Chronic diarrhea

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Abstract

This article focuses on the assessment and management of chronic diarrhea according to its pathophysiological mechanism, symptoms, complementary examinations and treatment. Diarrhea is classified as osmotic diarrhea and secretory diarrhea. It can also be divided into diarrhea due to maldigestion, when the digestive enzymes that hydrolyze proteins, fats and carbohydrates are not produced, and diarrhea due to malabsorption, when there is an alteration of the intestinal epithelium that prevents the transport of already digested nutrients. The warning signs and symptoms must be considered to make an initial diagnostic approach to diarrhea of organic or functional origin. The clinical history should define the characteristics of the stools, watery, bloody or greasy, which will help to orientate the possible pathophysiological mechanism. In the physical examination severity of malnutrition is specifically assessed. The differential diagnosis is broad and the complementary examinations numerous, but they must be carried out based on the clinical findings. First level investigations can lead to the diagnosis of the most common causes. In addition to nutritional support, specific treatment of the underlying disease is provided, which will often, but not always, be exclusively nutritional. Correct and early diagnosis and treatment of these patients will minimize the morbidity and nutritional consequences of chronic diarrhea.

Resumen

Valoración y manejo de la diarrea crónica en función de su mecanismo fisiopatológico, síntomas, exploraciones complementarias y tratamiento. La diarrea se clasifica en diarrea osmótica y diarrea secretora. También puede dividirse en diarrea por maldigestión, cuando no se producen las enzimas digestivas que hidrolizan las proteínas, grasas y carbohidratos, y diarrea por malabsorción, cuando existe una alteración del epitelio intestinal que impide el transporte de los nutrientes ya digeridos. Deben considerarse los signos y síntomas de alarma para efectuar una aproximación diagnóstica inicial de diarrea de origen orgánico o funcional. En la historia clínica se definirán las características de las heces, acuosas, con sangre o con grasa, lo que permitirá orientar el posible mecanismo fisiopatológico. En la exploración física se valorará especialmente la repercusión nutricional. El diagnóstico diferencial es muy amplio y las exploraciones complementarias numerosas, pero deben efectuarse en función de los hallazgos clínicos. Con las exploraciones de primer nivel se puede llegar al diagnóstico de las causas más frecuentes. Aparte del soporte nutricional, se efectuará el tratamiento específico de la enfermedad de base, que con frecuencia, pero no siempre, será exclusivamente nutricional. El correcto y temprano diagnóstico y tratamiento de estos pacientes minimizará la morbilidad y las consecuencias nutricionales de la diarrea crónica.

Key words: *Chronic diarrhea; Functional diarrhea; Organic diarrhea; Malabsorption; Maldigestion; Complementary tests; Management.*

Palabras clave: Diarrea crónica; Diarrea funcional; Diarrea orgánica; Malabsorción; Maldigestión; Exploraciones complementarias; Tratamiento.

OBJECTIVES

- To understand the pathophysiological mechanisms of chronic diarrhea so as to make an initial diagnostic approach.
- To know the different etiologies of chronic diarrhea in order to establish the differential diagnosis.
- To make a correct clinical history, giving the greatest importance to the characteristics of the stools and the physical examination of the patient.
- To select the different complementary examinations based on the clinical findings.
- To be aware of the treatment, and especially in chronic diarrhea where the management is essentially dietary.

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Introduction

Chronic diarrhea lasts more than 14 days and has an insidious onset. Differential diagnosis is complex due to the multiplicity of causes.

Diarrhea is not easy to define in children, as the frequency and consistency of stools will vary with age and with the introduction of food. It is expected that the number of stools

Table I. Digestion of immediate principles in the gastrointestinal tract

Sources of immediate principles	*Enzymes*	*Products of digestion*
Lipids (90% triglycerides)	Lingual, gastric and pancreatic lipase	Fatty acids, 2-monoglycerides, glycerol, phosphatidylcholine and free cholesterol
Proteins (dietary and recycled from the digestive tract)	Gastric pepsin, pancreatic peptidases and intestinal villi peptidases	Amino acids. Dipeptides and tripeptides
Carbohydrates (disaccharides, starch and glycogen)	Amylase (salivary and pancreatic): it acts on α1,4 bonds of oligosaccharides	Maltose and maltotriose
	Maltase (brush border)	Glucose
	Sucrase (brush border)	Glucose and fructose
	Isomaltase (brush border): it acts on α1,6 bonds of oligosaccharides	Glucose
	Trehalase (brush border)	Trehalose
	Lactase (brush border)	Glucose and galactose

will decrease and their consistency will increase over time. The WHO defines diarrhea as the passage of 3 or more stools per day, soft or liquid, or with a frequency greater than the patient's previous rate[1].

Prolonged diarrhea is diarrhea that lasts more than 14 days. It usually has an acute onset and is more common in children under 5 years of age. Chronic diarrhea is diarrhea that lasts more than 14 days, has an insidious onset and slow progression[2].

Chronic diarrhea can have multiple etiologies and different pathophysiological mechanisms, so the differential diagnosis is not simple. A detailed clinical history and a physical examination focused on the nutritional status and potential specific nutritional deficiencies are necessary to select complementary tests aimed at determining the cause.

Pathophysiology

Chronic diarrhea is classified into osmotic diarrhea and secretory diarrhea. It can also be divided into diarrhea due to malabsorption and diarrhea due to maldigestion.

The intestine handles a large amount of fluids that come from food intake and from secretions of saliva, gastric juice, bile, pancreatic and intestinal juice. There are numerous processes of transporting fluids, electrolytes and solutes that take place mainly in the small intestine. The rest of the fluids are reabsorbed in the large intestine to form the fecal bolus. Any imbalance in these processes will lead to diarrhea.

The most important mechanism for regulating fluid transport is through the active transport of ions (sodium, chloride and bicarbonate) through the enterocyte. The movement of sodium promotes absorption and that of chloride promotes fluid secretion. The integrity of the epithelial barrier is also necessary to prevent electrolytes and, therefore, fluid, from being passively transported after absorption or secretion. Finally, normal intestinal motility is necessary to ensure adequate contact between nutrients and the intestinal epithelium. The digestion process begins with the action of luminal enzymes and is completed by the action of brush border enzymes in the intestinal mucosa (Table I).

Chronic diarrhea is classified, according to its pathophysiological mechanism, into osmotic diarrhea and secretory diarrhea.

- *Osmotic diarrhea:* This is the result of malabsorption of solutes. As in all diarrhea, osmotic forces are produced; some authors prefer the term food-induced diarrhea[3]. The increase in osmolarity in the intestinal lumen produces movements in favor of the gradient of water and electrolytes. This type of diarrhea characteristically improves with fasting[3].
- *Secretory diarrhea:* In these diarrheas there is an increase in the secretion of liquids carried by anions (chlorine or bicarbonate) or potassium or by the loss of the mechanism of absorption of liquids through sodium. For this reason, some authors prefer to use the term of diarrhea related to the transport of electrolytes[3].

Chronic diarrhea can also be classified according to the digestive process by which the alteration occurs:

- *Maldigestion:* When the production of digestive enzymes, both intraluminal and brush border, which hydrolyze proteins, fats and carbohydrates, fails. Pancreatic enzymes are primarily involved and clinically steatorrhea predominates.
- *Malabsorption:* When there is an alteration of the intestinal epithelium that prevents the transport of already digested nutrients. The fermentation of unabsorbed food in the colon produces short-chain fatty acids, which have a cathartic effect in the small intestine, giving rise to very voluminous stools.

Etiology

Diarrhea of functional or organic origin should be suspected and the possible causes of organic diarrhea should then be assessed, taking into account the age of onset and the warning symptoms.

There are many causes of chronic diarrhea. It is important to take into account the patient's age in order to

logically consider the different etiological possibilities. Table II shows the main causes of chronic diarrhea by age group.

Chronic diarrhea may be of functional or organic origin. Warning signs and symptoms (Table III) should be sought, the absence of which indicates a diagnosis of functional diarrhea, with the consequent limitation of the complementary examinations to be performed.

Functional diarrhea

- Functional diarrhea in infants: It is characterized by the passage of at least 4 stools per day, abundant, unformed, with recognizable and light-colored foods, without pain, loss of appetite or alteration in weight gain. It begins at 6 months and usually resolves by 5 years, but can persist throughout childhood and adolescence[4,5].
- Irritable bowel syndrome: It is characterized by at least 4 days per month for 2 months of abdominal pain associated with one or more of the following symptoms: pain with defecation, change in frequency and change in appearance of stools, in this case with a predominance of diarrhea[6].

Organic diarrhea

The most important clinical characteristics of each disease are shown in table IV.

Diarrhea and congenital enteropathies

These are monogenic disorders, some of them extremely rare, with autosomal recessive inheritance, which manifest in the days immediately after birth and even in utero, although there are exceptions, such as the case of saccharase-isomaltase deficiency that begins with the introduction of complementary feeding (fruits, juices and starchy foods)[7]. They mainly cause liquid diarrhea, but they can also cause bloody diarrhea (very early-onset inflammatory bowel disease) or steatorrhea (primary deficiency of bile salts and alterations in the transport or metabolism of fat). Congenital diarrhea can be divided into 5 groups in relation to their pathophysiological mechanism:

1. Alterations in epithelial transporters[3,8,9].
2. Alterations in epithelial enzymes and metabolism[3,7,10,11].
3. Structural and functional alterations of absorption[3,8].
4. Enteric neuroendocrinopathies[3].
5. Enteropathies associated with alterations in immunoregulation[3,12] (Table IV).

The most common disorder in this group is primary lactase deficiency, adult-type hypolactasia or lactase non-persistence. It is due to a decrease in the function of lactase-phlorizin hydrolase, an enzyme present in the most apical area of the intestinal villi. It is an autosomal recessive disorder that can appear in Caucasians from the age of 5 years. Symptoms begin with the ingestion of milk or dairy products, when the percentage of enzyme activity is less than 50% and vary greatly in intensity, since the adaptation of the intestinal flora contributes to tolerance. Secondary lactase deficiency is temporary and acquired after injury to the intestinal mucosa.

Table II. Causes of chronic diarrhea by age group*

Newborns	*1 month - 2 years*	*>2 years*
Diarrhea and congenital enteropathies	Functional diarrhea	Functional diarrhea
Cow's milk protein allergy. Chronic FPIES	Cow's milk protein allergy. Chronic FPIES	Irritable bowel syndrome
Short bowel syndrome	Intestinal parasitosis (Giardiasis)	Intestinal parasitosis (Giardiasis)
Hirschsprung enterocolitis	Celiac disease	Celiac disease
Necrotizing enterocolitis	Cystic fibrosis	Inflammatory bowel disease
	Immunodeficiencies	SIBO
	Inflammatory bowel disease	Pseudomembranous colitis
	Autoimmune enteropathy	Eosinophilic gastritis and colitis
	Other causes of pancreatic insufficiency	Drugs (laxatives, antibiotics)
	Diarrhea and congenital enteropathies	Microscopic colitis

**FPIES: food protein-induced enterocolitis syndrome; SIBO: small intestinal bacterial overgrowth.*

Table III. Suspected chronic diarrhea of organic origin. Warning signs and symptoms

- Neonatal onset
- Polyhydramnios
- Dehydration
- Abdominal distension
- Visceromegaly
- Bloody stools
- Nighttime bowel movements
- Weight loss
- Specific micronutrient deficiencies
- Delayed growth, puberty or psychomotor development
- Anal alterations: fissures, fistulas and rash
- Edema
- Unexplained fever
- Joint, eye or skin involvement
- Family history of celiac disease or inflammatory bowel disease

Table IV. Chronic diarrhea: summary table of the different etiologies and their clinical manifestations

Disease	*Clinical picture*
Diarrhea and congenital enteropathies	
– Alterations in epithelial transporters	
• Congenital chlorinated diarrhea	Liquid diarrhea. Elevated chloride in stool. Hypochloremic, hypokalemic alkalosis.
• Congenital sodium diarrhea	Liquid diarrhea. Elevated sodium in stool. Metabolic acidosis
• Glucose-galactose malabsorption	Liquid diarrhea. Severe dehydration, metabolic acidosis. It worsens with rehydration solutions.
• Primary bile acid diarrhea	If not absorbed: liquid diarrhea If deficiency: fat malabsorption with steatorrhea
• Acrodermatitis enteropathica	Diarrhea, periorificial dermatitis and alopecia
– Alterations in epithelial enzymes and metabolism	
• Congenital lactase deficiency	Extremely rare. Liquid diarrhea. Metabolic acidosis and hypercalcemia.
• Primary lactase deficiency or adult-type hypolactasia	Abdominal pain, flatulence, nausea and liquid diarrhea
• Sucrase-isomaltase deficiency	Liquid diarrhea, vomiting, weight loss, irritability with sugar intake and perianal erythema
• Diacylglyceroltransferase-1 deficiency	Diarrhea (protein-losing enteropathy), vomiting and weight loss
• Alterations in fat transport or metabolism: abetalipoproteinemia, familial hypobetalipoproteinemia, and chylomicron retention disease	Steatorrhea and deficiency of fat-soluble vitamins
• Intestinal lymphangiectasia	Obstructed, distorted and dilated intestinal lymphatics that rupture, allowing lymph to leak into the intestine, causing protein-losing enteropathy: moderate diarrhea, edema, abdominal pain and weight loss
– Structural and functional alterations in absorption	
• Microvillus inclusion disease, congenital tufting enteropathy, tricho-hepato-enteric syndrome	Secretory type liquid diarrhea
– Enteric neuroendocrinopathies	
• Proprotein convertase 1 deficiency. Mitchell-Riley syndrome	Osmotic diarrhea with overall malabsorption. Associated with endocrine diseases: adrenal insufficiency, hypothyroidism, diabetes insipidus, type 1 diabetes and hypogonadotropic hypogonadism.
– Enteropathy associated with alterations in immunoregulation	
• Very early onset inflammatory bowel disease (<2 years)	Symptoms similar to those of an older child with inflammatory bowel disease
• Autoimmune enteropathies (including IPEX syndrome: X-linked syndrome with immune dysregulation, polyendocrinopathy, enteropathy)	Severe secretory liquid diarrhea and malnutrition. More frequent in men. IPEX syndrome includes polyendocrinopathy
• Immunodeficiencies	When an intestinal infection persists after the expected infectious period or recurs in an unexplained manner

(Continued)

In addition to congenital diarrhea, newborns may present diarrhea due to congenital digestive malformations, such as short intestine (<75 cm in length) and enterocolitis as a complication of Hirschsprung's disease. Other chronic diarrheas are acquired and more frequent in premature infants, such as intestinal anatomical defects (atresia) or necrotizing enterocolitis[3].

Abnormal immune response

This group includes diseases that are much more common in clinical practice, such as celiac disease, non-IgE-mediated cow's milk protein allergy

Table IV *(continued)*. Chronic diarrhea: summary table of the different etiologies and their clinical manifestations

Disease	*Clinical picture*
Abnormal immune response	
– Celiac disease	Classic form: diarrhea, bloating and weight loss
– Non-IgE mediated allergy to cow's milk proteins	
• Food protein-induced allergic proctocolitis	Diarrhea with mucus and blood in an infant with good general condition
• Food protein-induced enterocolitis (FPIES), chronic form	Chronic or intermittent vomiting, liquid diarrhea and poor weight gain in formula-fed infants under 4 months of age
– Eosinophil gastrointestinal disorders: eosinophilic gastritis and eosinophilic colitis	Eosinophilic colitis may present with tenesmus and stools with mucus and blood due to the presence of ulcers or erosions.
– Inflammatory bowel disease: Crohn's disease, ulcerative colitis, indeterminate forms	Crohn's disease: abdominal pain, diarrhea, and/or weight loss. Iron deficiency anemia, intermittent fever, or growth retardation. Perianal disease Ulcerative colitis: abdominal pain, diarrhea with blood and mucus, tenesmus and nocturnal bowel movements
– Microscopic colitis: lymphocytic colitis and collagenous colitis	Intermittent or chronic liquid diarrhea
Exocrine pancreatic insufficiency	
– Cystic fibrosis	Chronic diarrhea, steatorrhea, abdominal pain, flatulence and poor weight gain
– Schwachman-Diamond syndrome	Chronic diarrhea, bone marrow failure (hypoplasia and fatty infiltration), with hematological alterations and skeletal abnormalities
– Johanson-Blizzard syndrome	Chronic diarrhea with facial abnormalities, dental abnormalities, mental retardation and hypothyroidism
– Pearson syndrome	Chronic diarrhea, refractory sideroblastic anemia, neutropenia and thrombocytopenia and multiorgan dysfunction
– Congenital deficiency of specific pancreatic enzymes: enterokinase, lipase/colipase or trypsinogen	They present symptoms related to malabsorption of fats or proteins. In enterokinase deficiency there is protein-losing enteropathy.
Drug-induced diarrhea	
– Antibiotic-associated diarrhea	Liquid diarrhea
– Pseudomembranous diarrhea	Diarrhea that may contain blood
– Laxative abuse (polyethylene glycol, magnesium hydroxide), sorbitol and artificial sweeteners	Liquid diarrhea
– Nonsteroidal anti-inflammatory drugs, proton pump inhibitors	Inflammatory diarrhea
Miscellaneous	
– Small intestinal bacterial overgrowth syndrome (SIBO)	Chronic diarrhea, abdominal pain and distension, flatulence, belching, nausea, mucus-filled stools. Iron deficiency anemia, deficiency of fat-soluble vitamins and vitamin B12, steatorrhea and weight loss in severe cases with predisposing factors.

(CMPA)[13] and inflammatory bowel disease (IBD). Primary eosinophilic gastrointestinal disorders produce a wide variety of symptoms, including chronic diarrhea, and are becoming more prominent in specialized units. The two entities that cause diarrhea are eosinophilic gastritis and eosinophilic colitis[14]. Finally, in microscopic colitis, which includes lymphocytic colitis and collagenous colitis, the mucosa has a normal appearance and specific histological findings are what allow the diagnosis, as both diseases are clinically indistinguishable[15].

Exocrine pancreatic insufficiency

In exocrine pancreatic insufficiency, there is a decrease in the secretion of pancreatic enzymes, bicarbonate, or both, leading to maldigestion of nutrients. The main enzymes secreted are amylase for carbohydrate digestion, lipase for fat digestion, and proteases (trypsinogen and chymotrypsin) for protein digestion. Amylase insufficiency does not cause symptoms, since it is compensated by the secretion of amylase from the salivary glands and from the small intestine. When trypsin secretion is less than 5-10% of normal, there is an excess loss of nitrogen in the feces. Therefore, the main consequence of pancreatic insufficiency is fat malabsorption.

The most characteristic symptoms are chronic diarrhea, steatorrhea and weight loss associated with abdominal distension, which appear when pancreatic function is less than 10%. There is also a deficiency of fat-soluble vitamins (A, D, E, K) and trace elements, such as magnesium and zinc[16].

Drug-induced diarrhea

- Antibiotic-associated diarrhea: It appears up to 2 weeks after the start of antibiotics, such as cephalosporins, ampicillin and amoxicillin/clavulanic acid.
- Pseudomembranous colitis: Caused by *Clostridium difficile* in children treated with antibiotics (clindamycin, penicillin, fluoroquinolones and cephalosporins). It can also occur in children with inflammatory bowel disease or immunodeficiencies[17].
- Non-antibiotic-associated diarrhea: Laxative abuse (Polyethylene glycol, magnesium hydroxide), sorbitol and artificial sweeteners, and treatment with erythromycin, which accelerates intestinal transit, do not alter the intestinal mucosa. However, non-steroidal anti-inflammatory drugs and proton pump inhibitors (PPIs) can cause enteritis[17].

Miscellaneous

Small intestine bacterial overgrowth syndrome (SIBO) is characterized by an excessive growth of microorganisms in the small intestine, either colonic (coliforms) or oropharyngeal and respiratory bacteria. In a recent study, the two factors most frequently associated with its development were a history of gastrointestinal infection in the previous year and the use of PPIs in the previous month. Only 7.4% had a history of previous intestinal surgery and up to 22.2% had recurrence after treatment[18].

Diagnosis

The diagnosis of chronic diarrhea is based on a complete history and physical examination and on the performance of complementary tests and first and/or second level diagnostic tools.

Medical history and physical examination

When assessing a patient with chronic diarrhea, it is very important to evaluate the age of onset and its possible relationship with the introduction of new foods, previous or current drug treatments, stool characteristics, and family history of digestive diseases.

The characteristics of the stools can provide information about the mechanisms responsible for diarrhea: carbohydrate intolerance (liquid, explosive and acidic stools, which may be associated with perianal erythema); maldigestion of fats (sticky, shiny, pale and floating stools); autoinflammatory origin (frequent, small stools with mucus and/or blood, which may be associated with tenesmus and/or nocturnal habits) and functional origin (soft stools, whose consistency decreases throughout the day and which may contain food remains, sometimes alternating with normal or hard stools).

Physical examination and anthropometric assessment are essential to evaluate the possible nutritional impact of diarrhea and to detect warning signs and symptoms. The patient's weight and height should be plotted on a growth chart, since a decrease in height may be a sign of organic pathology.

In functional disorders, a compatible clinical picture and the absence of alarming data are sufficient to establish the diagnosis; whereas, if organic pathology is suspected, complementary tests are usually necessary based on the patient's age, clinical picture and findings on examination.

First level complementary tests

These are sufficient to establish the diagnosis of the most frequent causes of chronic diarrhea in Primary Care.

- **Blood tests:** Complete blood count, biochemistry with blood glucose, urea, creatinine, total proteins, albumin, cholesterol, triglycerides, ions, calcium, phosphorus, alkaline phosphatase and ferritin. In addition, it is recommended to request: immunoglobulins, TSH, celiac disease serology and acute phase reactants, such as ESR and C-reactive protein. These parameters will allow us to diagnose diseases such as celiac disease and hyperthyroidism, as well as assess the possible malabsorption of nutrients or the biochemical impact. Thus, in inflammatory processes we can find anemia (of multifactorial origin), thrombocytosis, hypoalbuminemia and elevated acute phase reactants. Anemia may also be present in cases of malabsorption of iron, folic acid and/or vitamin B12, and low levels of total protein and serum albumin may indicate protein-losing enteropathy[8].
- **Microbiological stool examination:**
  - Stool culture and viral antigens: Although these pathogens usually produce acute diarrhea, they can become chronic, mainly in children with immunodeficiencies.
  - Parasites in feces: Their determination is essential, since the *Giardia lamblia* infection is the most common infectious cause of chronic diarrhea in developed countries. Because of the intermittent shedding of the parasite cysts, collecting stool from three different days increases the sensitivity of the study.
  - *Clostridium difficile* toxin: Indicated if diarrhea is accompanied by blood in the stool, mainly in immunosuppressed patients, with inflammatory bowel disease or who have recently received antibiotic treatment.

- **Exclusion-provocation therapeutic test:** An empirical exclusion test and subsequent provocation may be considered if a non-IgE-mediated allergy or digestive intolerance is suspected, as may occur with cow's milk proteins (in infants) or with some carbohydrates (lactose or fructose).

Second level complementary tests

If a complete clinical assessment and a first-level study do not lead to a diagnosis of chronic diarrhea, specific studies must be performed by a pediatric gastroenterologist. The choice of tests to be performed will be guided by the diagnostic suspicion based on the symptoms and characteristics of the diarrhea.

- **Blood tests guided by clinical suspicion:**
  - Certain antibodies may be positive in IBD, such as *anti-Saccharomyces cerevisiae* (ASCA), more frequent in Crohn's disease, and anti-neutrophil cytoplasmic antibodies (p-ANCA), which may be elevated in ulcerative colitis[2].
  - Low levels of fat-soluble vitamins (A, E and D) are detected in cases of pancreatic insufficiency.
  - Low zinc levels, in the context of chronic diarrhea associated with acrodermatitis, may guide to acrodermatitis enteropathica.
- **Stool studies:**
  - Van de Kamer test: It consists of determining fat in 72 hour feces. Newborns and infants excrete between 15 and 20% of fat in their diet in their feces. The fat absorption coefficient increases with age and reaches adult values of >95% after one year of age. Normal values are <3 g/24 hours in children and <6 g/24 hours in adults. It is advisable to carry out a three-day dietary survey with determination of the fat absorption coefficient (fat ingested/fat excreted) to avoid false negatives due to low fat intake. Although it is the gold standard, other techniques have appeared, such as near-infrared reflection analysis (NIRA), which facilitates sample handling and also provides data on the absorption of sugars (normal values <2.5%), starch (normal values <1%) and water content (normal values <85%).
  - Stool osmolality: Stool electrolytes are used to calculate the fecal osmotic gap. In secretory diarrhea, the stool osmotic gap is <50 mOsm/kg, whereas in osmotic diarrhea it is >125 mOsm/kg[2].
  - Reducing substances (>1%) and stool pH (<5.3) indicate carbohydrate malabsorption. It should be noted that sucrose is a non-reducing sugar.
  - Fecal elastase-1: It is a pancreatic enzyme resistant to degradation by the intestinal flora, so when the value is low (<200 µcg/g of feces) it suggests pancreatic exocrine insufficiency[8].
  - Fecal α1-antitrypsin: It is a serum protein synthesized in the liver, resistant to proteolysis, which is normally present in low concentrations in the stool. Values ≥2 mg/g stool in a sample may indicate protein loss.
  - Fecal calprotectin: This cytosolic protein of neutrophils is elevated in cases of intestinal inflammation, with normal values <50 µg/g. Despite its high sensitivity, this parameter may be elevated in gastrointestinal infections, juvenile polyps, use of non-steroidal anti-inflammatory drugs or gastrointestinal bleeding. In addition, calprotectin values have a significant negative correlation with age, with very high levels of up to 1,500 µg/g being observed in healthy infants and a wide variability up to 4 years of age, so caution should be exercised when interpreting it in children under this age[19].
  - Fecal occult blood: Nonspecific marker indicating gastrointestinal blood loss.
- **Breath test:** Lactose and fructose breath tests consist of administering these labelled carbohydrates and subsequently measuring exhaled H_2. In cases of carbohydrate malabsorption, carbohydrates are not absorbed and are therefore fermented in the colon, producing H_2 and methane, which pass into the blood and are eliminated during exhalation. In SIBO, the bacteria in the small intestine ferment glucose before it is absorbed, with an early increase in hydrogen in the breath being detected. When carbohydrate intolerance is suspected, these tests are only indicated in cases of no conclusive clinical response to exclusion-provocation.
- **Endoscopy and histological study:** This test is essential in diseases such as inflammatory bowel disease, celiac disease, congenital enteropathies, microscopic colitis, primary eosinophilic gastrointestinal disorders, abetalipoproteinemia and intestinal lymphangiectasia, as well as for the study of disaccharidases in intestinal mucosa.
- **Genetic studies:** Most congenital diarrhea, cystic fibrosis (CF), monogenic IBD and immunodeficiency disorders have a genetic basis. Genetic analysis helps to make a definitive diagnosis and guide management.
- **Sweat test:** Stimulation of sweat by iontophoresis with pilocarpine. A first test is performed using conductivity and if the values are >50mmol/l, the concentration of chlorine in sweat will be measured. Two chlorine determinations of >60 mmol/L confirm the diagnosis of CF. Values between 40-60 mmol/L are considered doubtful.
- **Imaging tests:** Abdominal ultrasound and magnetic resonance play an important role in the study of IBD. Tc99-labeled albumin allows visualization of lymph leakage in intestinal lymphangiectasia.

At the end of the article, the diagnostic algorithm for chronic diarrhea is shown, with first and second level examinations of the different pathophysiological types of diarrhea and by etiology.

Treatment

Treatment of chronic diarrhea is based on general management of the disease, ensuring adequate nutritional support, and specific treatment of the underlying cause.

General treatment

The treatment of chronic diarrhea requires an accurate diagnosis for an adequate and specific management of the underlying cause, with nutritional rehabilitation being the most important aspect in the treatment of these patients. Adequate nutrient intake will facilitate the recovery of the intestinal mucosa, with the oral route being the route of choice. Occasionally, nutritional supplements may be necessary to cover the patient's requirements. In cases of poor oral tolerance or compromised swallowing safety or efficacy, feeding may be administered through a nasogastric or transpyloric tube with continuous or intermittent delivery. The parenteral route will be reserved for those patients with poor enteral tolerance, severe malnutrition and intractable diarrhea. The use of drugs that inhibit intestinal peristalsis is not recommended in the pediatric population. Probiotics would only be indicated for the prevention of antibiotic-associated diarrhea and there is insufficient evidence for the prevention or treatment of SIBO.

Specific treatment

- **Dietary treatment:** This will be the treatment of choice in pathologies in which there is malabsorption due to a deficiency of enzymes or transport proteins, as occurs in glucose-galactose malabsorption, lactose or fructose intolerance, or saccharase-isomaltase deficiency, where the management of these clinical pictures is based on the partial or total withdrawal of the carbohydrate involved[20]. It is also the treatment of choice in chronic diarrhea due to non-IgE mediated allergies, such as in CMPA[13]. The strict gluten-free diet is the treatment for celiac disease. In intestinal lymphangiectasia, nutritional management is essential, indicating a low-fat diet, with medium chain triglycerides (MCT) and rich in protein[20]. In alterations in the transport and metabolism of fats, such as abetalipoproteinemia, fats in the diet will be restricted and essential fatty acids will be provided[20]. In Crohn's disease, dietary treatment has an important role as an alternative to corticosteroids. In cystic fibrosis, supplementation with fat-soluble vitamins is required. In diarrhea associated with protein-losing enteropathy, a fat-free or low-fat diet is required, with MCT oil, rich in protein and supplementation with fat-soluble vitamins and essential fatty acids[20].
  In functional diarrhea, a diet low in oligosaccharides, disaccharides, monosaccharides and fermentable polyols (FODMAPS) may be useful in irritable bowel syndrome, although they should be prescribed with caution and closely monitored due to the risk of nutritional repercussions[20].

- **Pharmacological treatment:** Specific treatments will depend on the etiology of the diarrhea. Antibiotics are mainly used in diarrhea of infectious origin, although they may also be indicated in SIBO (rifaximin or metronidazole)[18]. Corticosteroids and immunomodulatory drugs are widely used in IBD and in less frequent pathologies, such as microscopic colitis[15], gastrointestinal eosinophilic disorders[14], autoimmune enteropathy and intestinal lymphangiectasia[8]. Other specific treatments include: enzyme replacement therapy in exocrine pancreatic insufficiency; ion exchange resins in bile acid diarrhea; and octreotide in intestinal lymphangiectasia[8].

Role of the Primary Care pediatrician

- To perform the initial clinical history and physical examination, detailing the characteristics of the stools and the nutritional status of the patient.
- To request first-level tests, which can diagnose the most common causes of chronic diarrhea.
- Referral to the pediatric gastroenterology consultation, if a diagnosis has not been reached and the patient´s symptoms remain.

Conflict of interest

There is no conflict of interest in the preparation of the manuscript.

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Asterisks indicate the authors' opinion of the article as being of interest.

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Recommended bibliography

– Tripathi PR, Srivastava A. Approach to a Child with Chronic Diarrhea. Indian J Pediatr. 2024; 91: 472-80.

Review article explaining the different clinical types of chronic diarrhea. It also updates the diagnostic procedures available and shows comprehensive diagnostic algorithms for making the differential diagnosis.

– Shankar S, Rosenbaum J. Chronic diarrhoea in children: A practical algorithm-based approach. JPed Child Health. 2020; 56: 1029-38.

Review article that, in addition to showing diagnostic algorithms, assesses the pharmacological treatments available for some types of chronic diarrhea.

– Shankar DS, Durairaj E. Diet and Management of Diarrhea. Indian Journal of Pediatrics. 2024; 91: 590-7.

Excellent review article that assesses in detail the treatment of the different causes of chronic diarrhea, whose therapy is exclusively dietary.

Clinical case

A 3-year-old boy with a history of atopic dermatitis and IgE-mediated egg allergy came to the clinic with diarrhea that had been ongoing for 6 months. The parents reported that he had previously had one or two episodes of Bristol type 4 stools per day. However, after starting nursery school he had multiple infectious processes, including acute gastroenteritis lasting for up to 5 days, with diarrhea, fever and vomiting. Since then, the patient has had 2-3 Bristol type 6 stools a day with abundant bloating. He has abdominal distension after meals and periumbilical discomfort. He has not had loss of appetite and has an ascending height and weight curve. They do not relate the diarrhea and the accompanying symptoms to the intake of any specific food. The parents removed lactose from the diet with partial improvement for a week. However, the symptoms described above subsequently relapsed again.

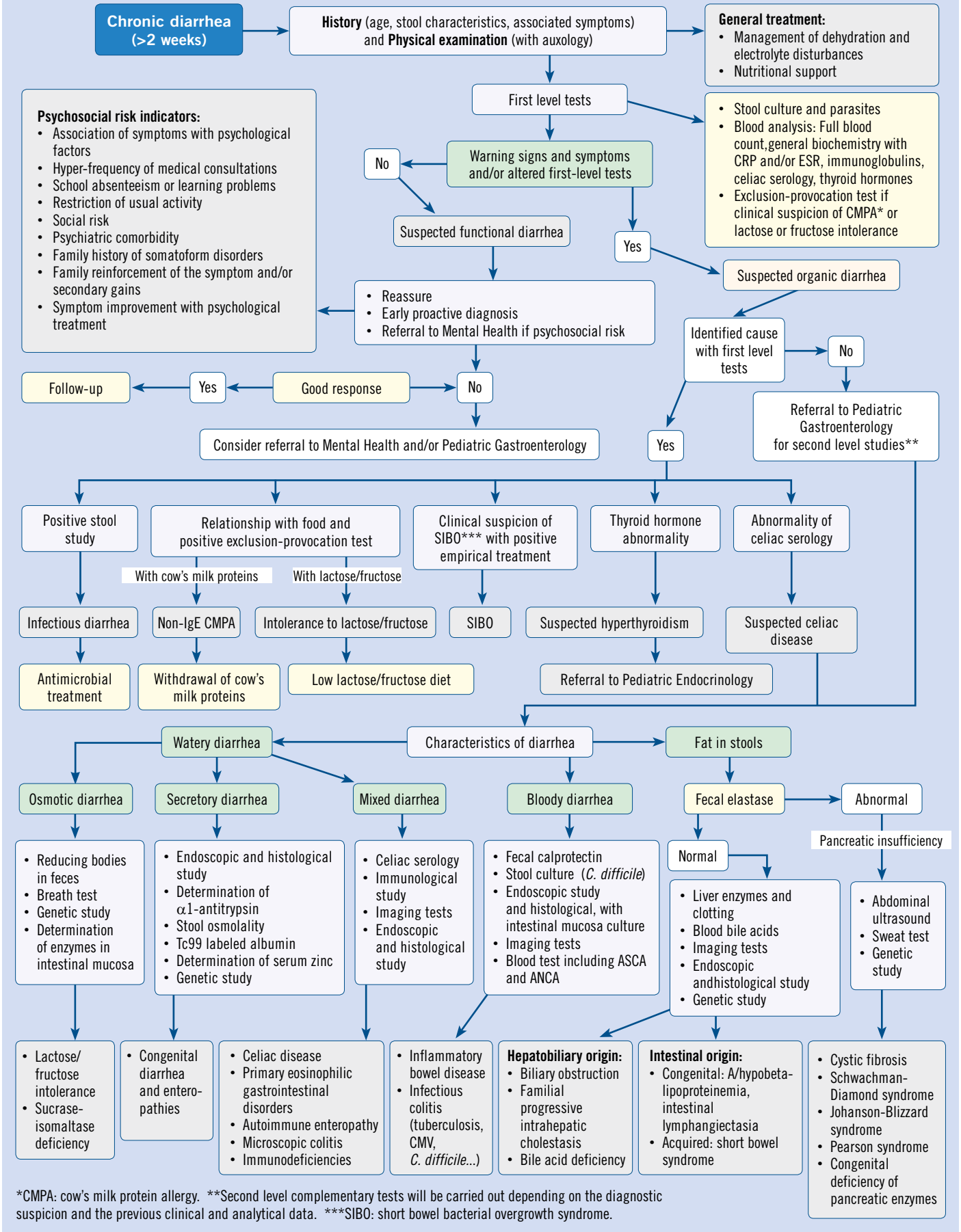
The patient's nutritional and hydration status was good, with a normal systematic examination, in which the only notable feature was a globular abdomen, although soft and depressible, without masses or megalies, and it did not seem painful to palpation.

Given the chronic diarrhea, a stool culture and stool parasites were obtained, which were negative, and a blood test with a normal complete blood count and biochemistry (with immunoglobulins), except for positive anti-deaminated gliadin peptide IgG (40 U/ml), with negative anti-transglutaminase IgA and antiendomysium.

Accreditation quiz

The Accreditation Questionnaires for FC topics can be done at "On line" through the web: www.sepeap.org and www.pediatriaintegral.es. To obtain the single continuous training accreditation from the accreditation system for health professionals for the entire national health system, 70% of the questions must be answered correctly. The accreditation questionnaires on the different issues in the journal may be carried out during the period stated in the online questionnaire.

Diagnostic algorithm for chronic diarrhea



*CMPA: cow's milk protein allergy. **Second level complementary tests will be carried out depending on the diagnostic suspicion and the previous clinical and analytical data. ***SIBO: short bowel bacterial overgrowth syndrome.

Accreditation quiz

Subsequently, the following accreditation quiz of Pediatría Integral collects questions on this topic, which must be answered online through the website: www.sepeap.org.
In order to obtain certification by the Spanish "formación continuada" national health system for health professionals, 70% of the questions must be answered correctly. The accreditation quizzes of the different numbers of the journal may be submitted during the period indicated in the "on-line" quiz.

Chronic diarrhea

9. In chronic diarrhea due to maldigestion of nutrients, all of the following answers are correct EXCEPT:

a. There is an alteration in the intestinal epithelium.
b. There is a failure in the production of intraluminal enzymes.
c. There is a failure in the production of the brush border enzymes.
d. Most often, pancreatic enzymes fail.
e. The most important consequence is steatorrhea.

10. In a child with exclusively milk-based diet and diarrhea, which begins in the first three months of life, all of the following causes are possible, EXCEPT:

a. Congenital chlorinated diarrhea.
b. Glucose-galactose intolerance.
c. Deficit of sucrase-isomaltase.
d. Microvillus inclusion disease
e. Cystic fibrosis.

11. Which of the following complementary examinations are NOT included in the first-level workup of an 18-month-old child with chronic diarrhea?

a. Full blood count.
b. Ferritin, total proteins and albumin.
c. Celiac disease serology.
d. Stool culture and study of parasites in stool.
e. Fecal elastase.

12. Which of the following statements is INCORRECT regarding fecal calprotectin?

a. It is found in the cytoplasm of neutrophils.
b. It is a noninvasive marker of intestinal inflammation.
c. It may be elevated in acute gastroenteritis.
d. Healthy children under 4 years of age have very low values.
e. It is elevated in cases of gastrointestinal bleeding.

13. In one of the following diseases, the treatment is EXCLUSIVELY dietary:

a. Ulcerative colitis.
b. Small intestine bacterial overgrowth syndrome (SIBO).
c. Cystic fibrosis.
d. Celiac disease.
e. Pseudomembranous diarrhea *(Clostridium difficile)*.

Clinical case

14. What do you think is the MOST PROBABLE diagnosis for the patient in the case described?

a. Celiac disease.
b. Bacterial overgrowth.
c. Fructose intolerance.
d. Diarrhea of functional origin
3. Eosinophilic colitis.

15. Which diagnostic tool/s do you consider to be the first CHOICE for the patient's pathology?

a. Performing endoscopy and taking biopsies at the duodenum level.
b. Performing colonoscopy with serial biopsies throughout the colon.
c. An adequate history and physical examination.
d. An exclusion-provocation test.
e. c and d are correct.

16. What is the treatment of CHOICE for this patient?

a. The strict gluten-free diet.
b. Empirical antibiotic treatment.
c. A low fructose diet.
d. Reassure and explain to the family the functional origin of the patient's condition.
e. Systemic corticosteroids and exclusion diet.

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