CHRONIC DIARRHEA IN CHILDREN

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OBJECTIVES

- Know how to evaluate a child who has chronic diarrhea, including appropriate elements of history, physical examination, stool analysis, and blood testing.
- 2. Be familiar with the many disorders that cause chronic diarrhea, both with and without failure to thrive.
- 3. Know the therapies for the many causes of chronic diarrhea.

Introduction

Recurrent, chronic, infantile diarrhea with malnutrition, causes the death of 4.6 million children globally each year. In the last 25 years, the following specific preventive measures have reduced further the number of infants who have this condition.

Introduction (cont.)

- renewed emphasis on breastfeeding
 reduction in the use of partial starvation regimens during diarrheal episodes and
 increased availability of age-
- increased availability of ageappropriate infant food for children living in poverty

PATHOPHYSIOLOGY

Osmotic diarrhea is caused by a failure to absorb a luminal solute, resulting in secretion of fluids and net water retention across an osmotic gradient.

Secretory diarrhea occurs when there is a net secretion of electrolyte and fluid from the intestine without compensatory absorption.



PATHOPHYSIOLOGY

Intestinal dysmotility typically occurs in the setting of intact absorptive abilities. Intestinal Transit time is decreased, the time allowed for absorption is minimized, and fluid is retained within the lumen.

Inflammatory diarrhea may encompass all of the above pathophysiologic mechanisms.



My baby whom I just deliver developed diarrhea from day 1 after birth, what is the cause?

Congenital Chloride Diarrhea A Study in Arab Children

J Clin Gastroenterol 1994; 19(1):36-40

Maternal polyhydrammics

Prematurity





- Abdominal Distention
- Diarrhea





Congenital Chloride Diarrhea

- Hypokalemia, hypochloremic
- Metabolic alkalosis
- Fecal chloride greater than

Fecal sodium and potassium

TREATMENT

Na + Kcl supplement

Congenital Sodium Diarrhea

- It is caused by a defect in a jejunal sodium/proton exchange that results in severe watery diarrhea.
- Polyhydramnios first manifestation of CSD
- Hyponatremia
- Metabolic Acidosis
- An autosomal recessive disease.

Congenital Sodium Diarrhea

DISEASE	GENE	LOCATION	FUNCTION
Congenital Sodium Diarrhea	SPINT2*	19q13.1	Serine – protease inhibitor

Microvillous Atrophy-Inclusion Disease (Familial Microvillous Atrophy)

- Watery diarrheat despite patients NPO
- Clinical forms are:
 - Congenital the onset of the diarrhea in the first week of life
 - Late onset when diarrhea start after neonatal period



Microvillous Atrophy-Inclusion Disease (Familial Microvillous Atrophy)

Diagnosis is based on the finding of villus atrophy and intracytoplasmic inclusions lined by intact microvilli in intestinal biopsy material



Inclusion containing microvilli, within apical cytoplasm of the cell

Apical surface with few/blunted microvilli

Microvillus Inclusion Disease

– Rx: TPN + intestinal transplant

Intestinal Epithelial Dysplasia (Tufting Enteropathy)

Definition

- Intestinal epithelial dysplasia (IED), is also known as tufting enteropathy.
- A congenital enteropathy presenting with early-onset severe intractable diarrhea and persistent villous atrophy.

Clinical description, associated disorders and diagnostic criteria

- Watery diarrhea within the first days after birth.
- Growth is impaired.
- No past history of hydramnios suggesting congenital chloride diarrhea or sodium malabsorption.
- Affected children are reported to have dysmorphic features.



Histological presentation

- Villous atrophy
- Epithelium
 - Abnormalities are localized mainly in the epithelium, includes disorganization of surface enterocytes with focal crowding.
- Specific features
 - Focal enterocyte crowding observed in crypt epithelium.
 - Crypts are dilated with features of pseudo cysts.







TREATMENT

Total parenteral nutrition

Intestinal transplantation

Autoimmune Enteropathy

- Severe protracted watery diarrhea during infancy or toddlerhood.
- Diarrhea may be isolated or may occur in, association with diabetes mellitus as part of the IPEX syndrome (Immune dysregulation, Polyendocrinopathy and Enteropathy, X-linked), associated with mutations in the FOXP3 gene.
- Circulating antibodies to enterocytes antismooth, antithyroid and islet-cell antibodies.

TREATMENT

- Total parenteral nutrition
 Produisono
- Prednisone
- Cyclosporine
- Azathioprine
- Intestinal transplant

I delivered this baby and I start to feed him/ her my breast milk and/ or bottle milk, since I start feeding the baby developed diarrhea. What is the cause?



- * Early onset
- Watery diarrhea
- Dehydration and metabolic acidosis
- * The diarrhoea ceases within one hour of removing the oral intake of lactose, glucose, and galactose.
- The diarrhoea returns with introduction of lactose, glucose and galactose.
- * Fructose is mandatory



Developmental Lactase Deficiency

- The relative lactase deficiency observed among preterm infants of less than 34 weeks gestation.
- The immature gastrointestinal tract, lactase and other disacharidases are deficient until at least 34 weeks gestation.

Primary Lactase Deficiency

- Relative or absolute absence of lactase.
- Develops in childhood at various ages in different racial groups.
- The most common cause of lactose malabsorption and lactose intolerance.




Secondary Lactase Deficiency

- Results from small bowel injury such as:
 > Acute gastroenteritis
 - Persistent diarrhea
 - Small bowel overgrowth
 - Cancer chemotherapy
 - Other causes of injury to the small intestinal mucosa
- Present at any age but is more common in infancy.

Treatment

 is relatively simple and aimed at reducing or eliminating lactose, by eliminating it from the diet or by "predigesting" it with supplemental lactase-enzyme replacement. Calcium must be provided by alternate nondairy dietary sources or as a dietary supplement to individuals who avoid milk intake.





I am feeding my baby milk feed and I start to feed him fruit juices, since I start the fruit juice my infant start to have diarrhea. What is the cause?

Congenital Sucrase -Isomaltase Deficiency







Congenital Sucrase -Isomaltase Deficiency

***Watery diarrhea**

***Abdominal distension**

***Older children irritability**

***Growth may be normal**

TREATMENT

Avoid sucrose or fructose- containing diet or supplement with:

-

SACROSIDASE

My infant developed vomiting and diarrhea and then I took him to the ER and the doctor diagnosed him as Acute Gastroenteritis. He gave me different medications and/ or fluid and then sent me back home. Since that time, my infant continue to have diarrhea. What is the cause?





Bacterial Causes of Chronic Diarrhea

Organism	Sources	Duration
Aeromonas sp	Untreated water	1 wk to 1 yr
Campylobacter sp	Raw poultry, diarrheic animals, unpasteurized milk, birds, water, ferrets	5 days to chronic
Clostridium difficile	Antibiotic use; can be nosocomial	10% have relapses
Plesiomonas shigelloides	Untreated water, shellfish	2 wks to mos
Salmonella sp	Poultry, fecal-oral, water	5 d to mos in infants
Yersinia	Handling of raw pig	3 wk to 3 mos
enterocolitica	intestines (chitterlings)	

Bacterial Diarrheas

- Non-typhoidal Salmonella infection
- Aeromonas and Plesiomonas
- Yersinia

Bacterial Diarrheas

Escherichia Coli (E-Coli)

Enteric pathotypes of E-Coli diarrhea may evolve to a chronic course due to persistent injury to the bowel.

- Enterotoxic and mucosa-adherent E-Coli cause a watery diarrhea. May lead to prolonged diarrhea due to mucosal damage of persistence of the primary infection.
- Enterohemorrhagic pathotype that produces toxin causes acute colitis and the hemolytic-uremic syndrome.

Parasitic Causes of Chronic Diarrhea

Organism	Sources	Duration
Giardia lamblia	Diapered infants, fecal- oral, water supplies	2 wks to yrs
Cryptosporidium parvum	Child care, petting zoos, swimming pools	1 to 2 wk w/ occasional reports of 6 wk
Cyclospora cayetanensis	Raspberries from Central America, water, unpasteurized apple cider	1 wk to 1 mo or more
Entamoeba histolytica	Fecal-oral, water	Weeks
Isospora belli	Fecal-oral, water	Chronic
Strongyloides stercoralis	Developing countries, Appalachia,fecal-oral	Chronic
Blastocystis	Uncertain if a pathogen	A ATTA
hominis		

Signs and Symptoms of Giardiasis

- Diarrhea (64 to 100%)
- Malaise, weakness (72 to 97%)
- Abdominal distention (42 to 97%)
- Flatulence (35 to 97%)
- Abdominal cramps (44 to 81%)
- Nausea (14 to 79%)
- Foul-smelling, greasy stools (15 to 79%)
- Anorexia (41 to 73%)
- Weight loss (53 to 73%)
- Vomiting (14 to 35%)

Giardia Lamblia

- Rare presentations of Giardiasis include anasarca (proteinlosing enteropathy).
- Diagnosis can be done by miscroscopic examination of feces.
- Organism sometimes is seen in intestinal biopsies.



Cryptosporidium Parvum

- The infection results from ingestion of the organism from fecal contamination of the hands.
- Giardia-Cryptosporidium antigen tests have better sensitivity.



Intractable Diarrhea of Infancy (IDI)

- IDI is also known as:
 - Postenteritis enteropathy
 - Protracted diarrhea of infancy
 - Secondary disaccharidase deficiency
- Enteric infection and associated compromise of intake and absorption lead to variable loss of digestive and absorptive capacity in infants.

Intractable Diarrhea of Infancy (IDI)

 Recurrent episodes of diarrhea and failure to regain weight in an infant.



- Suspicion should be raised further by the
 1. absence of breastfeeding
 2. administration of diluted or clear liquid feedings
 - 3. restriction of intake in a misguided effort to reduce diarrhea or vomiting.

Treatment

Lactose free-sucrose free formula

- IV hydration for short period
- If no improvement total parenteral nutrition

A 6 – month old infant with diarrhea for few weeks and chronic cough and recurrent skin abscesses. What is the cause of the diarrhea?

Immune deficiency diseases (IDD)

 Chronic diarrhea is a common complication of IDD

 Evaluation should include examination of lymph nodes, spleen, skin and peripheral blood smear.

Diarrhea in Immunodeficiency

Diseases

Condition	Condition	Condition
Human immunodeficiency virus infection	Common variable immunodeficiency	Selective IgA deficiency
Severe combined immunodeficiency syndrome (Raq1, Raq2, JAK3, ZAP-70, Omenn S)	Chronic Granulomatous disease	Immunodysregulation, polyendocrinopathy, enteropathy,
X-linked agammaglobulinemia	Wiskott-Aldrich syndrome	X-linked syndrome
Hyper IgM immunodeficiency	Major histocompatibility complex class II deficiency	

I have a 6 – month old infant who was well then I started to give him some milk formula and fruits, since that time he start to have diarrhea with skin rashes and recurrent wheezes. What is the cause of his diarrhea?

Dietary Protein Enteropathy

Age at onset	 Dependent on age of exposure to antigen Cow's milk and soy: up to 2 years failure to thrive 	
Proteins implicated	<section-header></section-header>	
Pathology	 Variable small bowel villous injury and increased crypt length; often patchy, sub-total intraepithelial lymphocytes; few eosinophils 	

Dietary Protein Enteropathy

Diarrhea

- Malabsorption
- Failure to thrive
- Emesis
- Abdominal distensions
- Anemia

Manifestations

Kissing and being touched by those who

have eaten a food

- Edema
- Hypoproteinemia
- Protein-losing enteropathy
- Anti-endomysium antibody negative
- Radiographic: small bowel edema
- Food challenge: vomiting and/or
 - diarrhea in 40 to 72 hours





	Sneezing Nasal Congestion Runny Nose Swelling & Tenderness of the Mouth Difficulty Breathing Difficulty Breathing Nausea / Vomiting Abdominal Cramps Diarrhea
Treatment	Strict elimination of offending antigen
Natural History	Most cases resolve in 2 to 3 years

My 8 – month old infant was well up to 6 – month of age when I start to introduce cereals and baby biscuits then he started to have diarrhea since that time. What is the cause of the diarrhea?

Celiac Disease

Age of onset	 Dependent on timing of gluten introduction typically more than 6 months
Proteins implicated	 Wheat, rye, barley, possibly oats
Pathology	 Extensive villous atrophy Elongated crypt length Increased intraepithelial lymphocytes
Genetics	* HLA-DQ2 (and DQ8) associated
Natural History	 Illness is life-long

Celiac Disease (cont.)

Chronic diarrhea
*Abdominal distension
Failure to thrive / growth failure
Complications of malabsorption
Abdominal pain Abdominal Abdominal pain Abdominal
Associated diseases: dermatitis
herpetiformis, diabetes mellitus, thyroid
disease, Down syndrome, IgA deficiency
 Gluten elimination












Diagnosis of Celiac Disease (New criteria)

1) Positive anti-issue transglutaminase or endomysium antibodies.

2) Villous atrophy on small bowel biopsy.

Diagnosis of Celiac Disease (Old criteria)

Biopsy	Histologic findings	Management
First	Compatible with diagnosis	Gluten-free diet initiated on trial basis, and clinical response observed
Second	Recovery documented	Gluten challenge subsequently administered
Third	Relapse documented	Lifelong gluten-free diet recommended
XXXXXX		







A 2 – year old child with chronic diarrhea which is associated with lymphedema or ataxia. What is the cause?

Intestinal Lymphangiectasia

- Disorder of the intestinal lymphatics
- Impaired fat absorption
- ***Protein-losing enteropathy**
- Secondary to fibrosis
- Hypo-albuminemia
- *Hypogammaglobulinemia
- Low lymphocyte count

Chylous ascites *Systemic infections *Generalized lymphatic abnormalities



Intestinal Lymphangiectasia

- Biopsy confirms
 lymphangiectasia
- Characteristic lymphatic dilatation
- Follow-through
 demonstrate oedema of the
 intestine
- Protein loss by Cr-labeled
 albumin



Abetalipoproteinemia

DISEASE	GENE	LOCATION	FUNCTION
Abetalipoproteinemia	MTP	4q22	Transfer lipids to apolipoprotein B

- Autosomal recessive trait
 Fat malabsorption failure
 to thrive
- Ataxia and retinitis
 pigmentosa
- Markedly decreased
 plasma levels of
 cholesterol triglycerides
 and phospholipids



Abetalipoproteinemia

- *Acanthocytosis
- Small intestinal biopsy
- Normal villous
 architecture
- Fat droplets in the enterocytes
- Low-fat diet with mediumchain triglycerides
 Vitamins A, D, E and K





A 1 – year old child with chronic diarrhea and skin rashes around the orifices and hair loss. What is the cause?

Acrodermatitis Enteropathica

DISEASE	GENE	LOCATION	FUNCTION
Acrodermatitis Enteropathica	SLC39A4	8q24.3	Zn ²⁺ transporter

- Recessive
- Chronic diarrhea and failure to thrive
- Dermatitis involving perioral and perianal regions
- ✤ Alopecia
- Low plasma zinc levels
- ✤ Alkaline phosphatase is low



Treatment

zinc sulfate 150 mg/d orally

A 3 – year old child with chronic diarrhea and growth failure and recurrent chest infection. What is the cause?

CYSTIC FIBROSIS (CF)





- In the neonatal period, with intestinal obstruction; meconium ileus
- With recurrent or persisting cough often associated with wheeze
- Malabsorption; large, pale, bulky and offensive stools
- Failure to thrive
- Rectal prolapse
- Rarely, heat stroke
- Sweat chloride concentration is 1
- Staphylococcus + pseudomonas aeruginosa
- Physiotherapy
- Enzyme replacement
- Hot weather
 - **†** fluid and salt intake

Short Gut Syndrome

Surgical resection of the small intestine

Volvulus

Adhesions

Vasoactive Intestinal Polypeptide-Secreting Tumors

- Pediatric:
 - Ganglioneuroma
 - Ganglioneuroblastoma
 - Pheochromocytoma
 - Mastocytoma
 - Non-beta cell hyperplasia
 - Medullary thyroid carcinoma



VIPoma and WDHA

- Vasoactive intestinal polypeptide (VIP)
- Chronic, high-volume, watery diarrhea, hypokalemia, and alkalosis (WDHA).
- Age range from 1 to 3 year olds.
- VIP is strikingly elevated, or imaging studies that show a mass in the adrenal gland or along sympathetic ganglia in abdomen or thorax

A 1 ½ year old child with chronic diarrhea and food particles in the stool with normal growth. What is the cause of the diarrhea?

Chronic Nonspecific Diarrhea (CNSD)/ Irritable Bowel Syndrome (IBS)

Symptoms

- Onset: 6 to 18 months of age
- Loose, explosive bowel movement containing food particles
- Bowel movement frequency: 6 to 12/d
- Growth: Normal (if not on restrictive diet)

Red Flags (Not Compatible with CNSD/IBS)

- Hematochezia or melena
- Persistent fever
- Weight loss or growth arrest
- Anemia

Chronic Nonspecific Diarrhea (CNSD)/

Irritable Bowel Syndrome (IBS)

• Diet:

Restrict apple juice (trial only)

Restrict lactose (trial only)

Laboratory Studies:

≻ tTg or EMA

Fecal Giardia antigen

• Therapy:

- Reassurance
- Lifestyle modifications
- Avoidance of restrictive diets

A 5 – year old child with chronic bloody diarrhea and growth failure. What is the cause?



at a glance

Ulcerative colitis and Crohn's disease



Differential Dx: Crohn's Disease Caution! Cobblestone regions of granulomas can appear fissured.





© Photo: Dr. Jerry Bouquot, The Maxillofacial Center, Morgantown, West Virginia



Differential Diagnosis Between Ulcerative Colitis and Crohn's Disease

Feature	Ulcerative colitis	Crohn's disease
	$(\setminus) \rightarrow$	
Relative incidence of	1	Rare
symptoms	Common	Moderate or even
Rectal bleeding (gross)	Often severe	absent
Diarrhea	Less frequent	Almost always
Pain	Mild or moderate	Can be severe
Anorexia	Moderate	Severe
Weight loss	Usually mild	Often pronounced
Growth retardation	Common	Common
Extraintestinal	1	
manifestations		1/ 3943636

Plan of Investigation in Children with Chronic Diarrhea

Investigation	Clinical Diagnosis for which indicated
Identification of bacterial, viral and protozoal	Infectious enteritis
agent in stool	
Stool PH and reducing substances; breath H2	Carbohydrate malabsorption
excretion; oral sugar tolerance tests	
Stool electrolyte	Chloride losing diarrhea
Lymphocyte count & immunoglobulin, profile;	Immunodeficiency, intestinal lymphangiectasia
macrophage function, serum opsonic activity	
Celiac Serology	Celiac Disease
Sweat chlorides; pancreatic function tests	Cystic fibrosis and other pancreatic deficiency
	disorders
Duodenal intubation	Bacterial overgrowth, excess deconjugated bile
	salts, enteric infections

Plan of Investigation in Children with Chronic Diarrhea (cont.)

Investigation	Clinical Diagnosis for which indicated
Intestinal Biopsy	Milk protein allergy by pre and post milk challenge histology
	Celiac disease, lymphangiectasia
Urinary catecholamines; immunoassay for VIP	Secretory tumors
Serum zinc	A crodermatitis enteropathica
Lipid profile	A beta liproteinemia
PT, PTT	Vitamin K malabsorption
Stool fat	Fat malabsorption
Alpha-1-antitrypsin in stool	Protein loosing enteropathy
Barium studies	Surgical disorders, inflammatory bowel disease
Colonoscopy	Inflammatory bowel disease 105

Differential Diagnosis of Prolonged Diarrhea of Infancy

- Congenital chloride diarrhea
- Congenital Sodium Diarrhea
- Microvillus inclusion disease
- Tufte enteropathy
- Autoimmune enteropathy
- Carbohydrate malabsorption
- Cow milk protein allergy
- Celiac disease
- Intractable diarrhea in infancy
- Enteric infection

- Immunodeficiency disease
- Intestinal Lymphangectasia
- A-beta-lipoproteinemia
- Congenital short gut (malrotation)
- VIPoma
- Acrodermatitis enteropathica
- Cystic Fibrosis
- Chronic Non-Specific Diarrhea
- ➢ IBD

TREATMENT CONSIDERATION

I. MALNUTRITION

Sufficient calories should be provided to allow for catch-up weight gain. When oral intake is inadequate or malabsorption precludes adequate intake, continuous enteral feedings or parenteral nutrition maybe necessary.

Micronutrient and Vitamin supplementation are part of nutritional rehabilitation:

- Vitamin A
- Zinc
- Folic Acid
- Copper
- Selenium

Deficiencies in these micronutrients can impair the function of the immune system.

II. MEDICATIONS

1. PROBIOTICS

Administration of probiotic bacteria and the administration if antibiotics

The utility if treatment with antibiotics is unclear.

2. ANTIDIARRHEAL DRUGS

- Children with protracted diearrhea
- Important side effects: sedation and risk for toxic megacolon
- Prolong excretion of the organism or promote the development of hemolyticuremic syndrome in patients infected with enterohemorrhagic E. coli.
3. SOMATOSTATIN

- > Treatment may be directed at modifying specific pathophysiologic processes.
- In severe secretory diarrheas for instance: neuroendocrine tumors microvillous inclusion disease and enterotoxin-induced severe diarrhea

Summary

- The differential diagnosis for chronic diarrhea in children is broad. Pediatric clinicians can narrow these possible diagnoses beginning with a detailed history and physical examination.
- Particular attention should be paid to growth measurements to distinguish between chronic diarrhea with and without associated growth failure.

Summary

- Understanding the four basic pathophysiologic mechanisms of diarrhea also may aid in making a diagnosis. The four categories are osmotic, secretory, dysmotility associated, and inflammatory.
- Although specific therapies vary for each disease, the importance of maintaining nutrition demands particular emphasis. Whatever the cause of the diarrhea, each patient requires adequate caloric intake to allow healing of the initial insult, or at least take to support the child while pursuing diagnostic and therapeutic interventions.



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