term “autoimmune enteropathy”(AIE) was proposed by Unsworth and Walker-Smith to describe a syndrome of protracted diarrhea with the presence of autoantibodies against gut epithelium[25].

More than 100 cases have since been reported in the past twenty years[26], most cases occurring in infancy or the first year of life. There is a strong male preponderance, family history of other affected siblings, frequent extra-intestinal involvement and various circulating autoantibodies[27, 28]. However, this entity has also been reported in older children[29] and even adults[30-32], in whom it may be responsible for a proportion of cases referred to as “refractory sprue”. Intestinal biopsies in most of the reported cases are characterized by severe villus atrophy and variable crypt hyperplasia. Concomitant colitis and gastritis are present in the majority of cases. Marked inflammatory destruction of intestinal crypts with extensive apoptosis is a feature noted in many of the cases. These findings are similar to those noted in severe intestinal graft-versus-host disease, and suggest an abnormal immune-mediated attack against intestinal epithelium.

The hallmark of this entity is the presence of circulating anti-enterocyte antibodies manifest as positive staining in a linear pattern along the apex and baso-lateral border of the

enterocyte by indirect immunofluorescence[27]. The antibodies are predominantly IgG, and have been described as complement-fixing, though IgM and IgA have also been described[33]. Antibodies reacting against mucus or goblet cells have also been described in occasional patients with an apparently related entity, and intestinal biopsies in these cases have shown a marked depletion of goblet cells[29, 34].

Extra-intestinal disease in these patients includes insulin-dependent diabetes, glomerulopathy and hemolytic anemia, as well as pulmonary and dermatologic manifestations[26]. Numerous autoantibodies have been detected in these patients, including anti-smooth muscle, anti-endoplasmic reticulum, anti-mitochondrial, anti-parietal, anti-adrenal, as well as anti-DNA and anti-ANA antibodies.

AIE has been associated with with several immunodeficiencies and autoimmune diseases:

Autoimmune Enteropathy: Associated Conditions

- IPEX Immunodysregulation / polyendocrinopathy / enteropathy / X-linked.
- Immunoosseous dysplasia, Schimke type
- Usher syndrome (hyperinsulinism with enteropathy and deafness)
- Autoimmune Polyendocrinopathy, Candidiasis and Ectodermal dysplasia

Perhaps the most well- recognized such association is with the X-linked syndrome of Immunodysregulation, Polyendocrinopathy and Enteropathy (IPEX) syndrome, initially described by Powell[35]. This syndrome has been related to mutations of the FOX P3 gene (Xp11.23-Xq13.3)[36, 37], and is the human equivalent of *scurfy* in the mouse[38]. The protein encoded by the gene, Foxp3, is expressed in regulatory CD4+/CD25+ T cells and is essential for immune homeostasis[39]. Scurfy mice are characterized by failure to thrive, overexpression of

CD4+/CD8+ lymphocytes, extensive multiorgan inflammatory infiltration and over production of cytokines[40].

Mortality in cases of AIE has been high, occurring in up to one-third of reported cases, but more frequent in the older descriptions. Diet changes and steroids alone have been largely ineffective, and the use of immunosuppressants appears to be necessary in most cases. Cyclosporine has induced a remission in several studies, though some remained resistant. A positive response to Tacrolimus has been reported in patients refractory to other therapies[41, 42].

“Syndromatic Diarrhea”

Girault et al described a group of patients with dysmorphic features, consisting of a prominent forehead, broad nose, hypertelorism and wooly, easily removable abnormal hair (trichorrhexis nodosa), in association with intractable diarrhea and immunodeficiency, which they termed “*syndromatic intractable diarrhea*”, because of the constellation of extra-intestinal manifestations[43]. Most of the patients reported were of Middle Eastern origin, and there was parental consanguinity and a history of similarly affected siblings. The immunodeficiency was characterized by impaired T-cell and antibody responses despite normal immunoglobulin levels. Intestinal biopsies revealed moderate villous atrophy without a conspicuous increase in inflammatory cells.

Other syndromes associated with early severe diarrhea include:

- Epidermolysis Bullosa with Pyloric atresia
- Tricho-hepato-enteric syndrome
- Infantile Systemic Hyalinosis
- Phosphomannose Isomerase Deficiency (CDG type Ib)
- Hypohidrotic Ectodermal Dysplasia
- Progressive Familial Cholestasis, PFIC I (ATP8B1)

- Lysinuric Protein Intolerance

Hair abnormalities can be seen in association with chronic diarrhea in other disorders, typically in *Menke's* disease, Zinc deficiency and Lysinuric protein intolerance. Distinct hair shaft anomalies have been reported in two siblings as the tricho-hepato-enteric syndrome, in which thin sparse hair (trichomalacia) was seen in association with hypertelorism, chronic diarrhea, a progressive hypermethioninemia and a hemochromatosis phenotype[44].

Congenital Immunodeficiencies

Over 50% of children with immunodeficiencies present with chronic diarrhea, and the gastrointestinal tract is the second most common site of infection in these cases, after the pulmonary system. Immunodeficiency states may predispose to various abnormal intestinal immune reactions because of increased intestinal permeability, resulting in heightened exposure to dietary or microbial antigens.

Primary Immunodeficiency Disorders with Prominent Gastrointestinal Manifestations

Antibody Deficiencies

- **X-linked agammaglobulinemia**
- **Common variable Immunodeficiency**
- **IgA deficiency**
- **Immunodeficiency with elevated IgM (hyper-IgM syndrome)**
- **Transient hypogammaglobulinemia of infancy**
- **IgG subclass deficiency**

Combined Immunodeficiencies

- **Severe combined immunodeficiency**
- **Major histocompatibility complex Class II deficiency**

T-Cell Disorders

- **Wiskott-Aldrich syndrome**
- **Ataxia telangiectasia**
- **DiGeorge syndrome**

Disorders of Phagocyte Functions

- **Chronic granulomatous disease**
- **CD11 / CD18 Leukocyte adhesion molecule deficiency**
- **Hermansky Pudlak syndrome**

- **Glycogen storage type IB**

Other Disorders

- **Chronic mucocutaneous candidiasis**
- **Autoimmune Polyendocrinopathy/candidiasis/ectodermal dystrophy**
- **IPEX (Immunodeficiency, Polyendocrinopathy, Enteropathy, X-linked)**

Common Variable Immunodeficiency(CVID) is one of the more common primary immunodeficiencies. Chronic diarrhea is frequent in these patients, and other gastrointestinal manifestations include chronic active hepatitis and hemorrhagic gastritis[45, 46]. Histologic findings in the intestines fall into four major categories: infections (frequently *Giardia*), nodular lymphoid hyperplasia (NLH), celiac-like villous atrophy, and a severe Crohn's-like enterocolitis. There is an absence of germinal follicles in the lymphoid tissues of the GI tract, and near absence of plasma cells in the lamina propria.

Chronic diarrhea refractory to a gluten-free diet in association with villus atrophy has been observed in patients with CVID, and major differentiating features from celiac disease include a crypt-destructive inflammatory process in association with prominent apoptosis, reminiscent of autoimmune enteropathy[47]. An accumulation of foamy macrophages in the lamina propria, resembling Whipple's disease or chronic granulomatous disease, has been noted[47].

IgA deficiency is the most common primary immunodeficiency, with a prevalence of approximately 1 in 300[48]. Gastrointestinal disorders include *Giardia* infection, celiac disease, chronic inflammatory bowel disease, atrophic gastritis with pernicious anemia, food allergies and nodular lymphoid hyperplasia[49]. There is a 10-20-fold increase in celiac disease in patients with IgA deficiency[50, 51], and the clinical presentation, histologic changes and response to gluten are similar to that of non-IgA- deficient patients, the distinguishing feature being an

absence of IgA-bearing plasma cells from intestinal biopsies in the former[52]. Chronic diarrhea may also result from a non-specific enteritis which does not respond to gluten withdrawal[53].

Severe Combined Immunodeficiency (SCID) is due to a genetically heterogeneous group of disorders, and is the most severe form of congenital immunodeficiency. Infections, severe protracted diarrhea, failure to thrive and malabsorption are the major clinical manifestations[54, 55]. Neonatal graft-versus-host disease may occur from transplacentally acquired maternal lymphocytes, from the use of non-irradiated blood products, and as a result of bone marrow transplantation, which until recently was the only effective therapy for these children. Intestinal biopsies are typically void of plasma cells, and germinal follicles are absent from the appendix. Chronic viral[56] and bacterial infections[55] may also cause chronic diarrhea.

Chronic Granulomatous Disease results from an inability to produce hydrogen peroxide, the oxidant molecules required to kill ingested microbes. Stomatitis, oral ulcers, esophageal and gastric strictures are relatively frequent complications, and intestinal involvement, most often due to infections, occurs in over 50% of patients[57]. A Crohn's disease-like picture is typically found, with thickening of the bowel wall, stenoses, ulcers and crypt abscesses with large granulomas[58-62]; pigmented histiocytes can be found in otherwise relatively uninvolved mucosa.

Characteristic Histologic Changes in Intestinal Biopsies

in Primary Immunodeficiency States

	XLA	CVID	IgA deficiency	SCID	CGD	CD11/CD18 deficiency
Paucity of plasma cells in lamina propria	+	+		+		
Nodular lymphoid hyperplasia		+	+			
Giardia	+	+	+			
Regional enteritis	+	+	+		+	+
Foamy macrophages in lamina propria		+			+	
Non-specific villous atrophy			+			

Abbreviations: XLA – X-linked Agammaglobulinemia; CVID – common variable immunodeficiency; SCID –severe combined immunodeficiency; CGD –chronic granulomatous disease

REFERENCES:

1. Catassi, C., E. Fabiani, M.I. Spagnuolo, et al., *Severe and protracted diarrhea: results of the 3-year SIGEP multicenter survey. Working Group of the Italian Society of Pediatric Gastroenterology and Hepatology (SIGEP)*. *J Pediatr Gastroenterol Nutr*, 1999. 29(1): p. 63-8.
2. Brousse, N., D. Canioni, C. Rambaud, et al., *[Intractable infantile diarrhea. A framework to subdivide]*. *Ann Pathol*, 1994. 14(5): p. 333-8.
3. Murch, S.H., *The molecular basis of intractable diarrhoea of infancy*. *Baillieres Clin Gastroenterol*, 1997. 11(3): p. 413-40.
4. Sherman, P.M., D.J. Mitchell and E. Cutz, *Neonatal enteropathies: defining the causes of protracted diarrhea of infancy*. *J Pediatr Gastroenterol Nutr*, 2004. 38(1): p. 16-26.
5. Levy, E., *The genetic basis of primary disorders of intestinal fat transport*. *Clin Invest Med*, 1996. 19(5): p. 317-24.
6. Berriot-Varoqueaux, N., L.P. Aggerbeck, M. Samson-Bouma, et al., *The role of the microsomal triglyceride transfer protein in abetalipoproteinemia [In Process Citation]*. *Annu Rev Nutr*, 2000. 20: p. 663-97 [MEDLINE record in process].
7. Roy, C.C., E. Levy, P.H. Green, et al., *Malabsorption, hypocholesterolemia, and fat-filled enterocytes with increased intestinal apoprotein B. Chylomicron retention disease*. *Gastroenterology*, 1987. 92(2): p. 390-9.

8. Boldrini, R., R. Biselli and C. Bosman, *Chylomicron retention disease--the role of ultrastructural examination in differential diagnosis*. *Pathol Res Pract*, 2001. 197(11): p. 753-7.
9. Davidson, G.P., E. Cutz, J.R. Hamilton, et al., *Familial enteropathy: a syndrome of protracted diarrhea from birth, failure to thrive, and hypoplastic villus atrophy*. *Gastroenterology*, 1978. 75(5): p. 783-90.
10. Phillips, A.D. and J. Schmitz, *Familial microvillous atrophy: a clinicopathological survey of 23 cases*. *J Pediatr Gastroenterol Nutr*, 1992. 14(4): p. 380-96.
11. Cutz, E., P.M. Sherman and G.P. Davidson, *Enteropathies associated with protracted diarrhea of infancy: clinicopathological features, cellular and molecular mechanisms*. *Pediatr Pathol Lab Med*, 1997. 17(3): p. 335-68.
12. Groisman, G.M., M. Amar and E. Livne, *CD10 A valuable tool for the light microscopic diagnosis of microvillous inclusion disease*. *Am. J. Surg. Pathol*, 2002. 26(7): p. 902-907.
13. Groisman, G.M., *Intestinal microvillous dystrophy*. *Hum Pathol*, 1995. 26(9): p. 1045-6.
14. Mierau, G.W., E.J. Wills, J. Wyatt-Ashmead, et al., *Microvillous inclusion disease: report of a case with atypical features*. *Ultrastruct Pathol*, 2001. 25(3): p. 275-9.
15. Raafat, F., N.J. Green, K.A. Nathavitharana, et al., *Intestinal microvillous dystrophy: a variant of microvillous inclusion disease or a new entity?* *Hum Pathol*, 1994. 25(11): p. 1243-8.
16. Weeks, D.A., C.W. Zuppan, R.L. Malott, et al., *Microvillous inclusion disease with abundant vermiform, electron-lucent vesicles*. *Ultrastruct Pathol*, 2003. 27(5): p. 337-40.
17. Oliva, M.M., J.A. Perman, J.M. Saavedra, et al., *Successful intestinal transplantation for microvillus inclusion disease*. *Gastroenterology*, 1994. 106(3): p. 771-4.
18. Ruummele, F.M., D. Jan, F. Lacaille, et al., *New perspectives for children with microvillous inclusion disease: early small bowel transplantation*. *Transplantation*, 2004. 77(7): p. 1024-8.
19. Croft, N.M., A.G. Howatson, S.C. Ling, et al., *Microvillous inclusion disease: an evolving condition [In Process Citation]*. *J Pediatr Gastroenterol Nutr*, 2000. 31(2): p. 185-9 [MEDLINE record in process].
20. Goulet, O., M. Kedinger, N. Brousse, et al., *Intractable diarrhea of infancy with epithelial and basement membrane abnormalities*. *J Pediatr*, 1995. 127(2): p. 212-9.
21. Reifen, R.M., E. Cutz, A.M. Griffiths, et al., *Tufting enteropathy: a newly recognized clinicopathological entity associated with refractory diarrhea in infants*. *J Pediatr Gastroenterol Nutr*, 1994. 18(3): p. 379-85.
22. Patey, N., J.Y. Scoazec, B. Cuenod-Jabri, et al., *Distribution of cell adhesion molecules in infants with intestinal epithelial dysplasia (tufting enteropathy)*. *Gastroenterology*, 1997. 113(3): p. 833-43.
23. Goulet, O.J., N. Brousse, D. Canioni, et al., *Syndrome of intractable diarrhoea with persistent villous atrophy in early childhood: a clinicopathological survey of 47 cases [see comments]*. *J Pediatr Gastroenterol Nutr*, 1998. 26(2): p. 151-61.
24. Lachaux, A., R. Bouvier, I. Loras-Duclaux, et al., *Isolated deficient alpha6beta4 integrin expression in the gut associated with intractable diarrhea*. *J Pediatr Gastroenterol Nutr*, 1999. 29(4): p. 395-401.

25. Unsworth, J., P. Hutchins, J. Mitchell, et al., *Flat small intestinal mucosa and autoantibodies against the gut epithelium*. *J Pediatr Gastroenterol Nutr*, 1982. 1(4): p. 503-13.
26. Russo, P., *Enteropathies associated with chronic diarrhea and malabsorption*, ed. P. Russo, E. Ruchelli, and D. Piccoli. 2004, New York: Springer-Verlag. 63-99.
27. Russo, P.A., P. Brochu, E.G. Seidman, et al., *Autoimmune enteropathy*. *Pediatr Dev Pathol*, 1999. 2(1): p. 65-71.
28. Lachaux, A., I. Loras-Duclaux and R. Bouvier, *Autoimmune enteropathy in infants. Pathological study of the disease in two familial cases*. *Virchows Arch*, 1998. 433(5): p. 481-5.
29. Rogahn, D., C.P. Smith and A. Thomas, *Autoimmune enteropathy with goblet-cell antibodies*. *J R Soc Med*, 1999. 92(6): p. 311-2.
30. Corazza, G.R., F. Biagi, U. Volta, et al., *Autoimmune enteropathy and villous atrophy in adults*. *Lancet*, 1997. 350(9071): p. 106-9.
31. Mirakian, R., P. Collins and G.F. Bottazzo, *Autoimmune enteropathy in adults*. *Lancet*, 1997. 350(9082): p. 959-60.
32. Mitomi, H., S. Tanabe, M. Igarashi, et al., *Autoimmune enteropathy with severe atrophic gastritis and colitis in an adult: proposal of a generalized autoimmune disorder of the alimentary tract*. *Scand J Gastroenterol*, 1998. 33(7): p. 716-20.
33. Mirakian, R., A. Richardson, P.J. Milla, et al., *Protracted diarrhoea of infancy: evidence in support of an autoimmune variant*. *Br Med J (Clin Res Ed)*, 1986. 293(6555): p. 1132-6.
34. Moore, L., X. Xu, G. Davidson, et al., *Autoimmune enteropathy with anti-goblet cell antibodies*. *Hum Pathol*, 1995. 26(10): p. 1162-8.
35. Powell, B.R., N.R. Buist and P. Stenzel, *An X-linked syndrome of diarrhea, polyendocrinopathy, and fatal infection in infancy*. *J Pediatr*, 1982. 100(5): p. 731-7.
36. Bennett, C.L., R. Yoshioka, H. Kiyosawa, et al., *X-Linked syndrome of polyendocrinopathy, immune dysfunction, and diarrhea maps to Xp11.23-Xq13.3*. *Am J Hum Genet*, 2000. 66(2): p. 461-8.
37. Bennett, C.L., J. Christie, F. Ramsdell, et al., *The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3*. *Nat Genet*, 2001. 27(1): p. 20-1.
38. Wildin, R.S., F. Ramsdell, J. Peake, et al., *X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy*. *Nat Genet*, 2001. 27(1): p. 18-20.
39. Hori, S., T. Nomura and S. Sakaguchi, *Control of regulatory T cell development by the transcription factor Foxp3*. *Science*, 2003. 299(5609): p. 1057-61. Epub 2003 Jan 09.
40. Clark, L.B., M.W. Appleby, M.E. Brunkow, et al., *Cellular and molecular characterization of the scurfy mouse mutant*. *J Immunol*, 1999. 162(5): p. 2546-54.
41. Bousvaros, A., A.M. Leichtner, L. Book, et al., *Treatment of pediatric autoimmune enteropathy with tacrolimus (FK506)*. *Gastroenterology*, 1996. 111(1): p. 237-43.
42. Steffen, R., R. Wyllie, M. Kay, et al., *Autoimmune enteropathy in a pediatric patient: partial response to tacrolimus therapy*. *Clin Pediatr (Phila)*, 1997. 36(5): p. 295-9.
43. Girault, D., O. Goulet, F. Le Deist, et al., *Intractable infant diarrhea associated with phenotypic abnormalities and immunodeficiency*. *J Pediatr*, 1994. 125(1): p. 36-42.

44. Verloes, A., J. Lombet, Y. Lambert, et al., *Tricho-hepato-enteric syndrome: further delineation of a distinct syndrome with neonatal hemochromatosis phenotype, intractable diarrhea, and hair anomalies*. *Am J Med Genet*, 1997. 68(4): p. 391-5.
45. Conley, M.E., C.L. Park and S.D. Douglas, *Childhood common variable immunodeficiency with autoimmune disease*. *J Pediatr*, 1986. 108(6): p. 915-22.
46. Hausser, C., J.L. Virelizier, D. Buriot, et al., *Common variable hypogammaglobulinemia in children. Clinical and immunologic observations in 30 patients*. *Am J Dis Child*, 1983. 137(9): p. 833-7.
47. Washington, K., T.T. Stenzel, R.H. Buckley, et al., *Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia*. *Am J Surg Pathol*, 1996. 20(10): p. 1240-52.
48. Buckley, R.H., *Chapter 123 T, B, and NK-Cell Systems*, in *Nelson Textbook of pediatrics*, R.E. Behrman, R.M. Kliegman, and H.B. Jenson, Editors. 2000, W. B. Saunders company: Philadelphia. p. 590-606.
49. Seidman, E. and O. Goulet, *Primary Immunodeficiency Diseases*, in *Pediatric Gastrointestinal Disease*, A.M. Walker, et al., Editors. 2004, BC Decker: Hamilton, Ontario. p. 707-733.
50. Meini, A., N.M. Pillan, V. Villanacci, et al., *Prevalence and diagnosis of celiac disease in IgA-deficient children*. *Ann Allergy Asthma Immunol*, 1996. 77(4): p. 333-6.
51. Heneghan, M.A., F.M. Stevens, E.M. Cryan, et al., *Celiac sprue and immunodeficiency states: a 25-year review*. *J Clin Gastroenterol*, 1997. 25(2): p. 421-5.
52. Savilahti, E., *IgA deficiency in children. Immunoglobulin-containing cells in the intestinal mucosa, immunoglobulins in secretions and serum IgA levels*. *Clin Exp Immunol*, 1973. 13(3): p. 395-406.
53. Lai Ping So, A. and L. Mayer, *Gastrointestinal manifestations of primary immunodeficiency disorders*. *Semin Gastrointest Dis*, 1997. 8(1): p. 22-32.
54. Stephan, J.L., V. Vlekova, F. Le Deist, et al., *Severe combined immunodeficiency: a retrospective single-center study of clinical presentation and outcome in 117 patients*. *J Pediatr*, 1993. 123(4): p. 564-72.
55. Seidman, E.G., *Gastrointestinal Manifestations of Primary Immunodeficiency Diseases*, in *Pediatric Gastrointestinal Disease*, W.A. Walker, et al., Editors. 2000, B.C. decker: hamilton, Ontario. p. 525-547.
56. Jarvis, W.R., P.J. Middleton and E.W. Gelfand, *Significance of viral infections in severe combined immunodeficiency disease*. *Pediatr Infect Dis*, 1983. 2(3): p. 187-92.
57. Barton, L.L., S.L. Moussa, R.G. Villar, et al., *Gastrointestinal complications of chronic granulomatous disease: case report and literature review*. *Clin Pediatr (Phila)*, 1998. 37(4): p. 231-6.
58. Mitomi, H., T. Mikami, H. Takahashi, et al., *Colitis in chronic granulomatous disease resembling Crohn's disease: comparative analysis of CD68-positive cells between two disease entities*. *Dig Dis Sci*, 1999. 44(2): p. 452-6.
59. Fisher, J.E., A.R. Khan, L. Heitlinger, et al., *Chronic granulomatous disease of childhood with acute ulcerative colitis: a unique association*. *Pediatr Pathol*, 1987. 7(1): p. 91-6.
60. Isaacs, D., V.M. Wright, D.G. Shaw, et al., *Chronic granulomatous disease mimicking Crohn's disease*. *J Pediatr Gastroenterol Nutr*, 1985. 4(3): p. 498-501.

61. Harris, B.H. and E.T. Boles, Jr., *Intestinal lesions in chronic granulomatous disease of childhood*. J Pediatr Surg, 1973. 8(6): p. 955-6.
62. Werlin, S.L., M.J. Chusid, J. Caya, et al., *Colitis in chronic granulomatous disease*. Gastroenterology, 1982. 82(2): p. 328-31.