

بیمارستان حضرت امام حسین (ع) اصفهان
گروه کودکان دانشگاه علوم پزشکی اصفهان

IN The Name Of God

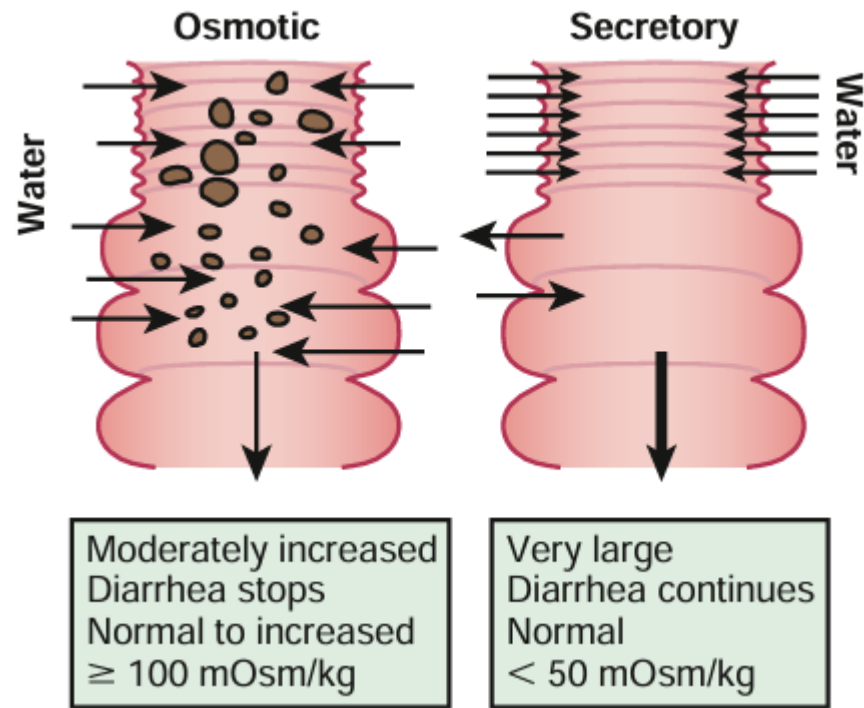
• ***Intractable diarrhea of infancy***

Dr. H.Saneian

خرداد ماه سال 1405

PATHOPHYSIOLOGY

- ▶ 1-**secretory**
- ▶ 2 -**osmotic**,
- ▶ 3- often diarrhea is a combination of **both** mechanisms.
- ▶ In many children chronic diarrhea may be caused by the **combination** of multiple mechanisms.
- ▶ 4- In addition, **inflammation** and **motility disorders** may contribute to diarrhea.
- ▶ The cessation of diarrhea after a 24- hour fasting trial may define “**diet- induced diarrhea**,” which is mainly **osmotic** in nature,
- ▶ whereas no or minimal change in stool volume and consistency despite fasting will suggest a **secretory** mechanism, also defined as “**electrolyte- transport- related diarrhea**.”



the main etiologies of chronic diarrhea in infants and children.

Table 388.1 Main Etiologies of Chronic Diarrhea in Children Older and Younger than 2 Years of Age		
ETIOLOGY	AGE <2 YR	AGE >2 YR
Infections	+++	+++
Postenteritis syndrome	+++	+++
Immune deficiency	++	Rare
Celiac disease	+++ (after gluten introduction)	+++
Food allergy	+++	+
Inflammatory bowel disease	+ (rare)	+++
Pancreatic insufficiency	++	++
Cholestasis and insufficient bile acids	++	++
Cystic fibrosis	++	+
Lactose intolerance	++ (mostly postinfectious)	+++
Intestinal lymphangiectasia	+	+
Motility disorders	++	Rare
Short bowel syndrome	+++	+
Toddler's and functional diarrhea	++	++
Excessive intake of fruit juices and fluids	++	++
Congenital diarrheal disorders, including structural enterocyte defects and enzymatic or transport malabsorption syndromes	++	Unlikely

Infectious:

- ▶ Enteric infections =the most frequent cause (both in **developing** and **industrialized** countries).
- ▶ In **developing countries**, comorbid conditions, such as HIV/AIDS, malaria, or TB, may result in malnutrition that impairs the child's immune response, thereby potentiating the likelihood of prolonging diarrhea or acquiring another enteric infection.
- ▶ Sequential infections with the **same** or **different** pathogens may also be responsible for chronic diarrhea.
- ▶ In **developing countries**, EAEC (entero adherent) and Giardia lamblia have been implicated in chronic diarrhea, whereas, in **developed countries**, chronic infectious diarrhea usually runs a **more benign course** and the etiology is **often viral**, with rotavirus and norovirus playing major roles

- ▶ **Opportunistic microorganisms** induce diarrhea exclusively, more severely, or for **more prolonged** periods, in **specific populations**, such as immunocompromised children.
- ▶ **Specific agents** cause chronic diarrhea or exacerbate diarrhea in many chronic diseases.
- ▶ **Clostridium difficile** or **CMV** act as opportunistic agents in patients with malignant diseases as well as in patients with IBD.
- ▶ **Cryptosporidium** may induce severe and protracted diarrhea in AIDS patients.

Table 388.2

Comparative List of Prevalent Agents and Conditions in Children with Persistent Infectious Diarrhea in Industrialized and Developing Countries

AGENT/DISEASE	
INDUSTRIALIZED COUNTRIES	DEVELOPING COUNTRIES
<i>Clostridium difficile</i>	Enterotoxigenic <i>E. coli</i>
Enterotoxigenic <i>Escherichia coli</i>	Atypical <i>E. coli</i>
Atypical <i>E. coli</i>	<i>Shigella</i> spp.
	Heat-stable/heat-labile enterotoxin-producing <i>E. coli</i>
Astrovirus	Rotavirus*
Norovirus	Cryptosporidium
Sapovirus	<i>Giardia lamblia</i>
Rotavirus*	Tropical sprue
Small intestinal bacterial overgrowth (SIBO)	
Postenteritis diarrhea syndrome	

*More frequent in industrialized than in developing countries as agent of chronic diarrhea.

Small intestinal bacterial overgrowth (SIBO)

results in chronic diarrhea by:

- ▶ either a direct interaction between the microorganism and the enterocytes,
- ▶ or the consequence of **deconjugation** and **dihydroxylation** of **bile salts** and **hydroxylation** of **fatty acids** due to an increased proliferation of bacteria in the proximal intestine.

Risk factors for SIBO in children include:

- ▶ acid- suppressive therapies,
- ▶ alterations in gastrointestinal (GI) motility and anatomy,
- ▶ poor sanitation conditions.

Postenteritis diarrhea syndrome

- ▶ is a clinic pathologic condition in which small intestinal **mucosal damage** persists after acute gastroenteritis.
- ▶ Cause ?
 - 1- Sensitization to food antigens,
 - 2- secondary disaccharidase deficiency,
 - 3- persistent infections,
 - 4- reinfection with another enteric pathogen
 - 5 - dysregulation of the intestinal microbiota.
 - 6- drugs side effects
 - 7- Functional diarrhea,(may be related to the pathogenesis of IBS).

Inflammatory/Immunologic:

- ▶ **Celiac disease** (reduction of intestinal absorptive surface is responsible for the diarrhea in celiac disease).
- ▶ **Food allergy** (mainly CMA ,) may present during infancy with chronic diarrhea (responds to withdrawal of the responsible food, + in EGID occasionally immune- suppressive therapy may be needed).
- ▶ **IBDs**, age of onset of IBD is broad, with rare cases described in the first few months
- ▶ **Autoimmune processes** may target the intestinal epithelium, **alone** or in association with **extraintestinal symptoms**.

Autoimmune enteropathy:

- is associated with the production of antienterocyte and antigoblet cell antibodies, primarily **IgA**, but also **IgG**, directed against components of the enterocyte brush border or cytoplasm and by a cell-mediated autoimmune response with mucosal T-cell activation.
- An X-linked immune-dysregulation, polyendocrinopathy, and enteropathy (IPEX syndrome) is associated with variable gene mutations and phenotypes of chronic diarrhea

CASE REPORT**Gastroenterology**

Intractable diarrhea in an infant—autoimmune enteropathy: A case report

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Abstract

Autoimmune enteropathy is a rare cause of chronic intractable diarrhea and is present in <1 in 100,000 infants. We report the case of a 9-month-old boy who presented with intractable diarrhea and vomiting. Genetic panel testing revealed a STAT3 heterozygous mutation in exon 6, suggesting infantile-onset multisystem autoimmune disease-1. The patient was initially treated with steroids and sulfasalazine. However, on tapering steroids, he had another episode of diarrhea and was subsequently put on baricitinib to which he responded.

KEYWORDS

baricitinib, gastroenteritis, malabsorption, STAT3, STAT3 mutation

- ▶ A 9-month-old male,
- ▶ second by birth order,
- ▶ born out of non-consanguineous marriage
- ▶ presented with **diarrhea for 1 month** and **vomiting for 2 weeks**.
- ▶ weight was 5.8 kg , length was 70 cm
- ▶ **perianal rash** which was suggestive of osmotic diarrhea.
- ▶ The child had been weaned onto solids including gluten-containing products before presentation.
The child was then diagnosed with persistent diarrhea with severe acute malnutrition.

- ▶ Blood investigations are depicted in Table 1.
- ▶ Stool routine microscopy and stool culture sensitivity were normal.
- ▶ Blood culture was negative.
- ▶ Tissue transglutaminase IgA was negative
- ▶ had normal levels of immunoglobulins IgM, IgG, IgA, and IgE.

TABLE 1 Investigations of the patient.

Investigations	Observed value	Normal values
Hemoglobin (gm/dL)	11.8	12–15.5
Total leukocyte count (cells/cumm)	21,500	4500–11,000
Platelet (cells/cumm)	660,000	150,000–450,000
SGOT (U/L)	35.7	<40
SGPT (U/L)	14.5	<40
GGT (U/L)	10	5–40
BUN (mg/dL)/Creatinine (mg/dL)	8.9/0.35	7–30/0.7–1.2
pH	7.18	7.35–7.45
HCO ₃ ⁻ (mEq/L)	6	22–26
C-reactive protein (mg/L)	1.7	
Sodium (mmol/L)	143	135–145
Potassium (mmol/L)	3.4	3.5–5
Chloride (mmol/L)	111	95–105
Free T3 (pg/mL)	2.17	2.0–4.4
Free T4 (ng/dL)	0.977	0.8–1.8
TSH (μIU/mL)	4.49	0.0–4.0

Free T3 (pg/mL)	2.17	2.0–4.4
Free T4 (ng/dL)	0.977	0.8–1.8
TSH (uIU/mL)	1.43	0.2–4.2
HbA1C	4.5%	<6%
Immunoglobulin G (g/l)	2.35	2.46–9.04
Immunoglobulin A (g/l)	0.72	0.16–0.5
Immunoglobulin M (g/l)	0.9	0.32–1.32
Immunoglobulin E (IU/ml)	17.80	0–34
Absolute B Lymphocytes (cumm)	1156	610–2600
Absolute T Lymphocytes (cumm)	4752	1900–5900
Absolute T _h Lymphocytes (cumm)	2312	1400–4300
Absolute T _c Lymphocytes (cumm)	1991	500–1700
Absolute NK cell (cumm)	450	160–950

The patient was started on:

- ▶ intravenous (IV) antibiotics,
- ▶ IV fluids,
- ▶ starter formula for SAM (75 kcal and 0.9 g protein/100 mL of milk) diet,

- ▶ shifted to a low lactose diet and multivitamins.

- ▶ Stool multiplex PCR was sent (which came back **negative**)

- ▶ an **aa-based formula** was started along with IV fluids while stopping all **sugar-containing syrups**.

▶ به دلیل عدم بهبودی:

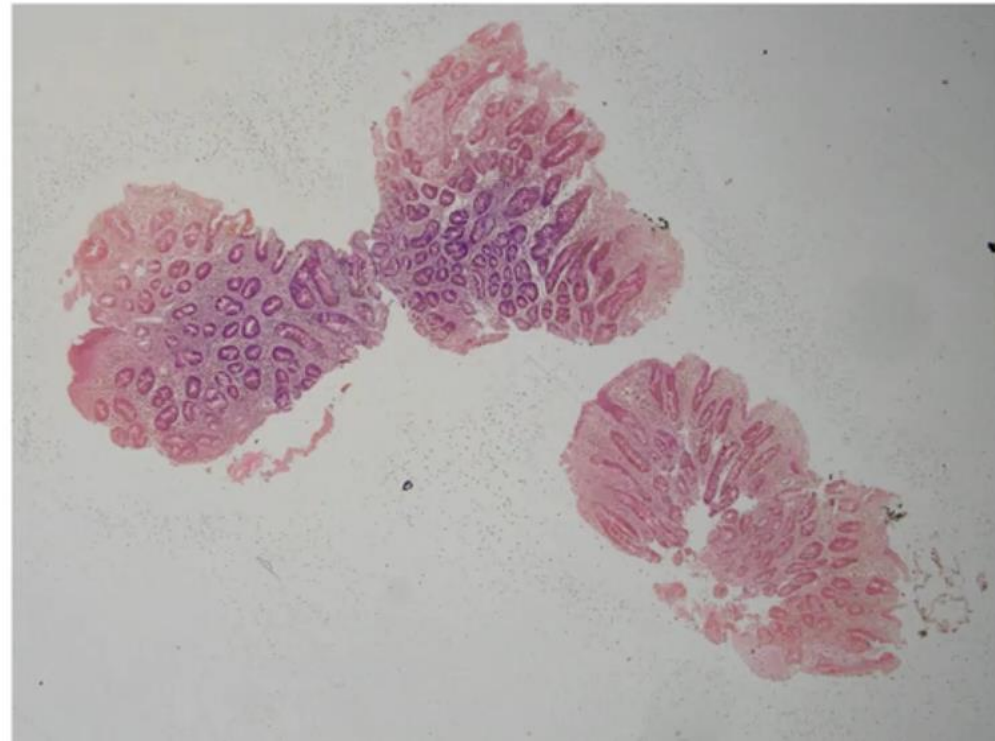
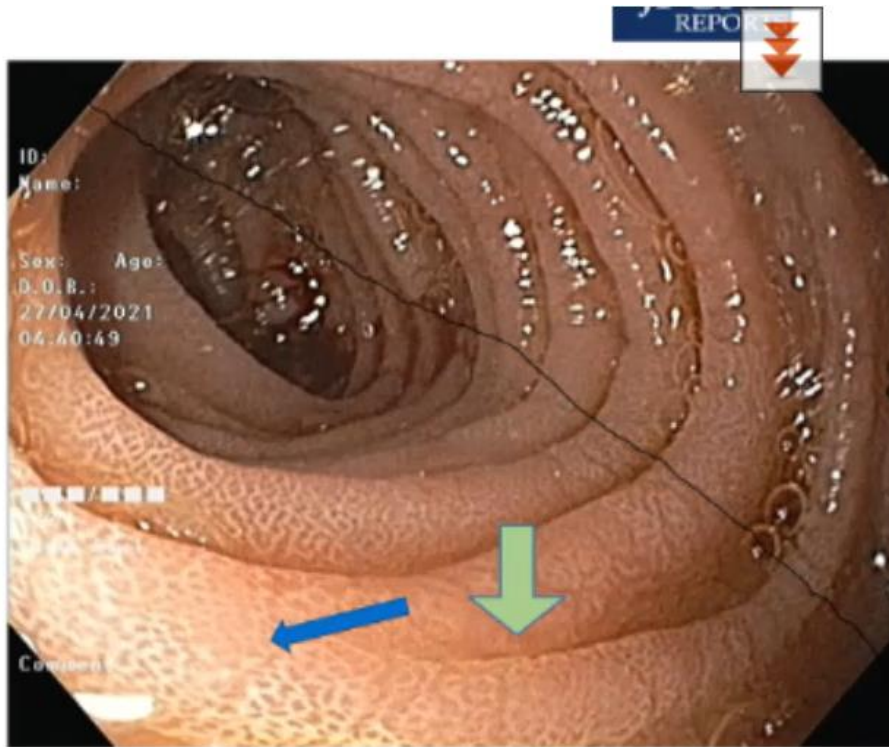
▶ ولی وجود : loose stools

Upper and lower GI endoscopy showed :

- ▶ diffuse whitish discoloration in the mucosa of the second part of the duodenum
- ▶ along with absence of villi
- ▶ scalloping sign
- ▶ diffuse edematous colonic mucosa,

histopathology showed:

- ▶ chronic active inflammation of the duodenum with moderate villous blunting
- ▶ mild chronic active colitis.



- ❑ *Sulphamethoxazole and trimethoprim* (Septran) combination was started with the continuation of an *amino acid-based formula* due to suspicion of tropical sprue.
- ❑ *Diarrhea* started decreasing and he *was discharged* from the hospital 2 months later, had a weight of 6.5 kg at the time of discharge, and passed 2-3 stools per day.
- ❑ He was continued on an *aa-based formula*.
- ❑ The patient was monitored weekly for weight gain, food input, and output.

- ▶ The patient presented 2 months later, when he was 13 months:
- ▶
- ▶ intractable diarrhea for a week and static weight after the **introduction of beetroot** with signs of dehydration and **hypovolemic shock**.
- ▶ He was managed in the intensive care unit with mechanical ventilation for 5 days.
- ▶ clinical exome sequencing was requested , and a heterozygous mutation in STAT 3 suggesting **Infantile Onset Multisystem Autoimmune Disease-1** (autosomal dominant) was found.
- ▶ Thyroid function tests and glycosylated hemoglobin were normal.

▶ on **oral prednisolone** at 1 mg/kg/day for 10 days followed by 2 mg/kg/day for the next 13 days but even after that, the patient showed persistent diarrhea, presence of fat globules in the stool, and a lack of weight gain.

▶ The patient was then started on **oral sulphasalazine** (50 mg/kg/day).

▶ After a month on the above therapy, there was **good clinical response** with resolution of diarrhea and consistent weight gain at 15 months of age.

▶ Steroids were slowly tapered and stopped after 10 months of initiation and sulfasalazine was continued but **diarrhea relapsed 1 month after stopping** steroid at 2 years of age and there was **weight loss**.

▶ **Oral prednisolone at 2 mg/kg/day** was restarted immediately and **baricitinib** (a JAK inhibitor) at a dose of 0.08 mg/kg/day was **introduced**.

▶ The steroid was **tapered after 3 weeks** and after 3 months of starting baricitinib, weight was 9.7 kg and diarrhea was under control.

- ▶ First-line treatment is usually = **steroids**
- ▶ followed by other forms of immunosuppressive therapy like mycophenolate mofetil (MMF), cyclosporine, and tacrolimus.⁵
- ▶ But MMF (2/5), Tacrolimus (1/4), Azathioprine (0/4), and Rituximab (1/3) all have **poor treatment outcomes**, .

▶ STAT 3 یک فاکتور رونویسی (transcription factor) است که بقای سلولی، تکثیر، تمایز و عملکرد مؤثر را تنظیم می‌کند.

▶ سیتوکین‌ها JAKها را فعال می‌کنند که باعث فسفوریلاسیون، دیمریزاسیون و جابجایی هسته‌ای STAT 3 می‌شود که منجر به expression of target genes میشود بنابراین، مهار JAK signaling در درمان جهش‌های STAT 3 GOF نقش دارد.

▶ JAK inhibitors برای درمان اختلال شدید تنظیم ایمنی در بیمارانی که جهش‌های افزایش عملکرد STAT1 or STAT3 دارند، استفاده شده‌اند و بهبود بالینی قابل توجهی در 10 نفر از 13 بیمار تحت درمان با JAKinibs مشاهده شده است

- ▶ پیوند سلول‌های بنیادی خون‌ساز (HSCT) **Hematopoietic stem cell transplantation** به عنوان یک درمان قطعی برای افراد مبتلا به AIE مورد استفاده قرار گرفته است و عملکرد آن در حال گسترش است.
- ▶ در بیمارانی که بیماری در حال پیشرفت دارند و درمان دارویی به کنترل بهینه بیماری منجر نشده است، HSCT مورد توجه قرار می‌گیرد.
- ▶ با پیوند **donor CD4 + CD25 + FOXP3+ regulatory T cells** که می‌توانند به طور مؤثر سلول‌های autoreactive T and B cells را سرکوب کنند، علائم با HSCT برطرف می‌شوند.
- ▶ داده‌های طولی منتشر شده در حال حاضر برای تعیین نهایی نقش و نتیجه طولانی مدت HSCT با توجه به multisystem expression of STAT3 کافی نیستند.
- ▶ این موضوع همراه با جنبه‌های عوارض مرتبط با پیوند به عنوان بخشی از یک بحث چند رشته‌ای با حضور والدین به دقت بررسی خواهد شد.
- ▶ میزان علائم (از جمله fecal output)، وسعت و شدت ضایعات بافتی در طول دستگاه گوارش و وجود درگیری extra-intestinal، همگی بر پیش‌آگهی AIE تأثیر می‌گذارند.

- ▶ **Immune deficiency** can present as chronic diarrhea in children.
- ▶ In these cases (for example, **SCID or AIDS**) the child can be infected by an **opportunistic** pathogen, can exhibit a **persistent diarrhea** due to a pathogen usually causing an acute gastroenteritis, or be infected by multiple and recurrent different pathogens causing mucosal damage to the intestines.
- ▶
- ▶ Other **immunoregulatory defects**, found in patients with agammaglobulinemia, isolated immunoglobulin A deficiency, and common variable immunodeficiency disorder, may result in **mild** persistent diarrhea.

Pancreatic Deficiency

- ▶ Chronic diarrhea may be the manifestation of maldigestion caused by exocrine pancreatic disorders .
- ▶ In most patients with cystic fibrosis, exocrine pancreatic insufficiency results in steatorrhea and protein malabsorption.
- ▶ In Shwachman- Diamond syndrome, exocrine pancreatic hypoplasia may be associated with neutropenia, bone changes, and intestinal protein- losing enteropathy.
- ▶ Specific isolated pancreatic enzyme defects, such as lipase deficiency, result in fat and/or protein malabsorption.
- ▶ **Familial pancreatitis**, associated with a pathogenic variant in the trypsinogen gene, may be associated with exocrine pancreatic insufficiency and chronic diarrhea. Pathogenic variants in CFTR, CTRC, PRSS1, PRSS2, SPINK 1, and SPINK 5 are associated with hereditary pancreatitis.

Liver and Bile Acids Disorders

- ▶ Liver disorders and cholestasis may lead to a reduction in the bile salts pool resulting in fat malabsorption causing chronic diarrhea in the form of steatorrhea.
- ▶ Bile acid loss may be associated with diseases affecting the terminal ileum, such as Crohn disease, or following ileal resection.
- ▶ In **primary bile acid malabsorption**, neonates and young infants present with chronic diarrhea and fat malabsorption caused by pathogenic variants of the **ileal bile transporter gene**.
- ▶ In addition to the **fat malabsorption**, the bile acid loss from the intestinal lumen is a form of **secretory diarrhea** by itself (called **cholerheic diarrhea** or **choleretic diarrhea**, which is usually associated with **significant diaper dermatitis**).

Carbohydrate Malabsorption:

- ▶ **Rare** genetic pathogenic variants (see Chapters 385.8 and 385.10) can cause carbohydrate malabsorption.
- ▶ More commonly, **lactose intolerance** is secondary to lactase deficiency caused by intestinal mucosal damage (usually as part of postenteritis syndrome, which is a self-limited process).
- ▶ Depending on **ethnicity**, a *progressive, age-related, loss of lactase activity* may *begin around 7 years of age* and affects **# 80% of the non- White population**, and ***acquired hypolactasia*** may be responsible for **chronic diarrhea in older** children receiving cow's milk (***adult- type lactase deficiency***).
- ▶ Similarly, **fructose malabsorption** is common in **Western** countries with estimates as high as **40% of the population**. These individuals can not absorb fructose and often develop bloating, abdominal pain, diarrhea, and flatulence.

- ▶ Typically, they (**fructose malabsorption**) do not have liver disease.
- ▶ This is in contrast to hereditary fructose intolerance, a **rare** genetic disorder with incidence estimated to be 1 in 20,000- 30,000.
- ▶
- ▶ This disease is associated with pathogenic variants in the ASDOB gene that encodes for the aldolase B enzyme that is found primarily in the liver and is involved in the metabolism of fructose.
- ▶ Individuals with hereditary fructose intolerance may have nausea, abdominal pain/bloating, vomiting, diarrhea, and hypoglycemia. Continued ingestion of fructose results in **hepatomegaly** and eventually **cirrhosis**.

Protein- Losing Enteropathy

- ▶ Chronic diarrhea can be the manifestation of obstructed intestinal lymphatic drainage, causing protein- losing enteropathy with steatorrhea, diarrhea, and lymphopenia.
- ▶ Early- onset **protein- losing enteropathy** and **lymphangiectasia**, together with **complement activation**, could be associated with **congenital CD55 deficiency**.
- ▶ Infantile- onset **severe protein- losing enteropathy** and **altered lipid metabolism** could be attributed to pathogenic variants in **DGAT1**.
- ▶ Along with intestinal lymphangiectasia, many diseases that cause intestinal mucosal injury can also result in a **secondary protein-losing enteropathy**, characterized by low serum protein levels and elevated fecal α 1- antitrypsin (see Chapter 385.2).

Motility Disorders

- ▶ Disorders of intestinal motility include **abnormal** development and function of the enteric nervous system, such as in **Hirschsprung disease** and **pediatric intestinal pseudoobstruction (PIPO)**, previously termed **chronic intestinal pseudoobstruction**.
- ▶ PIPO encompasses both the neurogenic and the myogenic forms, and is sometimes associated with genitourinary manifestations.
- ▶ Other motility disorders may be secondary to extraintestinal disorders, such as in **hyperthyroidism** and **scleroderma**.
- ▶ Motility disorders are associated with either constipation or diarrhea, or both, with the former usually dominating the clinical picture.

Short Bowel Syndrome(SBS)

- ▶ SBS is the single most frequent etiology of intestinal failure in children .
- ▶ Many intestinal abnormalities such as **stenosis**, **segmental atresia**, **gastroschisis**, and **malrotation** may require surgical resection, but the most frequent primary cause of short bowel is NEC.
- ▶ Rarely, a child can be born with **congenital short bowel**.
- ▶ In these conditions, the residual intestine may be insufficient to carry on its digestive-absorptive functions, resulting in severe chronic diarrhea, malnutrition, and failure to thrive, requiring long- term treatment with parenteral nutrition.

- ▶ شیرخوار 6.5 ماهه ای که حاصل ازدواج غیر فامیلی با وزن هنگام تولد ۲۹۳۰ گرم بوده، به دلیل اسهال مزمن از ۳ روزگی بستری می شود.
- ▶ تعداد دفعات مدفوع ۸ تا ۱۰ بار در روز بود که با ویژگی‌های اسهال آبکی همراه با مقداری مخاط در مدفوع و گاهی اوقات با چند لکه خون همراه بود.
- ▶ عدم تحمل لاکتوز و آلرژی به پروتئین شیر گاو (CMPA) مشکوک بودند و مکمل لاکتاز شروع شد. برای نوزادی که کاملاً از شیر مادر تغذیه می‌شد، مادرش رژیم غذایی کاملاً پرهیز از آلرژن (شیر گاو، سویا، تخم مرغ و آجیل) را شروع کرد، اما تأثیر کمی داشت.
- ▶ در سن ۳ ماهگی، یک شیر خشک مبتنی بر پروتئین هیدرولیز شده (بدون لاکتوز و فشار اسمزی پایین ۱۹۸ میلی اسمول بر کیلوگرم) شروع شد که بهبود کمی در علائم او داشت.
- ▶ سپس یک شیر خشک مبتنی بر اسید آمینه (بدون لاکتوز) شروع شد، اما با موفقیت محدودی همراه بود.
- ▶ آندوسکوپی مری و معده، کولونوسکوپی و سی تی اسکن شکم در یک بیمارستان قبلی بدون ناهنجاری واضح انجام شده بود.

- ▶ در سن ۶/۵ ماهگی، او با اسهال مزمن شدید، هیپوآلبومینمی مقاوم به درمان و اختلال رشد به بیمارستان ما منتقل شد.
- ▶ در زمان بستری، وزن و قد او به ترتیب ۵/۳ کیلوگرم و ۶۳/۰ سانتی‌متر بود.
- ▶ پروتئین کل و آلبومین سرم او به ترتیب 2.8 و 1.8 بود.
- ▶ او همچنین سطح ترانس آمیناز بالا، هیپوگاماگلوبولینمی و اختلالات انعقادی داشت .
- ▶ هیچ ناهنجاری قابل توجهی در سطح سدیم، پتاسیم و کلرید خون وجود نداشت.
- ▶ اطلاعات دقیق در مورد آزمایش‌های آزمایشگاهی در جدول ۱ ارائه شده است.
- ▶ او مشکوک به CODE با انتروپاتی از دست دهنده پروتئین (PLE) بود.

	Case 1	Case 2	Reference value
Age (month)	6.5	7.5	—
Total protein (TP, g/L)	29.8	29.2	55–75
Albumin (Alb, g/L)	18.28	18.62	39–54
Hemoglobin (Hb, g/L)	131	105	97–141
Lymphocyte count ($\times 10^9/L$)	2.09	1.19	2.50–9.0
pH value	7.38	7.33	7.35–7.45
Serum sodium (Na^+ , mmol/L)	132	133	136–146
Serum potassium (K^+ , mmol/L)	3.5	2.8	3.5–5.3
Serum chlorine (Cl^- , mmol/L)	110	112	98–106
Alanine transaminase (ALT, U/L)	135.52	106.11	8–71
Aspartate transaminase (AST, U/L)	145.86	92.94	21–80
Immunoglobulin G (IgG, g/L)	0.70	1.4	3.5–8.9
Immunoglobulin M (IgM, g/L)	0.41	0.26	0.33–1.25
Immunoglobulin A (IgA, g/L)	0.24	0.29	0.06–0.54
Activated partial thromboplastin time (APTT, s)	69.5	45.2	28–45
International normalized ratio (INR)	1.53	1.13	0.8–1.2
Prothrombin time (PT, s)	18.6	14.6	11–14.5
Prothrombin time activity (PTA, %)	51.0	79.0	80–120
Fibrinogen (FIB, g/L)	1.55	1.34	2–4

- ▶ پس از الگوریتم تشخیصی برای اسهال آبکی، یک دوره ناشتایی به مدت ۴۸ ساعت آغاز شد که با بهبود قابل توجه در میزان دفع اسهال همراه بود، که نشان دهنده اسهال ناشی از رژیم غذایی بود.
- ▶ آندوسکوپی مری-گاسترودئودنوم، کولونوسکوپی، ارزیابی بافت شناسی، تحقیقات ایمونولوژیکی و WES مبتنی بر خانواده انجام شد.
- ▶ آندوسکوپی مری-گاسترودئودنوم و کولونوسکوپی هیچ ناهنجاری را نشان ندادند. ارزیابی بافت شناسی هیچ نشانه‌ای از انتروپاتی خودایمنی (AIE)، بیماری میکروویلی اینکلوزن (MVID) یا انتروپاتی مادرزادی تافتینگ (CTE) را نشان نداد.
- ▶ هیچ گونه بیماری‌زایی توسط WES شناسایی نشد.

Intestinal malrotation به طور اتفاقی در سی‌تی‌اسکن شکم (شکل A1) تشخیص داده شد.

Upper gastrointestinal imaging (UGI) and transabdominal ultrasonography این یافته را تأیید کردند.

پس از بحث گسترده با اعضای تیم جراحی به بخش جراحی کودکان ارجاع شد.

در طول عمل لاپاروسکوپی، intestinal malrotation with a 270° chronic midgut volvulus تشخیص داده شد. همچنین مشخص شد که بخشی از روده کوچک به مزوکولون سیگموئید چسبیده است. هیچ نشانه‌ای از ایسکمی یا نکروز در روده کوچک وجود نداشت.

بیمار تحت عمل Ladd's procedure, adhesiolysis, and an appendectomy قرار گرفت.

پس از عمل، علائم اصلی اسهال مزمن و هیپوآلبومینمی به تدریج تسکین یافت و افزایش وزن او بهبود یافت.

علائم اسهال 4 ماه پس از جراحی به طور کامل برطرف شد.

یک سال پس از عمل، نیازی به تزریق مکرر آلبومین و ایمونوگلوبولین نبود.

آخرین پیگیری ۲۶ ماه پس از عمل انجام شد. او هیچ علامتی از اسهال نداشت.

بدون هیچ درمان پزشکی اضافی، آلبومین سرم بیمار طبیعی بود و سوء تغذیه او به تدریج بهبود یافت.

وزن و قد او به ترتیب ۱۳/۵ کیلوگرم و ۹۵ سانتی‌متر بود

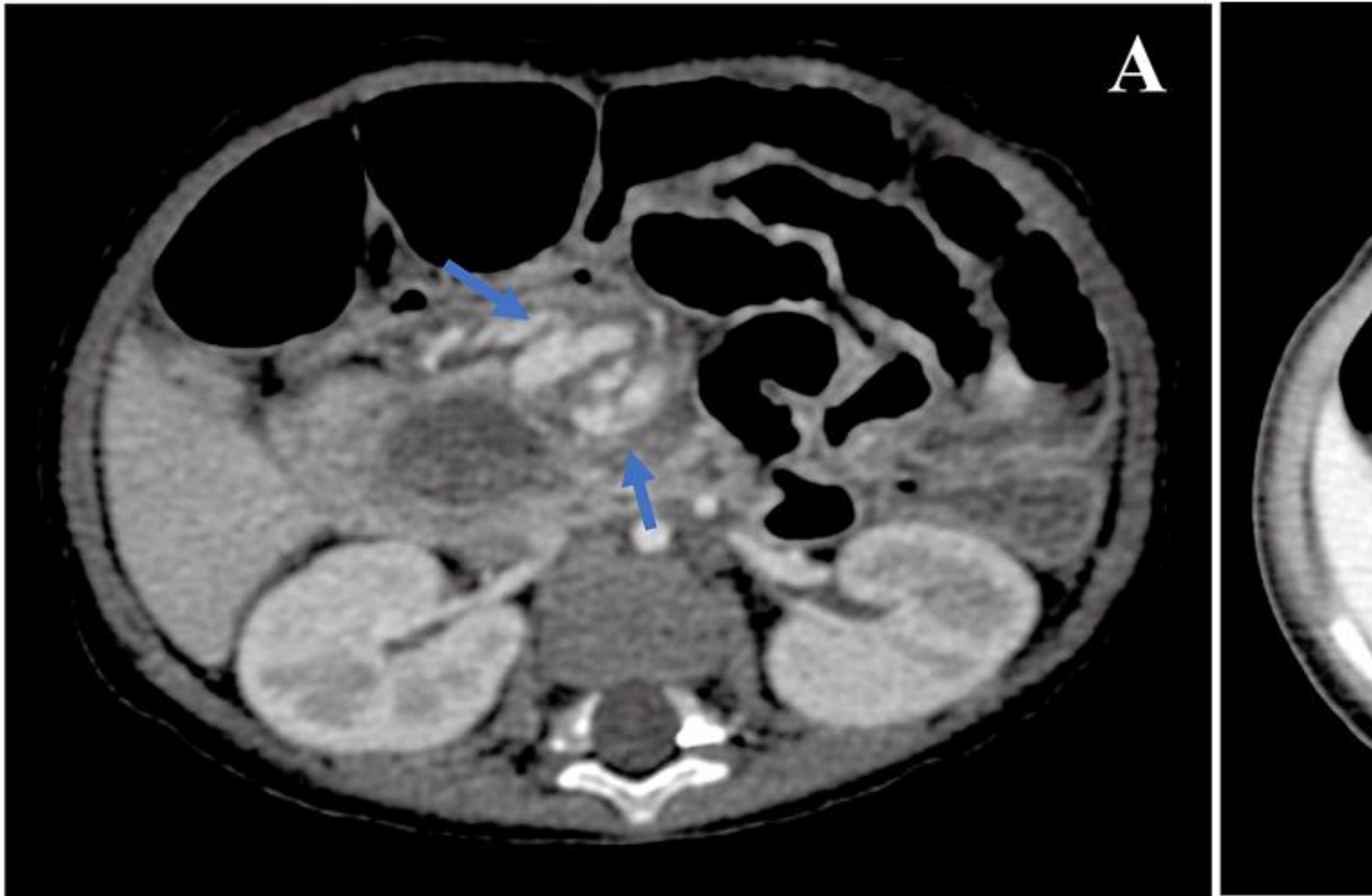


FIGURE 1
CT images. Whirlpool sign in the superior mesenteric vessel's branches was detected

Nonspecific Diarrhea, Including Toddler's Diarrhea

- ▶ The most **benign** and **common** etiology of chronic diarrhea is **non specific diarrhea** that encompasses functional diarrhea (or **toddler's diarrhea**) in children < 4 years of age and **irritable bowel syndrome** in those, usually, 5 years of age and older.
- ▶ Toddler's diarrhea is defined by the **daily painless recurrent** passage of four or more large unformed stools, for 4 or more weeks, with onset in **infancy** or **pre school years**.
- ▶ **Night-time defecation** is usually **absent** (Awakening at night to pass stool, beyond the period of infancy, is **often** a sign of an **organic cause** of diarrhea).
- ▶
- ▶ The child appears **unperturbed** by the diarrhea, there is **no evidence of FTT**, and the symptoms resolve spontaneously by **school age**.
- ▶

- ▶ Diarrhea may also be the result of an **excessive intake of fluids and nonabsorbable carbohydrates.**
- ▶ If the child's fluid intake was $>150 \text{ mL/kg/24 hr}$, fluid intake should be reduced not to exceed 90 mL/kg/24 hr to decrease the stool frequency and volume.
- ▶ If the dietary history suggests that the child is ingesting significant amounts of fruit juice, especially apple juice, then the consumption of juice should be decreased.
- ▶ Sorbitol, which is a nonabsorbable sugar, is found in apple, pear, and prune juices and often causes diarrhea in toddlers.
- ▶ Moreover, apple and pear juices contain higher amounts of fructose than glucose, a feature postulated to cause diarrhea in toddlers.
- ▶ In older children, irritable bowel syndrome is often associated with abdominal pain and may be related to anxiety, depression, and other psychological disturbances (see Chapter 389).
- ▶ When the cause of the diarrhea remains undetermined and the clinical course is inconsistent with organic disorders, **factitious** disorder by proxy should be considered.

Congenital Diarrheal Disorders:

- ▶ The **most severe etiology** of chronic diarrhea includes a number of **heterogeneous congenital** conditions leading to syndromes often referred to as **intractable or protracted diarrhea**.
- ▶ The genetic and molecular basis of many causes of protracted diarrhea has been identified recently, and the classification of **congenital diarrheal disorders (CDDs)** has been proposed, also referred to as **congenital diarrheas and enteropathies (CODEs)**.
- ▶ These terms represent a group of rare but **severe** enteropathies, with a **similar clinical presentation** despite **different pathogenesis** and *outcome*.
- ▶ Often **severe** diarrhea (secretory, osmotic, or combined) presents at birth or shortly thereafter, but in **milder** forms diarrhea may go unrecognized for years.

► *CDDs can be classified in **four** groups:*

- 1- defects of digestion, absorption, and transport of nutrients and electrolytes;
- 2- defects of enterocyte differentiation and polarization;
- 3- defects of enteroendocrine cell (EEC) differentiation;
- 4- defects of modulation of intestinal immune response.

Table 388.3 Classification of Congenital Diarrheal Disorders Based on Their Molecular Defect and Their Inheritance

DEFECTS OF DIGESTION, ABSORPTION, AND TRANSPORT OF NUTRIENTS AND ELECTROLYTES				
DISEASE	GENE NAME	GENE LOCATION	TRANSMISSION AND INCIDENCE	MECHANISM
GENES ENCODING BRUSH-BORDER ENZYMES				
Congenital lactase deficiency (LD)	<i>LCT</i>	2q21.3	AR, 1 in 60,000 in Finland; lower in other ethnic groups	Osmotic
Congenital sucrase-isomaltase deficiency (SID)	<i>SI</i>	3q26.1	AR, 1 in 5,000; higher incidence in Greenland, Alaska, and Canada	Osmotic
Congenital maltase-glucoamylase deficiency (MGD)	Not defined	—	Few cases described	Osmotic
GENES ENCODING MEMBRANE CARRIERS				
Glucose-galactose malabsorption (GGM)	<i>SLC5A1</i>	22q13.1	AR, few hundred cases described	Osmotic
Fructose malabsorption (FM)	Not defined	—	Up to 40%	Osmotic
Fanconi-Bickel syndrome (FBS)	<i>SLC2A2</i>	3q26.2	AR, rare, higher frequency in consanguineous	Osmotic
Acrodermatitis enteropathica (ADE)	<i>SLC39A4</i>	8q24.3	AR, 1 in 500,000	Osmotic
Congenital chloride diarrhea (CCD)	<i>SLC26A3</i>	7q31.1	AR, sporadic; frequent in some ethnicities	Osmotic
Lysinuric protein intolerance (LPI)	<i>SLC7A7</i>	14q11.2	AR, about 1 in 60,000 in Finland and Japan; rare in other ethnic groups	Osmotic
Primary bile acid malabsorption (PBAM)	<i>SLC10A2</i> <i>SLC51B</i>	13q33.1 15q22.31	AR	Secretory
Cystic fibrosis (CF)	<i>CFTR</i>	7q31.2	AR, 1 in 2,500	Osmotic
GENES ENCODING PANCREATIC ENZYMES				
Enterokinase deficiency (EKD)	<i>PRSS7</i>	21q21	AR	Osmotic
Hereditary pancreatitis (HP)	<i>PRSS1</i> <i>PRSS2</i> <i>SPINK1</i> <i>CTRC</i> <i>CFTR</i>	7q34 7q34 5q32 1p36.21 7q31.2	AD, cases with compound pathogenic variants in different genes; <i>SPINK1</i> pathogenic variants may also cause tropical pancreatitis	Osmotic, malabsorption
Congenital absence of pancreatic lipase (APL)	<i>PNLIP</i>	10q25.3	AR	Osmotic, malabsorption
GENES ENCODING PROTEINS OF LIPOPROTEIN METABOLISM				
Abetalipoproteinemia (ALP)	<i>MTP</i>	4q27	AR, about 100 cases described;	Osmotic

GENES ENCODING OTHER TYPES OF PROTEINS				
Congenital sodium diarrhea (CSD)	<i>SPINT2</i> (only syndromic CSD) <i>SLC9A3</i>	19q13.2 5p15.33	AR	Osmotic
Shwachman-Diamond syndrome (SDS)	<i>SBDS</i>	7q11	AR	Osmotic
Activating guanylate cyclase-C pathogenic variant	<i>GUCY2C</i>	12p12.3	AD	Secretory
GENES ENCODING FOR OTHER ENZYMES				
Defect in triglyceride synthesis	<i>DGAT1</i>	8q24.3	AR	Protein-losing enteropathy
DEFECTS OF ENTEROCYTE DIFFERENTIATION AND POLARIZATION				
Microvillus inclusion disease (MVID)	<i>MYO5B</i> <i>STX3</i>	18q21.1 11q12.1	AR; rare	Secretory
Congenital tufting enteropathy (CTE)	<i>EPCAM</i>	2p21	AR; 1 in 50,000-100,000; higher among Arabs	Secretory
Trichohepatoenteric syndrome (THE)	<i>TTC37</i> <i>SKIV2L</i>	5q15 6p21.33	AR; 1 in 400,000	Secretory
Neonatal-onset chronic diarrhea-9 (DIAR9)	<i>WNT2B</i>	1p13.2	AR; few cases described	Osmotic

Continued

Table 388.3

Classification of Congenital Diarrheal Disorders Based on Their Molecular Defect and Their Inheritance—cont'd

DEFECTS OF DIGESTION, ABSORPTION, AND TRANSPORT OF NUTRIENTS AND ELECTROLYTES

DISEASE	GENE NAME	GENE LOCATION	TRANSMISSION AND INCIDENCE	MECHANISM
DEFECTS OF ENTEROENDOCRINE CELL DIFFERENTIATION				
Congenital malabsorptive diarrhea (CMD), Enteric anendocrinosis	<i>NEUROG3</i>	10q22.1	AR; few cases described	Osmotic
Proprotein convertase 1/3 deficiency (PCD)	<i>PCSK1</i>	5q15	AR	Osmotic
Intractable malabsorptive diarrhea of infancy (DIAR11)	<i>PERCC1</i>	16p13.3	AR; few cases described in Jewish Iraqi families	Presumed impaired function of enteroendocrine cells (EECs)
DEFECTS OF MODULATION OF INTESTINAL IMMUNE RESPONSE				
Autoimmune polyglandular syndrome type 1 (APS1)	<i>AIRE</i>	21q22.3	AR; AD (1 family)	Inflammatory
Immune dysfunction, polyendocrinopathy, X-linked (IPEX)	<i>FOXP3</i>	Xp11.23	X-linked (autosomal cases described), very rare	Inflammatory
IPEX-like syndrome	<i>CD25</i> <i>STAT5b</i> <i>STAT3</i> <i>STAT1(GOF)</i> <i>LRBA</i> <i>CTLA4</i>	Multiple	Not X-linked	Inflammatory
CD55 deficiency	<i>CD55</i>	1q32.2	AR, rare	Protein-losing enteropathy

AD, Autosomal dominant; AR, autosomal recessive; GOF, gain of function.

- ▶ Although **CDDs** are **rare** diseases, in most specific disorders the **genetic defect** and **transmission** are known.
- ▶ The incidence of genetic disorders associated with CDD can range from :
- ▶ 1 in 2,500 for cystic fibrosis,
- ▶ 1 in 5,000 for sucrose- isomaltase deficiency,
- ▶ 1 in 60,000 for congenital lactase deficiency,
- ▶ 1 in 400,000 for trichohepatoenteric syndrome.

- ▶ For **most CDDs**, such as IPEX syndrome or autoimmune polyglandular syndrome type 1, the clinical application of exome sequencing is likely to increase identification of more patients with these **rare** causes of chronic diarrhea.
- ▶ **Selected CDDs** are more frequent in ethnic groups where consanguineous marriages are common, or in some geographic areas because of founder effects.
- ▶ **Congenital lactase deficiency** is more common in **Finland**;
- ▶ **lysinuric protein intolerance** has a higher incidence either in **Finland** and in **Japan** because of founder effect, and a specific pathogenic variant is typically found in each of the two ethnic groups.

- ▶ A defect in the **DGAT1 gene** was first identified using **WES** in an Ashkenazi Jewish family and associated with the early onset of **vomiting** and **nonbloody diarrhea** with **protein-losing enteropathy**.
- ▶ In few families of **Jewish Iraqi** origin with intractable diarrhea of infancy, a noncoding deletion was **recently** identified on **chromosome 16p13**, presumably leading to **impairment in EEC function**.
- ▶ For specific CDDs see Chapters 385.2 and 385.10.

- ▶ Most cases of protracted diarrhea syndrome *are not easily* treated.
- ▶ The natural history of protracted diarrhea is related to the primary intestinal disease or the specific defect in nutrient absorption.
- ▶ Although some specific conditions may improve with nutritional therapy and dietary eliminations (for example, glucose- galactose malabsorption or congenital protein-losing enteropathy), most cases of CDDs result in chronic intestinal failure requiring long- term parenteral nutrition, with poorer prognosis, and are more likely to be candidates for intestinal transplantation (see Chapter 386).
- ▶ Some late- onset CDDs may be relatively mild and are recognized only later in life.

EVALUATION OF PATIENTS

- ▶ **Early onset in the neonatal period** is rare and may suggest a **congenital** or **severe condition** (i.e. **VEO-IBD**); however, **infections** and **food allergy** are more frequent in this age group, and together with GI malformations should be high on the differential diagnosis.
- ▶ **In later infancy and up to 2 years of age**, **infections** and **allergies** are the most common causes, while inflammatory diseases are more frequent in older children and adolescents.
- ▶ **Celiac disease** as well as functional nonspecific diarrhea should always be considered independently of age because of their relatively high frequency at all ages beyond early infancy.

Some useful Specific clues

- ▶ A history of **polyhydramnios** is consistent with **congenital chloride/ sodium diarrhea** (where a typical sonographic finding of dilated fetal bowel loops is present), **microvillus inclusion disease**, **cystic fibrosis**, and **other CDDs**, as well as a family history of a **chronic or intractable diarrhea in a relative** presenting in the first month of life, and particularly consanguinity.
- ▶ An **acute onset of diarrhea that runs a protracted** course suggests **postenteritis diarrhea**, **secondary lactase deficiency**, **SIBO**, or the **onset of nonspecific functional diarrhea**.
- ▶ The **association of diarrhea with specific foods** may indicate a nutrient basis, such as intolerance to selected nutrients (fructose).

- ▶ In infants with chronic diarrhea, **feeding history** must be carefully obtained, providing clues for **allergy** or **specific food intolerance**, such as cow's milk protein allergy or sucrose- isomaltase deficiency.
- ▶ **Signs of general inflammation** such as fever, mucoid or bloody stools, and abdominal pain may suggest IBD.
- ▶ The presence of **eczema** or **asthma** is associated with an **allergic disorder**,
- ▶ **specific extraintestinal** manifestations (arthritis, diabetes, thrombocytopenia, etc.) may suggest an **autoimmune disease**.
- ▶ **Specific skin lesions** may be suggestive of **acrodermatitis enteropathica**, which might respond to zinc supplementation.
- ▶ Typical **facial abnormalities** and woolly hair are associated with **phenotypic diarrhea** (trichohepatoenteric syndrome).

INVESTIGATIONS

- ▶ **Microbiologic investigation** should include a thorough list of intestinal bacterial, viral, and protozoan pathogens.
- ▶ Proximal intestinal bacterial overgrowth may be determined using the **lactulose hydrogen breath test**, but false- positive tests are common .
- ▶ Initial investigations of a child with chronic diarrhea beyond the period of infancy should always include an assessment of intestinal inflammation using fecal markers as **calprotectin or lactoferrin**, and **serology for celiac disease** .
- ▶ The role of **intestinal mucosal biopsy** is determined by the noninvasive diagnostic evaluation in consultation with a pediatric gastroenterologist.

► Noninvasive assessment of digestive- absorptive function and of intestinal inflammation plays a key role in the diagnostic workup (Table 388.4).

Table 388.4 Noninvasive Tests for Intestinal Digestive–Absorptive Function and Inflammation

TEST	NORMAL VALUES	IMPLICATION
α_1 -Antitripsin concentration	<0.9 mg/g	Increased intestinal permeability/protein loss
Steatocrit	<2.5%-fold (older than 2 yr) increase over age-related values (younger than 2 yr)	Fat malabsorption
Fecal-reducing substances	Absent	Carbohydrate malabsorption
Elastase concentration	>200 μ g/g	Pancreatic function
Chymotrypsin concentration	>7.5 units/g >375 units/24 hr	Pancreatic function
Fecal occult blood	Absent	Blood loss in the stools/inflammation
Fecal calprotectin concentration	<100 μ g/g (in children upto 4 yr of age) <50 μ g/g (older than 4 yr)	Intestinal inflammation
Fecal leukocytes	<5 per microscopic field	Colonic inflammation
Fecal lactoferrin	Absent	Inflammation
Nitric oxide in rectal dialysate	<5 μ M of $\text{NO}_2^-/\text{NO}_3^-$	Rectal inflammation
Dual sugar (cellobiose/mannitol) absorption test	Urine excretion ratio: 0.010 ± 0.018	Increased intestinal permeability
Xylose oral load	25 mg/dL	Reduced intestinal surface

- It is also important to measure Cl^- concentration in the stool to rule out congenital chloride diarrhea, which is characterized by low osmolar gap combined with high fecal Cl^- loss ($>90 \text{ mmol/L}$).

- ▶ **Histology** is important in establishing mucosal involvement, noting changes in the epithelial cells and villus/crypt ratio, presence of mucosal inflammation or in identifying specific intracellular inclusion bodies caused by pathogens, such as cytomegalovirus, or the presence of parasites.
- ▶ Electron microscopy is essential to detect subcellular structural abnormalities such as microvillus inclusion disease, though the latter can be diagnosed with specific staining of the basal membrane on regular biopsies.
- ▶ Immunohistochemistry allows the study of mucosal immunity as well as of other cell types (smooth muscle cells and enteric neuronal cells).

Imaging

- ▶ Abdominal **ultrasound** may help in detecting **liver** and **pancreatic** abnormalities or an increase in bowel wall thickness that suggests **IBD**.
- ▶ A preliminary plain abdominal **x-ray** is useful for detection of abdominal distention, suggestive of intestinal **obstruction**, or increased **retention of colonic feces**.
- ▶ Intramural or portal gas may be seen in **necrotizing enterocolitis** or **intussusception**.
- ▶ Structural abnormalities such as **diverticula**, **malrotation**, **stenosis**, **blind loop**, and congenital **short bowel**, as well as **motility disorders**, may be investigated through a **barium meal** and a **small bowel follow-through**.

Specific investigations should be carried out for **specific diagnostic indications**.

- ▶ In **older** children, **capsule endoscopy** may be considered to further assess intestinal **inflammation** or **bleeding**, and **capsule technology** can be used to measure **pressure**, **pH**, and **temperature** through the GI tract, assessing **motility**.
- ▶ **Bile malabsorption** may be explored by the **retention of the bile acid analog** ^{75}Se -homocholic acid- taurine ($^{75}\text{SeHCAAT}$) in the enterohepatic circulation.
- ▶ **Prick** and **patch** test may support a diagnosis **of food allergy**. However, an elimination diet with withdrawal of the suspected harmful food from the diet and subsequent challenge is the most reliable strategy by which to establish a diagnosis.
- ▶ The use of **whole exome sequencing** or **specific molecular analysis** may be especially essential in children suspected of having **CDD**, and **early genomic testing** is recommended in these circumstances.

- A step- by- step diagnostic approach is important to minimize the unnecessary use of invasive procedures as well as the cost, while optimizing the yield of the diagnostic evaluation (Table 388.5).

Table 388.5 Stepwise Diagnostic Approach to Children and Infants with Chronic Diarrhea	
INITIAL EVALUATION	
Personal and family history: Prenatal sonography; feeding history; family history of protracted diarrhea; consanguinity	Infectious workup: Stool cultures; parasites; viruses Allergic workup: Elimination diet trial
Physical examination: Signs of malnutrition; dysmorphism; skeletal abnormalities; organomegaly; dermatitis	
↓	
LABORATORY TESTS	
Stool analysis: Stool volume following fasting; stool electrolytes and ion gap; pH and reducing substances; steatocrit; fecal leukocytes and calprotectin; fecal elastase; α_1 -antitrypsin	Blood and serum analysis: Serum electrolytes; lipid profile; albumin and prealbumin; amylase and lipase; inflammatory markers; ammonia; celiac serology
↓	
IMAGING	

IMAGING

Abdominal ultrasound: Bowel wall thickening; liver and bile disorders

X-ray, contrast studies, computed tomography, magnetic resonance imaging: Congenital malformation; signs of motility disorders



ENDOSCOPIES AND INTESTINAL HISTOLOGY

Endoscopy and standard jejunal/colonic histology*; morphometry; PAS staining; intestinal immunohistochemistry; electron microscopy



GENETIC INVESTIGATION

Specific molecular analysis

Whole exome sequencing



OTHER SPECIAL INVESTIGATIONS

Sweat test; specific carbohydrates breath tests; ^{75}Se HCAT measurement; antienterocyte antibodies; metabolic diseases workup; motility studies; neuroendocrine tumor markers

*The decision to perform an upper or a lower endoscopy may be supported by noninvasive tests.

PAS, Periodic acid–Schiff; ^{75}Se HCAT, ^{75}Se -homocholic acid-taurine.

TREATMENT:

- ▶ Chronic diarrhea associated **with impaired nutritional status** should **always** be considered a **serious disease**, and **therapy** should be started **promptly**.
- ▶ 1-Treatment includes general supportive measures, nutritional rehabilitation, elimination diet, and medications.
- ▶ 2- The latter include **therapies for specific etiologies** as well as interventions aimed at counteracting fluid secretion and/or promoting restoration of disrupted intestinal epithelium.
- ▶ Because death may be caused by dehydration or electrolyte abnormalities, replacement of fluid and electrolyte losses is the most important early intervention.

- ▶ **Nutritional rehabilitation** is often essential and is based on clinical and biochemical assessment. In **moderate to severe malnutrition**, caloric intake should be carefully advanced to avoid the development of **refeeding syndrome** and may be progressively increased to 50% or more above the recommended dietary allowances to also allow catch-up growth.
- ▶ In children with steatorrhea, MCT may be a major source of lipids.
- ▶ A lactose-free diet should be considered in children with chronic diarrhea. In these cases, lactose is generally replaced by maltodextrin or a combination of complex carbohydrates.
- ▶ A sucrose-free formula is indicated in sucrase-isomaltase deficiency.

- ▶ **Semi- elemental or elemental diets** have the dual purpose of overcoming food intolerance, which may be the primary cause of chronic diarrhea, particularly in infancy and early childhood, and facilitating nutrient absorption.
- ▶ The sequence of elimination should usually begin from less to more restricted diets, that is, cow's milk protein hydrolysate to amino- acid-based formulas, depending on the child's condition.
- ▶ In severely compromised infants, it may be prudent to start with amino- acid-based feeding.

- ▶ When oral nutrition is not feasible or fails, **enteral** or **parenteral** supplementation should be considered.
- ▶ Enteral nutrition may be provided via nasogastric or gastrostomy tube and is indicated in a child who is not able to be adequately fed orally.
- ▶ In extreme wasting and in cases of significant intestinal mucosal damage or dysfunction, enteral nutrition may not be tolerated, and **parenteral nutrition** is required.

- ▶ **Micronutrient and vitamin supplementation** are part of nutritional rehabilitation, especially in malnourished children in developing countries.
- ▶ Zinc supplementation is important in both prevention and therapy of chronic diarrhea, since it promotes ion absorption, restores epithelial proliferation, and stimulates immune response.
- ▶ Nutritional rehabilitation has a general beneficial effect on the patient's general condition, intestinal function, and immune response.

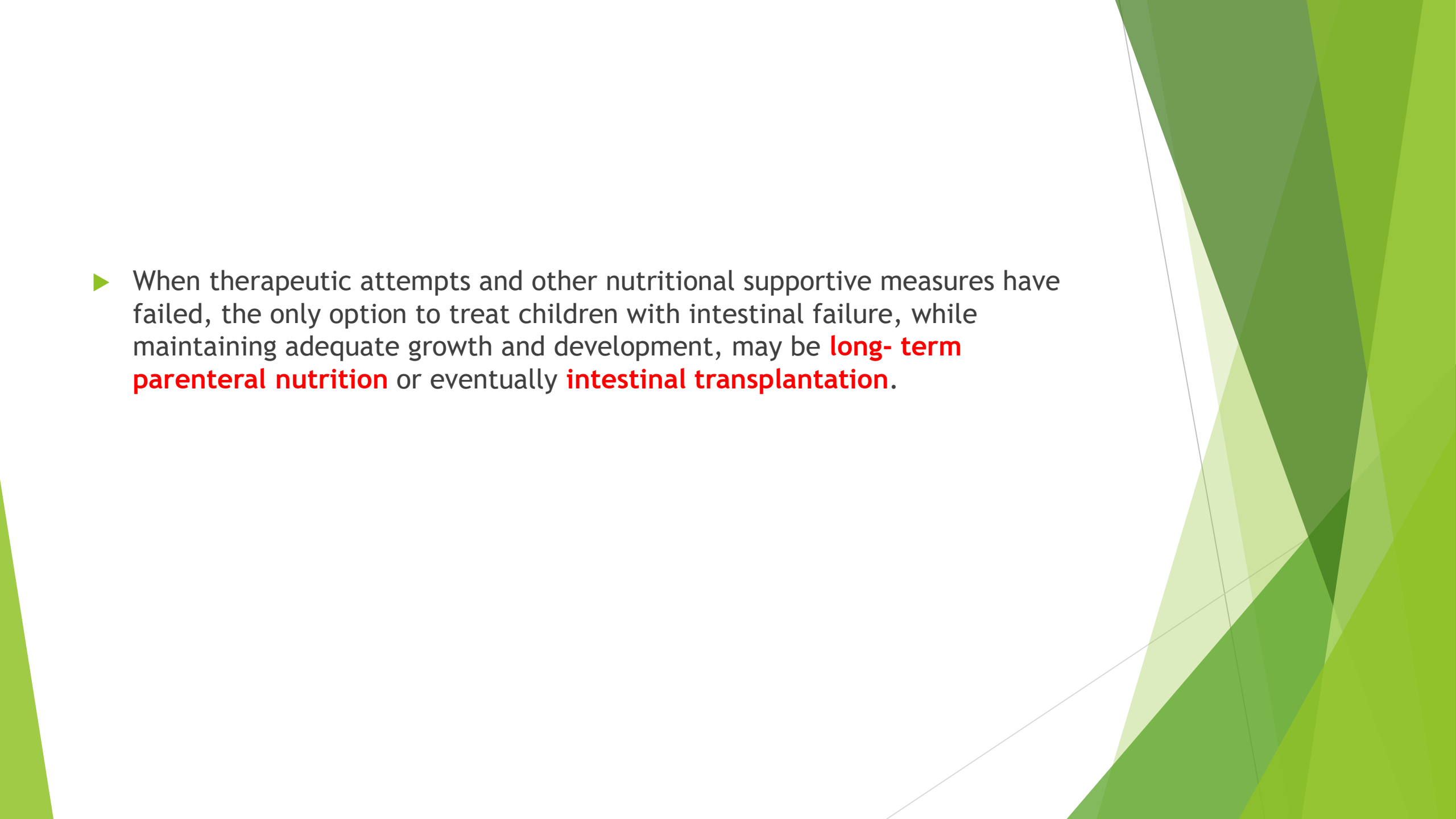
- ▶ **Functional diarrhea** in children may benefit from a diet based on the “4 F” principles (reduce fructose and fluids, increase fat and fiber).
- ▶ The use of probiotics (mostly Lactobacillus GG or Saccharomyces boulardii) in infectious and postinfectious diarrhea in children may be tried as adjunctive therapy with reduction in symptom duration, but there is insufficient evidence to recommend their routine use for chronic diarrhea.

Pharmacologic therapy includes, based on the etiology, anti-infectious drugs, immune suppression, and drugs that may inhibit fluid loss and promote cell growth. If a bacterial agent is detected, specific antibiotics should be prescribed. Empiric antibiotic therapy may be used in children with either small bowel bacterial overgrowth or with suspected infectious diarrhea. Table 388.6 summarizes the anti-microbial treatment of infectious persistent diarrhea.

Table 388.6 Antimicrobial Treatment for Persistent Diarrhea				
	DRUG	INDICATIONS	DOSAGE	DURATION
Antibiotics	Trimethoprim-sulfamethoxazole	<i>Salmonella</i> spp., <i>Shigella</i> spp.	6-12 mg/kg/day (of trimethoprim) in 2 divided doses daily per os	5-7 days
	Azithromycin	<i>Shigella</i> spp., <i>Campylobacter</i>	1 day: 12 mg/kg/day once daily per os 2-5 days: 6 mg/kg/day once daily per os * Alternative: 10 mg/kg/day once daily per os, for 3 days	5 days
	Ciprofloxacin	<i>Shigella</i> spp.	20-30 mg/kg/day in 2 divided doses, per os or IV	3 days
	Ceftriaxone	<i>Shigella</i> spp.	50-100 mg/kg/day once daily per IM or IV	2-5 days
	Metronidazole	<i>Giardia</i> , <i>Amebiasis</i> , <i>Blastocystis</i> , <i>Clostridium difficile</i>	15-35 mg/kg/day in 2-3 divided doses per os	7-10 days
	Paromomycin	<i>Amebiasis</i>	25-35 mg/kg/day in 3 divided doses per os	7 days
	Vancomycin	<i>C. difficile</i>	40 mg/kg/day in 4 divided doses per os	10 days
Antiparasitic	Nitazoxanide	<i>Amebiasis</i> , <i>Giardiasis</i> , <i>Blastocystis</i> , <i>Cryptosporidiosis</i>	100 mg every 12 hr for children ages 12-47 mo 200 mg every 12 hr for children ages 4-11 yr 500 mg every 12 hr for children older than 11 yr	3 days
	Albendazole	<i>Ascaris</i> , hookworm, and pinworm infection	400 mg	Once

*Depends on local susceptibility profile.
IM, Intramuscular; IV, intravenous; os, by mouth.

- ▶ **Immune suppression** should be considered in selected conditions such as autoimmune enteropathy and IBD.
- ▶ Treatment may be also directed at modifying specific pathophysiologic processes.
- ▶ Secretion of ions may be reduced by **antisecretory agents**, such as the enkephalinase inhibitor racecadotril. Some benefit from absorbents, such as diosmectite, has been described, with reduction of diarrhea duration in infectious diarrhea.
- ▶ In diarrhea caused by neuroendocrine tumors (NETs), microvillus inclusion disease and enterotoxin-induced severe diarrhea, a trial of **somatostatin** analog octreotide may be considered.
- ▶ **Zinc** promotes both enterocyte growth and ion absorption and may be effective when intestinal atrophy and ion secretion are associated.

- 
- The background of the slide features abstract, overlapping green geometric shapes, primarily triangles and polygons, in various shades of green, creating a modern and dynamic visual effect.
- ▶ When therapeutic attempts and other nutritional supportive measures have failed, the only option to treat children with intestinal failure, while maintaining adequate growth and development, may be **long-term parenteral nutrition** or eventually **intestinal transplantation**.

Diarrhea from Neuroendocrine Tumors

- ▶ The incidence of NETs originating in the GI tract is **increasing globally**.
- ▶ **Physicians' awareness, endoscopic screening, and increased sensitivity of diagnostic tools** may at least in part explain this trend.
- ▶ Most of these tumors involve the **gastro- entero- pancreatic** tract.
- ▶ Neuroendocrine neoplasm cells possess features of both neural and epithelial cells.
- ▶ The commonly perceived notion of NETs is of slow- growing malignancies with a benign course.
- ▶ Although well- differentiated GI- NETs may exhibit indolent clinical behavior, studies indicate that they are frequently already metastatic at diagnosis, and in which case they are **neuroendocrine carcinomas**.

- ▶ The majority of NETs (75-90%) are not associated with elevated hormone levels and do not cause a clinical syndrome such as diarrhea.
- ▶ Functional tumors are tumors that make excess hormone, leading to clinical syndromes. These include insulinoma, gastrinoma, vasoactive intestinal polypeptide (VIP) secreting tumors, glucagonoma, and somatostatinoma.
- ▶ A child with persistent watery secretory diarrhea should be evaluated for a functional NET.

- ▶ The most common NET in children is **carcinoid**, which is generally a **low- grade** tumor, especially when it is **small (<1cm)**.
- ▶ It is equally distributed between the small and large intestine and can commonly be found in **the appendix**.
- ▶ Most carcinoids are found **incidentally** and are **asymptomatic**, especially those that are located in the appendix.
- ▶ Some NET patients (around 10%) will develop **secretory diarrhea** requiring symptom control to optimize quality of life and clinical outcomes.
- ▶ Such patients are defined as having **carcinoid syndrome**, characterized by **excessive production of one or more peptides**, which, when released into the circulation, exert their endocrine effects and can be measured by **radioimmunologic methods** (in the **plasma** or as their **urinary** metabolites).
- ▶ These peptides, therefore, also act as tumor markers.

- ▶ Compared to carcinoid, VIPomas are much less frequent. Because VIP is a more potent vasoactive peptide, it induces more **profuse diarrhea**, with up to 70% of patients having volumes greater than 3 L/day.
- ▶ Though rare as a cause of watery diarrhea, a NET should be considered in the differential diagnosis when diarrhea is unusually severe or takes a chronic course (resulting in electrolyte and fluid depletion).
- ▶ GI- NETs may be associated with **flushing, palpitations, or broncho spasm.** Family history may reveal multiple endocrine neoplasia (MEN) 1 or 2 syndromes (Table 388.7).

Table 388.7 Diarrhea Caused by Neuroendocrine Tumors

TUMOR AND CELL TYPE	SITE	MARKERS	SIGNS OF HORMONE HYPERSECRETION	THERAPY
Carcinoid	Intestinal argentaffin cells, typically midgut, also foregut and hindgut, ectopic bronchial tree	Serotonin (5-HT), urine 5-HIAA* (diagnostic) Also produce substance P, neuropeptide K, somatostatin, VIP, chromogranin A	Secretory diarrhea, crampy abdominal pain, flushing, wheezing (and cardiac valve damage if foregut site)	Resection Somatostatin analog, (palliative) Genetic MEN-1
Gastrinoma, Zollinger-Ellison syndrome	Pancreas, small bowel, liver, and spleen	Gastrin	Multiple peptic ulcers, secretory diarrhea	H ₂ -blockers, PPI, tumor resection, (gastrectomy) Genetic MEN-1
Mastocytoma	Cutaneous, intestine, liver, spleen	Histamine, VIP	Pruritus, flushing, apnea if VIP, diarrhea	H ₁ - and H ₂ -blockers, steroids, resection if solitary
Medullary carcinoma	Thyroid C-cells	Calcitonin, VIP, prostaglandins	Secretory diarrhea	Radical thyroidectomy ± lymphadenectomy (genetic MEN-2A/B, familial MTC)
Ganglioneuroma, pheochromocytoma, ganglioneuroblastoma, neuroblastoma	Chromaffin cells; abdominal > other sites; extraadrenal or adrenal	Metanephrines and catecholamines, VIP VMA, HMA in neuroblastoma	Hypertension, tachycardia, paroxysmal palpitations, sweating, anxiety, watery diarrhea [†]	Perioperative α-adrenergic (BP) and β-adrenergic blockade with volume support tumor resection Genetic MEN-2 (RET gene), VHL, NF-1, SDH
Somatostatinoma	Pancreas	Somatostatin	Secretory diarrhea, steatorrhea, cholelithiasis, diabetes	Resection Genetic MEN-1
VIPoma	Pancreas	VIP, prostaglandins	Secretory diarrhea, achlorhydria, hypokalemia	Somatostatin analogs, resection Genetic MEN-1

***Bold** indicates major markers.

[†]Diarrhea has been reported only in adult patients with pheochromocytoma.

BP, Blood pressure; H₁, histamine receptor type 1; H₂, histamine receptor type 2; HMA, homovanillic acid; MEN-1, multiple endocrine neoplasia type 1; MTC, medullary thyroid carcinoma; NF-1, neurofibromatosis type 1; PPI, proton pump inhibitor; SDH, succinate dehydrogenase; VHL, von Hippel-Lindau disease; VIP, vasoactive intestinal polypeptide; VMA, vanillylmandelic acid.

- ▶ Baseline tests should include plasma chromogranin A and urinary 5-hydroxyindoloacetic acid (a metabolite of serotonin) and other specific biochemistry being guided by the suspected syndrome (see Table 388.7).
- ▶ Localization of any NET is best achieved using a multimodality approach.
- ▶ Whole body CT or MRI with somatostatin receptor PET screening may be required with gallium- 68 DOTATOC (synthetic octreotate) PET.

- ▶ Therapeutic interventions to be considered include **surgical, pharmacologic, and radioisotope** therapy; choice of therapy is based on disease extent and location, tumor grade, pace of disease progression, symptoms, and comorbidities.
- ▶ Tumor resection is the treatment of choice when the tumor is small and localized. The goals of resection are twofold: (1) management of the endocrine syndrome to control symptoms and (2) tumor control to improve survival.
- ▶ However, resection can precipitate life-threatening adrenergic crises. When arising in the appendix, carcinoid tumors less than 2 cm in size can be managed by simple appendectomy.

- ▶ When greater than 2 cm in size or arising from the base of the appendix, a **right hemicolectomy** is indicated.
- ▶ Fortunately, in pediatric patients, metastases are rare; when they occur, it is usually in the liver.
- ▶ Tumor histochemistry will confirm the NET type and classification.
- ▶ Pharmacologic treatment may include the use of **long- acting somatostatin** analogues as first- line therapy.
- ▶ This usually results in a pronounced improvement of symptoms including diarrhea.
- ▶ However, many patients become resistant to somatostatin.
- ▶ Diarrhea caused by pancreatic insufficiency, secondary to somatostatin analog use, is often oily and malodorous and should be treated with pancreatic enzyme replacement.
- ▶ **Everolimus** is an oral medication and a more specific target of rapamycin (mTOR) inhibitor, and has been reported as add- on treatment to octreotide, primarily in adult patients.
- ▶ The tyrosine kinase inhibitor **sunitinib** is another option.
- ▶ Data suggest a positive effect of **ondansetron**, a serotonin- 3- receptor antagonist, on diarrhea.
- ▶ **Peptide receptor radioisotope** therapy also has been reported as a therapeutic modality.

- ▶ Diarrhea and flushing associated with the carcinoid syndrome can be debilitating.
- ▶ Telotristat ethyl is an inhibitor of tryptophan hydroxy lase that acts to reduce serotonin levels and has emerged as a promising agent for control of refractory carcinoid syndrome diarrhea.
- ▶ The diagnosis of NET in children should prompt a genetic referral to exclude a familial syndrome.

