

Esophageal pathology

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Abstract

Esophageal diseases are diverse in nature: malformative, motor, traumatic, infectious, immunological and functional. The common embryological origin with the upper airway has led to the development of 'Aero-Digestive Medicine' units covering the different pathological processes common to both. In a previous edition published in this same journal in 2019⁽¹⁾, dedicated to Esophagitis and Gastritis, some esophageal pathologies were already reviewed. This article describes the most prevalent esophageal diseases, approached from a conceptual and practical point of view, especially from a Primary Care perspective. This is a review and update of the most prevalent pathologies, with special attention to the recommendations of the clinical practice guidelines of scientific societies. The pediatrician must bear in mind the possibility that the patient's symptoms are due to a specific esophageal pathology; he/she must know the advantages and limitations of the diagnostic methods as well as the coexistence of urgent pathology that requires immediate assessment and, conversely, functional problems that are frequently overtreated.

Key words: Esophageal motility disorders; Esophagitis; Eosinophilic esophagitis; Gastroesophageal reflux; Caustic ingestion.

Palabras clave: Trastornos de motilidad esofágica; Esofagitis; Esofagitis eosinofílica; Reflujo gastroesofágico; Ingestión de cáusticos.

Resumen

Las enfermedades esofágicas son de diversa índole: estructurales-malformativas, motoras, traumáticas, infecciosas, inmunológicas y funcionales. El origen embriológico común con la vía respiratoria superior ha propiciado el desarrollo de unidades de "Medicina Aero-Digestiva", que abarcan los distintos procesos patológicos comunes a ambos. En una edición anterior, publicada en esta misma revista en 2019⁽¹⁾, dedicada a Esofagitis y gastritis, ya fueron revisadas algunas patologías esofágicas. En este artículo se describen aquellas enfermedades esofágicas más prevalentes, enfocadas desde un punto de vista conceptual y práctico, especialmente desde la Atención Primaria. Revisión y actualización de las patologías más prevalentes, con especial atención a las recomendaciones de las guías de práctica clínica de sociedades científicas. El pediatra debe tener presente la posibilidad de que los síntomas del paciente se deban a una patología esofágica concreta; debe conocer las ventajas y limitaciones de los métodos diagnósticos, así como la coexistencia de patología urgente que requiere una valoración inmediata y, al contrario, problemas funcionales que frecuentemente son sobretreadados.

Introduction

Esophageal diseases are of diverse nature: structural-malformative, motor, traumatic, infectious, immunological and functional. The common embryological origin with the upper respiratory tract has led to the

development of "Aero-Digestive Medicine" units, which cover the different pathological processes common to both.

The pediatrician must be aware of the possibility that the patient's symptoms may be due to a specific esophageal pathology; he or she must be aware of the advantages and limitations of the diagnostic methods, as well as the coexistence of urgent pathology that

requires immediate assessment and, conversely, functional problems that are frequently overtreated.

Cardinal symptoms

Regardless of the etiology responsible for the injury, the symptoms are common in many of the diseases and different depending on the age of the patient,

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OBJECTIVES

- To recognize the symptoms and signs suggestive of esophageal disease.
- To assess the information provided by each diagnostic test: when to request it and what information to expect from it, in order to discriminate between functional and organic pathology, thus avoiding unnecessary treatments.
- To be familiar with the most prevalent pathologies such as eosinophilic esophagitis and gastroesophageal reflux disease.
- To identify that the increased survival rate of infants undergoing esophageal surgery, such as esophageal atresia, has led to the appearance of late-onset problems that need to be identified, studied and treated correctly.
- To know how to identify the drugs responsible for esophageal lesions. It is the primary function of the primary care pediatrician to give instructions to the patient (age permitting) or to his/her family to minimize the risk of developing these lesions, in addition to choosing the pharmaceutical forms with the lowest risk of producing them.
- To be aware that the widespread use of button cells made of lithium salts has changed the paradigm in their accidental handling. Early and appropriate attention is necessary in the management of these accidents and their referral to appropriate hospitals.

as reflected in Table I taken from the article by Thomson et al.⁽²⁾.

Study techniques

The etiological diagnosis of esophageal symptoms is a diagnostic challenge. It is essential to choose the most appropriate test based on the clinical case.

Diagnostic tests focused on etiological diagnosis are a challenge for the pediatrician, given the overlap of symptoms, already mentioned, and the absence of specific diagnostic guidelines for Pediatrics. The choice of the most appropriate technique should be based on the diagnostic hypothesis. Thus, esophagogastroduodenoscopy is the test of choice for the study of mucosal alterations; esophagogram to detect structural abnormalities and achalasia; chest CT or

magnetic resonance imaging (MRI) for the study of the mediastinum; manometry is the most sensitive in the detection of motor alterations and pH-impedance (pH-MMI) for the assessment of gastroesophageal reflux. A more detailed description of the advantages and disadvantages of each technique is summarized in table II, modified from Lanzoni et al.⁽³⁾.

Esophageal trauma

We pediatricians need to become aware of the importance of traumatic injuries to the esophagus and learn how to prevent them.

Drug-induced esophagitis

Pediatricians must raise awareness of the potential harm that some drugs can cause. It is essential to provide clear

instructions to the patient or his/her family to minimize the risk of developing esophageal injuries.

Epidemiology

The prevalence of drug-induced esophageal injuries is unknown, due to the lack of medical awareness of the relationship between drugs and esophageal injury, and the bias of thinking of more serious pathologies as responsible for the symptoms. In the USA, approximately 10,000 cases of drug-induced esophageal injuries are described each year at any age. To our knowledge, we have only found one publication of a series of exclusively pediatric cases⁽⁴⁾. In it, the results of 532 esophagogastrosopies performed over 4 years were retrospectively analyzed, identifying drug-induced esophageal injuries in 26 patients with a mean age of 10.76 years. The responsible drugs were exclusively nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics (doxycycline) and ferrous sulfate. Over time, 8 cases developed an esophageal stricture. More than 70 drugs responsible for the injury have been described, summarized in table III⁽⁵⁾.

Pathophysiology

The pathophysiological mechanism is varied: production of a caustic acid substance (ascorbic acid, ferrous sulphate), production of an alkaline caustic (alendronate), creation of a hyperosmolar substance in contact with the mucosa (potassium chloride) and direct cellular toxicity on esophageal epithelium (doxycycline)⁽⁵⁾.

Clinical manifestations

Symptoms include chest pain, generally of abrupt onset and almost always temporally related to the start of

Table I. Symptoms of esophageal disease

Infants and young children		Older children
General symptoms	Specific symptoms	
– Excessive crying	– Hematemesis/melena	– Epigastralgia, especially postprandial and nocturnal
– Irritability	– Anemia	– Nausea, regurgitation and vomiting
– Colic pain	– Sandifer Syndrome	– Anorexia
– Refusal to eat	– Aspiration	– Specific disorders of feeding and refusal to eat
– Failure to thrive	– Wheezing	– Pyrosis
– Excessive regurgitations	– Apnea, stridor	– Chest pain
– Vomiting	– BRUE*	– Odynophagia
	– Sudden infant death syndrome	– Early satiety
	– Dysphagia	– Hematemesis/melena
		– Anemia
		– Dysphagia

Modified from: Thomson et al⁽²⁾.

*BRUE (Brief Resolved Unexplained Events): Episode in an infant <1 year of age, sudden, short and resolved on consultation, in which two or more of the following symptoms are combined: cyanosis or pallor; cessation, slowing or marked irregularity of breathing; sudden alteration of muscle tone, with hyper or hypotonia; and/or alteration of the response to stimuli.

	<i>Pros</i>	<i>Cons</i>
Endoscopy	<ul style="list-style-type: none"> – Direct visualization of light and mucosa – Sampling for histological and microbiological studies – Extraction of foreign bodies – Pneumatic dilation of the esophagus 	<ul style="list-style-type: none"> – Need for sedation – It is not useful for diagnosing motor disorders – Possibility of complications (rare): bleeding, perforation and infection
pH-Multichannel Impedance	<ul style="list-style-type: none"> – Accurate assessment of gastroesophageal reflux – Possibility of placing the study probe together with endoscopy 	<ul style="list-style-type: none"> – Requires patient cooperation – No anatomical or motor alterations are reported
Esophagogram	<ul style="list-style-type: none"> – Widely available – Detailed information on esophageal anatomy – Identifies motor abnormalities (e.g., achalasia) – Can demonstrate extrinsic compressions 	<ul style="list-style-type: none"> – Radiation – Requires cooperation – Contraindicated in intestinal obstruction and suspected perforation – Possibility of complications: aspiration of barium and leaks due to perforation (pneumonitis, mediastinitis, peritonitis)
High resolution manometry	<ul style="list-style-type: none"> – Characterization of motor abnormalities – Allows the classification of subtypes of achalasia – Can report subtypes of congenital stenosis 	<ul style="list-style-type: none"> – Requires patient cooperation – It does not report the anatomy or mucosal alterations
Chest X-ray	<ul style="list-style-type: none"> – Identification of radiopaque foreign bodies – Identify mediastinal widenings and pneumomediastinum 	<ul style="list-style-type: none"> – Radiation
Thoracic CT/MRI	<ul style="list-style-type: none"> – Diagnosis of structural abnormalities or extrinsic compressions – Coupled with angiography is the gold standard for the diagnosis of vascular abnormalities responsible for dysphagia 	<ul style="list-style-type: none"> – Radiation (CT only) – Sedation in young children

Modified from: Lanzoni et al⁽³⁾.

medication (not the case with quinidine), odynophagia, dysphagia, vomiting and, more rarely, hematemesis.

Diagnosis

The technique of choice is endoscopy, which reveals mucosal erythema, erosions, ulcers (typically “mirror-image” in almost half of cases), bleeding, or in more severe cases, extensive mucosal dissection or perforation. It is not necessary to perform it in mild cases; although it is not only diagnostic, but also allows for differentiating lesions produced by other mechanisms and taking samples for histology and cultures. In most cases, the lesions are located in the middle third of the esophagus, coinciding with the imprint of the aortic arch in the esophageal lumen.

Treatment

Beyond the withdrawal of the responsible drug when possible or, at least, its substitution with another galenic form, the treatment consists of oral or

<i>Antibiotics</i>	<i>Antivirals</i>	<i>Bisphosphonates</i>
Clindamycin Doxycycline Penicillin Rifampicin Tetracycline Cloxacillin	Nelfinavir Zalcitabine Zidovudine	Alendronate Etidronate Pamidronate
<i>Non-steroidal anti-inflammatory drugs</i>	<i>Others</i>	<i>Chemotherapeutic agents</i>
Aspirin Ibuprofen Naproxen	Ascorbic acid Ferrous sulphate Lansoprazole Multivitamins Potassium chloride Quinidine Theophylline	Bleomycin Cytarabine Dactinomycin Daunorubicin 5-fluorouracil Methotrexate Vincristine Crizotinib

Source: Katzka et al⁽⁵⁾.

intravenous hydration as required and systemic and topical analgesics (viscous lidocaine or similar). The administration of antisecretory agents (omeprazole or derivatives) and sucralfate, although they

are common practice, lack clinical trials that demonstrate their efficacy. From the point of view of Primary Care, it is essential to give instructions to the patient or his family that minimize

the risk of developing esophageal lesions: do not take the tablets or capsules lying down or do not lie down until about 30 minutes after ingestion, ingest them with a sufficient quantity of liquid (in adults it is estimated at about 100 ml), preferably use tablets or capsules with gelatin coating and, if they are not available, syrups, sachets and other galenic forms. These indications are especially important in patients at risk: esophageal motor disorders, left atrial enlargement, previous cardiac surgery, diabetics, etc.

The most interested reader can refer to the review by Petersen and Jaspersen⁽⁶⁾, where what is presented here is described in more detail, as well as the individualized mechanism of production of the injury of the most frequent drugs.

Accidental ingestion of lithium batteries (button cells)

The gradual replacement of lithium button cells with silver, copper, mercury or other types of cells has led to an increase in morbidity and, in some cases, mortality following accidental ingestion. The mere suspicion of ingestion requires immediate medical evaluation.

The increase in electronic devices in homes to which children have access leads to an increase in accidental ingestion of the batteries of these devices.

Epidemiology

According to reports from the National Battery Ingestion Hotline (NBIH), in 2015 there were 1.5 cases per 100,000 children per year. The majority (75%) occurred in children under 6 years of age, with a peak between 1 and 2 years of age, and the most frequent electronic devices where batteries were housed were, in this order: hearing aids, toys and remote controls. In parallel with this increase in ingestion, an increase in morbidity has been observed caused by the progressive replacement of silver, copper, mercury, etc. batteries by lithium batteries, which are much more durable, lighter, stable at different temperatures and have a higher electrical charge (3 V versus 1.5 V), but with a larger diameter. As a result, accidental ingestion of lithium batteries by children went from 1% of all button cell battery ingestions in 1990 to 25% in 2008.

Pathophysiology

The importance of lithium batteries is that the mechanism of injury is liquefaction necrosis of the tissue in contact with the negative pole. When one of these batteries is impacted in the esophagus, the esophageal tissue in contact acts as a conductor, creating a current towards the negative pole (the one not labeled), which produces hydroxyl ions in the tissue that raise the pH above 12, thus being a necrosis equal to that produced by ingestion of a strong alkali, that is, deep, potentially producing perforations or fistulas to the trachea, aorta, right subclavian artery or lower thyroid, and prolonged, since the necrosis process persists after the battery is removed.

Clinical manifestations

Injury has been shown to occur after only 2 hours after impaction, and is especially severe after 8-12 hours. Ingestion of a discharged lithium battery should not be reassuring, as it still retains a residual charge of 1.5 V and experimental studies have shown that voltages of 1.2 V or higher are sufficient to injure tissue. In 2015, the endoscopy committee of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) published its recommendations for the management of foreign body ingestion in children⁽⁷⁾. Among these, it placed special emphasis on batteries larger than 20 mm in diameter and in children under 5 years of age. The recommended approach was immediate endoscopic removal if the patient was stable. In cases where the patient presented hemorrhage or hemodynamic instability, the removal should be performed in the operating room with the presence of a thoracic or cardiovascular surgeon. Any patient with an endoscopic esophageal injury should be admitted for treatment with a complete diet and antibiotics. Prior to discharge, the presence of perforation, vascular fistulas, etc. should be ruled out with appropriate tests, chest CT, angioCT or chest MRI.

A few years later, in 2021, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published its specific recommendations for the ingestion of button batteries in children⁽⁸⁾. It particularly highlights the location and time of ingestion, without mentioning the age or size of the battery.

Treatment

The main recommendations are summarized below:

- Ingestion of a button battery or even the mere suspicion thereof requires immediate clinical and radiological evaluation to confirm ingestion and the location of the battery.
- In cases where the battery lodges in the esophagus, immediate endoscopic removal of the battery is recommended, preferably within 2 hours after ingestion.
- If <12 hours have passed since ingestion, a weak acid may be administered in stable patients to try to minimize the damage prior to endoscopy. Experimental studies with sucralfate (10 ml every 10 minutes, maximum 3 doses) or honey in patients over 1 year of age (10 ml every 10 minutes, up to 6 doses) have shown a certain protective effect. In no case should administration delay endoscopic removal.
- In cases where ingestion has occurred >12 hours, it is advisable to perform a chest CT scan prior to removal, to rule out the presence of fistulas to large vessels that could cause massive bleeding after removal of the battery. The removal will be performed in the operating room, with the presence of a thoracic or cardiovascular surgeon.
- If the battery is lodged in the stomach and ingestion was <12 hours, the patient will be monitored and re-administered until the evaluation. A simple abdominal X-ray will be performed between 7 and 14 days to confirm its expulsion (the previous recommendation was to perform the X-ray after 2-4 days).
- A battery lodged in the stomach, ingested >12 hours previously, requires endoscopy to rule out the possibility that, before reaching the stomach, it remained lodged in the esophagus for a sufficiently long time to cause an esophageal injury.

From a practical and primary care point of view, the mere suspicion of accidental ingestion of a battery requires immediate evaluation. Sucralfate is considered a foreign drug, so it is unlikely to be available in health centers, but honey is a cheap and accessible remedy. Given the recommendation of the presence of a surgeon during endoscopic removal in

Table IV. Classification of esophageal atresia

<i>Classification</i>	<i>Gross</i>	<i>Vogt</i>	<i>Frequency</i>
Atresia without TEF	A	II	8%
Atresia with proximal TEF	B	III	1%
Atresia with distal TEF	C	IIIb	84%
Atresia with proximal and distal TEF	D	IIIa	3%
TEF without atresia (type H)	E	IV	4%

TEF: tracheoesophageal fistula.

cases of prolonged ingestion (>12 hours before), we recommend referring the patient directly to a tertiary center. Evaluation in a center without these possibilities would only delay assistance.

Malformations and motor disorders

Esophageal malformations

Esophageal atresia should be suspected in a newborn with respiratory difficulty, hyper-salivation and regurgitation that worsens with feeding, in addition to the inability to pass a nasogastric tube.

Epidemiology

Esophageal atresia (EA) is the most common congenital anomaly of the esophagus, with 90% of cases presenting with an associated tracheoesophageal fistula (TEF). EA is associated with other anomalies in 50% of cases, often as part of the VATER or VACTERL association, CHARGE syndrome, and especially with cardiac and genitourinary defects. Table IV presents the classification of the different types of EA.

Clinical manifestations

In the prenatal period, it may present with polyhydramnios, prematurity, or other associated malformations may be detected. In the postnatal period, it usually presents with hypersalivation and drooling. Episodes of coughing, cyanosis, and respiratory distress may appear. Feeding accentuates these symptoms, causes regurgitation, and may cause aspiration. Aspiration of gastric contents through a distal fistula may cause pneumonitis. In less frequent cases of isolated TEF in the absence of EA (type H), the symptoms usually appear in later stages

of life, generally with chronic respiratory problems.

Diagnosis

EA should be suspected in a newborn if respiratory distress of early onset develops and there is inability to pass a nasogastric or orogastric tube. Findings on fetal ultrasound of an absent gastric bubble and the presence of polyhydramnios may guide the diagnosis before delivery. On postnatal plain radiographs, the tip of the tube appears coiled in a spiral in the esophageal pouch and/or gastric distension with air is seen, indicating the presence of a coexisting TEF. In contrast, in isolated EA, the abdomen appears excavated and devoid of air. Isolated TEF (type H) can be identified by a contrast-enhanced esophagram or by bronchoscopy.

Treatment

General measures, such as maintaining a patent airway and decompressing the proximal pouch, are essential to prevent aspiration of secretions. In newborns with TEF without other associated pathologies, early surgical intervention is performed. The surgical technique consists of sectioning the TEF and primary end-to-end anastomosis. If the distance between the ends of the esophagus is wide, a fragment of stomach, jejunum or colon must be interposed as a neo-esophagus⁽⁹⁾.

Prognosis

The prognosis of isolated EA is generally good, with a survival rate of >90%, conditioned mainly by birth weight and the presence of associated severe cardiac malformations. Long-term complications are frequent and the primary care pediatrician must be aware of them in order to increase diagnostic suspicion

and initiate appropriate treatment early. Long-term complications include respiratory complications and gastroesophageal reflux disease. Patients operated on for EA require treatment with proton pump inhibitors, at least during the first year of life, subsequently re-evaluating the persistence of reflux⁽¹⁰⁾.

Motor disorders of the esophagus

The clinical presentation of achalasia is gradual and insidious, with chronic respiratory symptoms predominating in young children and digestive symptoms in older children. A high diagnostic suspicion is necessary to avoid a delay in treatment.

Esophageal motor disorders are rare and have little known etiology. They may be primary or secondary to esophageal pathology (reflux esophagitis, caustic esophagitis, etc.), or to systemic diseases (scleroderma, dermatomyositis, Chagas disease, etc.). Achalasia is a primary motor disorder, characterized by the absence of peristalsis and insufficient relaxation of the lower esophageal sphincter.

Epidemiology

It is rare in children and is sometimes associated with various syndromes, such as trisomy 21 or Allgrove syndrome (achalasia, alacrimia and adrenal insufficiency).

Clinical manifestations

Symptoms are insidious. Initially, they are usually mild and nonspecific and increase with age. In young children, chronic respiratory symptoms predominate, such as a cough that occurs predominantly at night, recurrent pneumonia, or bronchial hyperreactivity; while in older children, symptoms are more similar to those in adults, with dysphagia initially to solids and later to liquids, regurgitation of food contents, weight loss, retrosternal pain, or difficulty belching⁽¹¹⁾.

Diagnosis

It is suspected based on the clinical history, but in children this is often delayed because the symptoms of achalasia can be misinterpreted and attributed to other pathologies, such as gastroesophageal reflux or an eating disorder. The gold standard for diagnosis is high-resolution esophageal manometry. Other

complementary tests can also help with the diagnosis. A contrast-enhanced esophagogram can show a dilated proximal esophagus, with a narrowing at the esophagogastric junction in a “bird’s beak”. Upper gastrointestinal endoscopy can show a retention esophagus, with a dilated esophageal body and food remains.

Treatment

It is aimed at reducing the pressure of the lower esophageal sphincter, allowing food to pass into the stomach, thus improving symptoms. It is recommended to maintain an upright posture during and after meals, take sips of water between swallows, and favor textures that are easy to swallow. Regarding pharmacological treatment, its effect is transitory and is not free of side effects, so its use is reserved for limited periods or as a bridge to surgery. Endoscopic injection of botulinum toxin also has a transitory effect, so it is reserved for patients who refuse surgery or who continue to have symptoms despite it. Current therapeutic options consist of laparoscopic Heller myotomy or pneumatic dilation, both of which have considerable relapse rates. Peroral endoscopic myotomy (POEM)

is a less invasive treatment option with promising short-term results⁽¹²⁾.

Infectious esophagitis

Infectious esophagitis is the third most common cause of esophagitis in children after reflux esophagitis and eosinophilic esophagitis, and should be considered in the differential diagnosis of a patient with dysphagia and odynophagia.

Risk factors such as immunosuppression, esophageal motility disorders, which occur, for example, in the context of esophageal atresia, or esophageal dysbiosis secondary to the use of antacids, antibiotics or topical corticosteroids, have been described. The most common causative agents are *Candida*, herpes simplex virus (HSV) and cytomegalovirus (CMV). We have summarized the clinical, diagnostic and therapeutic characteristics in table V⁽¹³⁻¹⁴⁾.

Eosinophilic esophagitis

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease that has experienced an exponential increase in incidence in recent years.

Epidemiology and pathophysiology

EoE is caused by a non-IgE-mediated immune response to food antigens and other factors such as alteration of the esophageal epithelial barrier and predisposing genetic variants⁽¹⁵⁾. In 2007, in Spain, the incidence was 10.6 cases per 100,000 inhabitants/year and the prevalence was 111 cases per 100,000 inhabitants⁽¹⁶⁾.

Clinical manifestations

Clinical manifestations vary according to age. In young children, vomiting, abdominal pain and refusal to eat predominate; whereas, in older children, dysphagia and impaction are more common. Allergic comorbidity is frequently associated.

Diagnosis

The gold standard test is endoscopy. Two distinct patterns can be distinguished: the inflammatory pattern and the fibrostenosing pattern, which is more common in adolescents and adults. Diagnosis requires the presence of symptoms of esophageal dysfunction, infiltration ≥15 eosinophils/high power field (HPF), and exclusion of other causes of esophageal eosinophilia.

Table V. Characteristics of the main infectious esophagitis^(13,14)

	<i>Esophagitis due to Candida</i>	<i>Esophagitis due to Aspergillus</i>	<i>Esophagitis due to VHS</i>	<i>Esophagitis due to CMV</i>
General characteristics	Most common cause of esophagitis. <i>C. albicans</i> most common species	Species: <i>A. fumigatus</i> and <i>A. flavus</i>	Second cause of infectious esophagitis. HSV-1 more than HSV2. Primary infection or reactivation of latent infection	Primary infection or reactivation of latent infection. Second most frequent gastrointestinal location after the colon
Risk factors	Immunosuppression	Immunosuppression	Immunosuppression	Immunosuppression
Symptoms	Odynophagia, dysphagia, oral thrush, vomiting and abdominal pain	Odynophagia, dysphagia, vomiting and abdominal pain	Odynophagia, dysphagia, fever and chest pain	Odynophagia, dysphagia, vomiting and food refusal
Endoscopic findings	Friable mucosa and whitish plaques	Friable mucosa and whitish plaques	Small ulcers that may merge (volcano-like image)	Serpiginous and circumferential ulcers
Histological findings	Pseudohyphae by silver stain, gram stain or Schiff technique	Septate hyphae with dichotomous branching at 45° angles	Multinucleated giant cells with inclusion bodies Crowdy A	Hypertrophic cells with intranuclear inclusions, with a clear “bull’s eye” halo
Treatment	Fluconazole and amphotericin B	Caspofungin and amphotericin B	Acyclovir	Ganciclovir and valganciclovir

At the macroscopic level, the following stand out: edema, longitudinal grooves, whitish plaques, concentric rings and stenosis, which give a degree of severity to esophagitis according to the Hirano Classification. Histologically, the main finding is the infiltrate ≥ 15 eosinophils/hpf or 50 eosinophils/mm² at any level⁽¹⁷⁾.

Treatment

There are 3 therapeutic tools that can be offered in the first step and that should be maintained between 8 and 12 weeks⁽¹³⁾.

- Proton pump inhibitor (PPI): omeprazole, lansoprazole and esomeprazole.
- Elimination diet: the only strategy that addresses the cause of the disease. It allows for long-term remission and avoids adverse drug effects, although it involves a deterioration in quality of life. There are 3 options: elemental diet, diet directed by allergy tests (not very commonly used nowadays due to the poor results obtained, although it can be tried when the tests are positive and there is a clinical context that supports it) and empirical diet, which begins with the 2 most frequently implicated foods, which are wheat and milk.
- Swallowed topical corticosteroids: budesonide and fluticasone. Systemic corticosteroid should only be considered in situations of severe stenosis or dysphagia.

In recent years, alternative immunomodulatory drugs are being sought. Dupilumab, a monoclonal antibody that blocks IL-4 and IL-13 signaling and has been shown to be effective in refractory asthma and atopic dermatitis, could also be effective in poorly controlled EoE, administered subcutaneously weekly. It has recently been approved by the Spanish Agency for Medicines and Health Products (AEMPS) for use in patients over 12 years of age⁽¹⁸⁾.

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is a pathology whose diagnosis is based on clinical history. Treatment is based on proton pump inhibitors, for 4 to 8 weeks, in older children. In infants, a non-IgE-

mediated allergy to cow's milk proteins must be ruled out first, in which case treatment should be with a hydrolyzed formula, which serves as both diagnosis and treatment.

Definition and epidemiology

Gastroesophageal reflux (GER) is defined as the passage of gastric contents into the esophagus (with or without regurgitation or vomiting)⁽¹⁹⁾. It frequently occurs during childhood, both in primary and specialized care, and affects approximately 50% of infants under three months of age. It usually resolves itself before one year of age, thanks to increased sitting time, increased tone of the lower esophageal sphincter and a change to a more solid diet⁽²⁰⁾.

Physiological gastroesophageal reflux and GERD

In children under 1 year of age, GERD is mostly physiological, so its diagnosis should be based on anamnesis and physical examination, avoiding unnecessary additional tests and treatments.

The distinction between GERD and gastroesophageal reflux disease (GERD) is fundamental and, in many cases, difficult to carry out in routine clinical practice. GERD is defined as GERD that presents symptoms severe enough to warrant treatment and/or digestive complications (esophagitis, Barrett's esophagus, hematemesis or stenosis) or extradigestive complications (apneas, apparently life-threatening episodes (BRUE in its English acronym), anemia, failure to thrive, cough, chronic wheezing, sinusitis or otitis). GERD is characterized by onset after 6 months, although it is rare, GERD can occur before 6 months of age, or by symptoms that persist or worsen after 12-18 months of age. Certain pathologies have a higher risk of presenting GERD, such as: infantile cerebral palsy, cystic fibrosis, congenital diaphragmatic hernia or chronic lung diseases.

Clinical manifestations

Signs and symptoms differ depending on age:

- In infants they are nonspecific, highlighting repeated vomiting/regurgitation associated or not with irritability, failure to thrive, refusal to

eat and dystonic neck postures (Sandifer syndrome)⁽²⁰⁾.

- In older children or adolescents they may present the classic triad, consisting of heartburn, epigastric pain and retrosternal chest pain. In addition, they may present other symptoms, such as vomiting, dysphagia, cough, stridor or wheezing, or signs such as dental erosions, esophagitis, asthma or recurrent pneumonia.

It is essential to investigate the patient's history for warning signs or symptoms that suggest pathologies other than GERD, such as:

- Morning vomiting, bulging fontanelle, seizures and macrocephaly: intracranial hypertension.
- Bilioes vomiting: intestinal obstruction.
- Hematemesis: Mallory Weiss syndrome or esophagitis.
- Abdominal distension: celiac disease, anatomical abnormalities.
- Fever, lethargy and dysuria: infections.

Diagnosis

To date, there is no diagnostic tool for diagnosing GERD. However, there are several techniques that allow the evaluation of its severity, possible complications, as well as the differential diagnosis of pathologies that clinically resemble GERD and require specific treatment. The most notable are:

- Endoscopy with biopsy: allows to identify digestive complications of GERD and diseases that affect the esophageal mucosa (eosinophilic esophagitis, infectious esophagitis, etc.). However, a normal endoscopy does not rule out GERD and is not indicated to diagnose this pathology in itself.
- pH monitoring with or without impedance measurement: A technique that involves placing a nasogastric tube with electrodes, which allows the measurement of weakly acidic and non-acidic reflux, with the aim of: 1) correlating persistent symptoms with GERD events; 2) clarifying the role of acid reflux in the etiology of esophagitis and other signs and symptoms suggestive of GERD; 3) determining the efficacy of acid suppression therapy; and 4) differentiating non-erosive GERD,

esophageal hypersensitivity, and functional heartburn in patients with normal endoscopy.

Other techniques may be used if complicated GERD or warning signs secondary to anatomical malformations are suspected: abdominal ultrasound in infants and barium swallow in older children⁽¹⁹⁾.

Treatment

Treatment is summarized in algorithms 1 and 2, based on the 2018 ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) and NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) recommendations.

In infants under one year of age, it is initially recommended to divide the feedings and thicken the food. No benefit has been shown from massage treatment, so it should not be recommended. Prone postural treatment should also not be recommended as it is a risk factor for sudden infant death. If no improvement is seen, a 2 to 4 week exclusion-provocation test of cow's milk protein (CMP) will be performed, either by eliminating dairy products from the mother's diet (if exclusively breastfed) or with an extensively hydrolyzed formula, hydrolyzed rice formula or elemental formula, in the case of artificial feeding. This is because non-IgE-mediated cow's milk protein allergy (CMPA) has the same clinical course as GERD at this age, so if this test is positive, they will be diagnosed with non-IgE-mediated CMPA⁽²¹⁾. Otherwise, the patient should be referred to Pediatric Gastroenterology, where a therapeutic trial with an acid suppressant for 4-8 weeks will be considered. Ranitidine (histamine H2 receptor antagonist), widely used in this age group previously, has been ruled out due to the health alert published by the AEMPS (Spanish Agency for Medicines and Health Products) in 2019, which indicated its withdrawal from the market due to the presence of nitrosamines, a probable carcinogen. For this reason, omeprazole is used even outside the technical data sheet. Clinical improvement with massage has not been demonstrated, and antacids and positional therapy are contraindicated, the latter due to the risk of sudden infant death.

In older children and adolescents, treatment should be started by indicating hygienic-dietary measures such as:

- Healthy diet low in gastric irritants (chocolate, coffee, spicy foods, excessive processed foods).
- Reaching a normal weight.
- Postural measures such as raising the head of the bed and lying on the left side.

If there is no improvement, a 4- to 8-week cycle of PPIs should be prescribed, periodically evaluating their effectiveness. The PPIs approved for use in children are omeprazole, lansoprazole and esomeprazole. They should always be administered on an empty stomach, 30 minutes before breakfast or dinner and without opening the gastro-resistant capsules; otherwise, their effectiveness is drastically reduced. In prolonged treatments, it is advisable to prescribe a gradual reduction in the dose to avoid acid rebound.

In patients over 12 years of age, antacids such as almagate may be used occasionally after main meals, but never chronically due to the high aluminum and magnesium content.

It is not indicated for the treatment of GERD at any age: domperidone (AEMPS alert 2020), metoclopramide (both can produce extrapyramidal symptoms), erythromycin, probiotics, acupuncture or medicinal herbs⁽¹⁹⁻²⁰⁾.

As a last resort, in severe or refractory cases, surgery using Nissen fundoplication could be performed.

It is recommended that patients with GERD who present the following be referred from Primary Care to Pediatric Gastroenterology:

- Warning signs or symptoms that suggest an underlying gastrointestinal disease.
- Patients refractory to optimal PPI treatment after 8 weeks.
- Inability to permanently withdraw drug treatment (6 to 12 months)⁽¹⁹⁾.

Role of the Primary Care pediatrician

- The primary care pediatrician must know how to recognize the symptoms and signs suggestive of esophageal disease.
- He/she must assess the information provided by each diagnostic test:

when to request it and what information to expect from it, in order to discriminate between functional and organic pathology, thus avoiding unnecessary treatments.

- He/she needs to be familiar with the most prevalent pathologies, such as eosinophilic esophagitis and gastroesophageal reflux disease.
- The increased survival of infants undergoing esophageal surgery, such as esophageal atresia, has led to the appearance of late-onset problems that need to be identified, studied and treated correctly.
- Recently, multiple drugs have been identified as responsible for esophageal lesions. It is the primary function of the primary care pediatrician to give instructions to the patient (if age permits) or to his/her family to minimize the risk of developing these lesions, in addition to choosing the pharmaceutical forms with the lowest risk of producing them.
- The widespread use of button cells made of lithium salts has changed the paradigm in their accidental handling. Early and appropriate attention is necessary in the management of these accidents and their referral to appropriate hospital centers.

Conflict of interest

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

Additional note from the authors

Following submission to the publisher and subsequent acceptance for publication, ESPGHAN has published an update of its management document for eosinophilic esophagitis that does not modify what is stated in this review. For the interested reader, it is available at: Amil-Dias J, Oliva S, Papadopoulou A, Thomson M, Gutiérrez-Junquera C, Kalach N, et al. Diagnosis and management of eosinophilic esophagitis in children: an update from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2024; 79: 394-437. <https://doi.org/10.1002/jpn3.12188>.

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

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Clinical case

A 12-year-old girl was referred to the Gastroenterology clinic due to intermittent dysphagia to solids that had been developing for 4 months. She also mentioned an episode of impaction with meat (lamb) 1 month ago, which resolved spontaneously after vomiting. Her personal history included allergy to nuts and seasonal rhinoconjunctivitis.

Physical examination

Weight: 43 kg (38th centile). Size: 151 cm (39th centile). BMI: 18.86% (41st centile).

Good general condition. Good nutritional status. Normal cardiopulmonary auscultation. Abdomen: soft, depressible, not painful, without masses or visceromegalies. ENT: normal. Rest of the examination without abnormalities.

Complementary tests

Blood analysis: normal, except eosinophilia of 700/ μ L.

Gastroscopy with sedation (Figs. 1 and 2): esophageal mucosa with edema and loss of vascular pattern. Longitudinal grooves and whitish deposits predominantly in the distal 2/3. Marked trachealized appearance, especially with contraction. No stenosis. Z line at level. Good coaptation of cardia by retro. Mucosa of *fundus*, body and antrum of normal appearance. Pylorus centered and permeable. Mucosa of bulb and 2nd portion of duodenum, normal.

Histology: Distal and mid-proximal esophageal biopsies showed basal cell hyperplasia, papillomatosis, spongiosis, papillary congestion and the presence of a predominantly eosinophilic inflammatory infiltrate throughout the entire epithelial thickness, with up to 35 eos/hpf in the distal sample and 67 eos/hpf in the mid-proximal sample, with the presence of isolated microabscesses. The infiltrate does not affect the chorion. Biopsies of the body and antrum of the

gastric cavity and second portion of the duodenum showed no significant alterations.

Progress

Given the diagnosis of eosinophilic esophagitis, the therapeutic options were discussed jointly with the parents and the patient, and it was decided to start treatment with high doses of esomeprazole, 40 mg every 12 hours, with endoscopic control at 12 weeks. In the control gastroscopy, macroscopic findings compatible with eosinophilic esophagitis persisted and, in the biopsies, an inflammatory infiltrate of predominantly eosinophilic nature with up to 40 eos/hpf was maintained, both at the proximal and distal esophagus level. Given the lack of response to proton pump inhibitors, an exclusion diet (milk and gluten) or viscous budesonide was proposed. Treatment with budesonide was decided upon, prescribing 1 mg every 12 hours for 12 weeks, with new endoscopic control in which a clear improvement was observed with a normal esophagus, except for mild mucosal edema. Esophageal biopsies show histological remission without the presence of eosinophils. After clinical and histological remission, it was decided to reduce the budesonide dose to 1 mg every 24 hours, which was maintained for 6 months, at which time a new endoscopic control was performed. The patient remained asymptomatic after a dose reduction, but endoscopy showed a somewhat friable mucosa with whitish plaques that did not come off when washed. The pathology showed an inflammatory infiltrate without eosinophils, with pseudohyphae invading the epithelium perpendicularly. In the esophageal biopsy culture for fungi, *C. albicans* grew. Given the diagnosis of esophageal candidiasis, treatment with oral fluconazole was prescribed for 14 days.

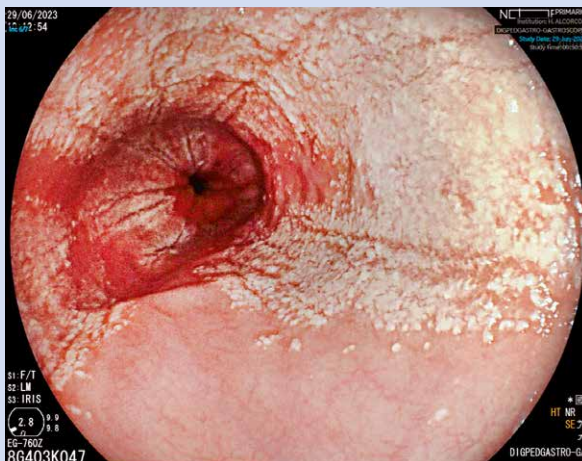


Figure 1. Gastroscopy. Esophagus with longitudinal grooves and marked whitish deposits, predominantly in the distal 2/3.

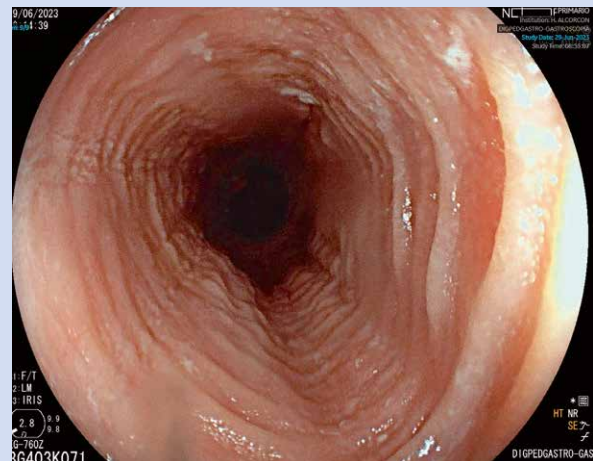


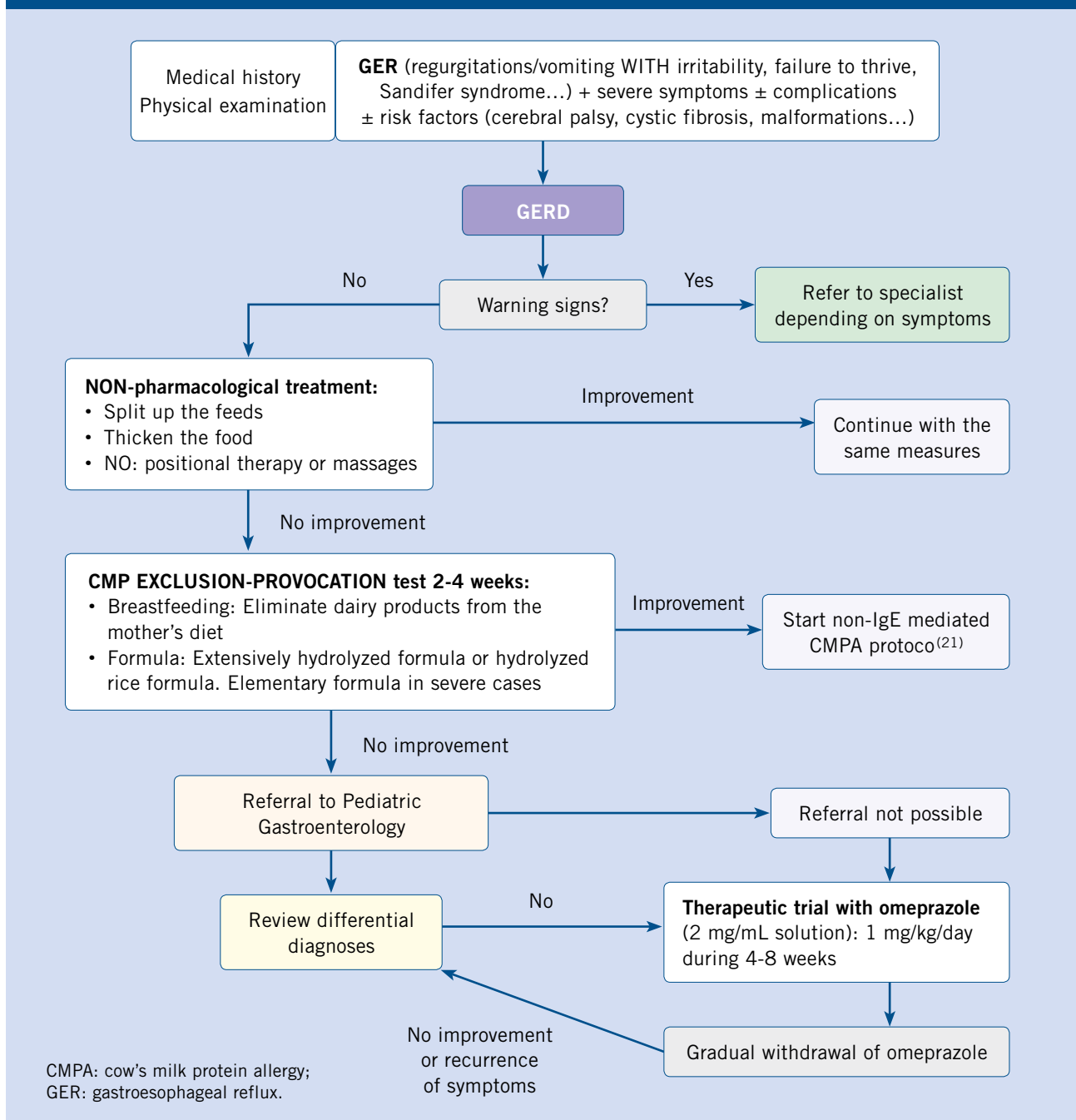
Figure 2. Gastroscopy. Esophagus with trachealized appearance.



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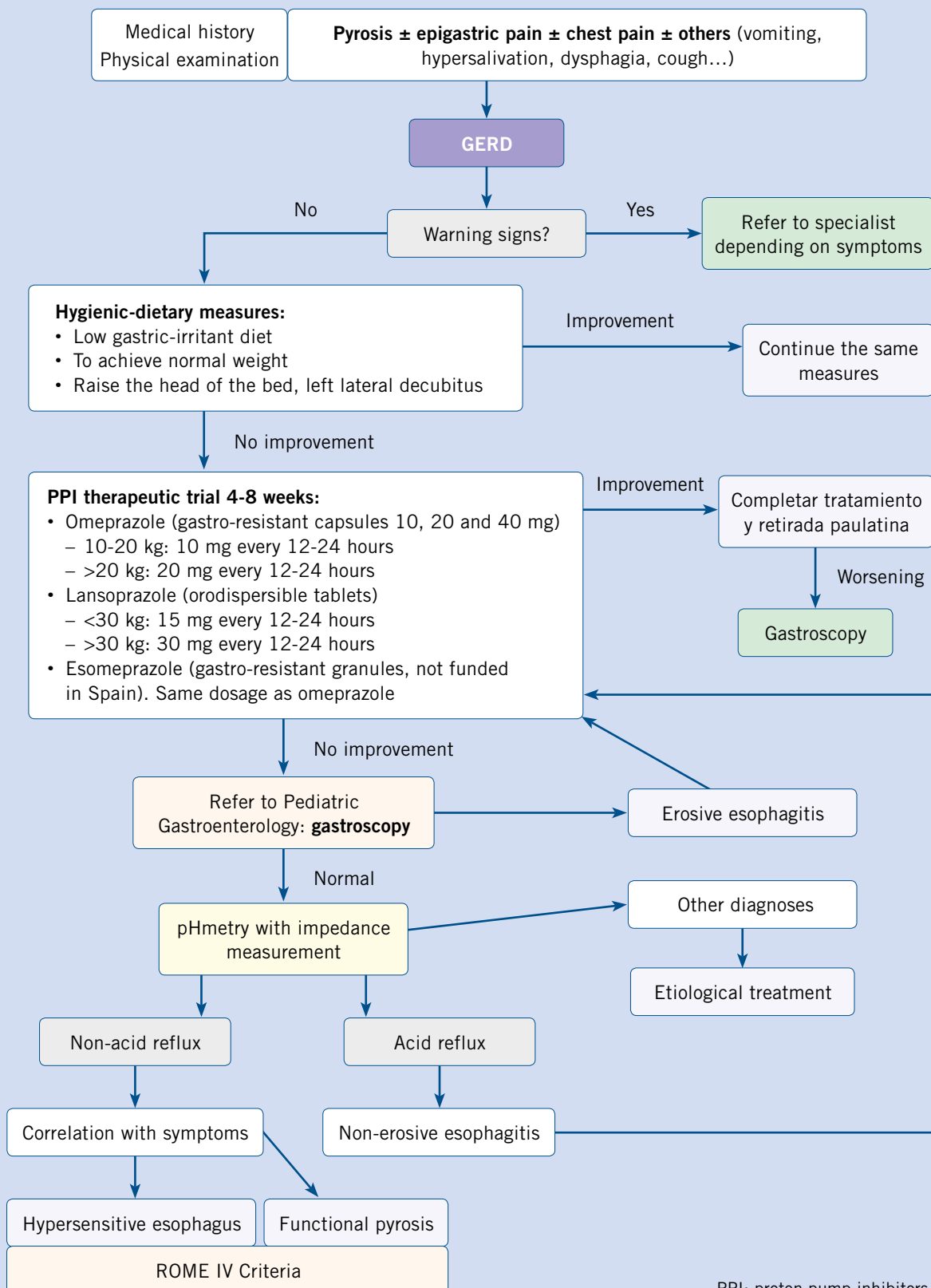
Algorithm 1. Gastroesophageal reflux disease (GERD) in infants



Accreditation quiz

The Accreditation Questionnaires for FC topics can be done at "On line" through the web: www.sepeap.org and www.pediatrintegral.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.

Algorithm 2. Gastroesophageal reflux disease (GERD) in older children and adolescents



PPI: proton pump inhibitors.



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.

Esophageal pathology

9. Indicate the INCORRECT answer in the handling of the ingestion of lithium button batteries:

- If after radiological evaluation it is found to be lodged in the stomach and we are certain that less than 12 hours have passed since ingestion, the approach may be expectant with radiological controls every 7-14 days.
- If it is located in the esophagus, the treatment cycle should be completed with honey or sucralfate and wait to perform endoscopic removal until the stomach has emptied.
- There are cases in which the patient should be referred directly to tertiary centers, given the need for the presence of a cardiothoracic surgeon during endoscopic removal.
- The mechanism of injury is the generation of strong alkalis in the tissue in contact with the negative pole.
- After extraction, the patient must remain hospitalized for observation due to the possibility of late complications.

10. Regarding esophageal atresia, which of the following statements is INCORRECT?

- In 90% they are associated with the presence of tracheoesophageal fistula.
- Polyhydramnios findings on fetal ultrasounds and absence of fetal gastric bubble may guide the diagnosis.

- It should be suspected in a newborn with early-onset respiratory difficulty, drooling, and inability to pass a nasogastric tube.
- The prognosis of the disease is conditioned, above all, by birth weight and the presence of associated severe cardiac formations.
- Patients require continued treatment with proton pump inhibitors during the first month of life.

11. Indicate the INCORRECT answer regarding infectious esophagitis:

- Esophagitis due to *C. albicans* is the most common infectious esophagitis in children.
- It appears that immunosuppression, esophageal motility disorders and dysbiosis are involved in the pathophysiology of infectious esophagitis.
- Infectious esophagitis only occurs in immunosuppressed patients.
- Odynophagia is usually a constant in esophagitis of infectious origin.
- The whitish plaques of *C. albicans* esophagitis may be confused with the exudates of eosinophilic esophagitis.

12. Indicate the CORRECT answer regarding eosinophilic esophagitis:

- Fibrotic phenotype is more common in children than in adults.
- The incidence of eosinophilic esophagitis has remained stable over the last decade.

- The diagnosis consists of the presence of symptoms of esophageal dysfunction, infiltrate ≥ 5 eosinophils/hpf and exclusion of other causes of eosinophilia.
- In young children, the presentation may be very nonspecific, with vomiting, abdominal pain or food refusal.
- There are 3 therapeutic tools that should be offered in a staggered manner, always starting with the proton pump inhibitors.

13. Regarding gastroesophageal reflux disease (GERD), indicate the INCORRECT answer:

- In infants, before starting treatment with PPIs, a non-IgE mediated cow's milk protein allergy should be ruled out.
- Antacids, such as almagate, can be used daily in patients with chronic GERD.
- Endoscopy with biopsy can identify digestive complications of GERD.
- In adolescents, typical symptoms are heartburn, epigastric pain and retrosternal chest pain.
- Postural changes are not recommended in infants due to the risk of sudden death.

Clinical case

14. Regarding the diagnosis of eosinophilic esophagitis, indicate the INCORRECT answer:

- A high index of suspicion is required, because patients may develop coping strategies such as

- eating very small pieces, eating slowly, or drinking water after each swallow.
- b. Allergic comorbidity is more frequent in patients with eosinophilic esophagitis than in the general population, which may increase diagnostic suspicion.
 - c. Upper gastrointestinal endoscopy is the first diagnostic test when eosinophilic esophagitis is suspected.
 - d. Diagnosis requires the presence of symptoms of esophageal dysfunction, an infiltrate ≥ 50 eosinophils/hpf and exclusion of other causes of esophageal eosinophilia.
 - e. The esophageal mucosa may have a normal appearance in 10-30% of cases, so it is essential to perform biopsies in all patients with a suspected diagnosis.
- 15. Regarding the treatment of eosinophilic esophagitis, indicate the INCORRECT answer:**
- a. One of the therapeutic options is the use of high-dose proton pump inhibitors.
 - b. Empirical dietary treatment usually begins with the exclusion of 2 food groups (milk and gluten).
 - c. After the taking of viscous budesonide, the ingestion of liquids or solids should be avoided for at least 30 minutes afterwards.
 - d. After starting treatment, an endoscopic check should be performed after 4-6 weeks to assess the response.
 - e. The administration of Dupilumab, a recombinant IgG4 monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling, may be useful in cases of poor control or refractory to other treatments.
- 16. Regarding candida esophagitis, indicate the INCORRECT answer:**
- a. It is the most common cause of infectious esophagitis.
 - b. Risk factors include immunosuppression and chronic treatment with certain drugs, such as corticosteroids or proton pump inhibitors.
 - c. It almost always coincides with oral candidiasis, but the absence of the latter does not exclude esophageal involvement.
 - d. It usually occurs with odynophagia, dysphagia and retrosternal pain, although some patients may be asymptomatic.
 - e. The treatment of choice is caspofungin.



Accreditation quiz

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