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Approach to Gastroesophageal Reflux: A Cause of Chest Pain in Infants with Congenital Heart Disease

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Abstract

The life expectancy and quality of life of infants with congenital heart disease have increased in the last 30 years with significant advances in technological facilities, treatment methods, and surgeries. GER is a condition that can be seen in infants with CHD, which needs to be well followed up and to be differentiated between physiological and nonphysiological reflux. GER is a physiological condition that is common in infants with CHD and usually resolves spontaneously in the first 6–12 months of life. If the baby has adequate weight gain and nutrition status and there is no abnormal restlessness, the baby is considered to be uncomplicated GER. GERD is a pathological clinical entity that is accompanied by insufficient weight gain, esophagitis, and persistent respiratory system findings. When gastroesophageal reflux disease is considered, the first thing to be done is to complete the detailed anamnesis and physical examination of the infant. The reflux status of the infants can be examined with the surveys that were prepared for GERD and followed up for 1–2 months. If necessary, diagnostic methods such as esophageal pH monitoring and radiological and endoscopic examinations can be used. Conservative approaches such as thickening of formulas and thickening of formulas and positional feeding are the the first treatment approaches for reflux.

Keywords: congenital heart disease, gastroesophageal reflux disease, infant, treatment, surveys

1. Introduction

The prevalence of congenital heart disease (CHD) is known to be approximately 0.5–0.8% in all live births [1]. It is estimated that approximately 30–35% of children with CHD require medical treatment, interventional procedures, or surgical treatment [2]. Over the last 30 years, significant advances in surgical techniques and medical treatment have been made in the treatment of CHD in the world [3]. Nutritional status of CHD patients in the first year has an important role in growth and neurodevelopmental functions. GERD, which is closely related to nutrition and malnutrition, should be considered in these patients [4].

Gastroesophageal reflux is a common condition in children in all age groups, with gastric contents retrograde passage to the esophagus, even pharynx and mouth. This condition is defined as gastroesophageal reflux disease (GERD) if it

continues more frequently and continuously and causes worrisome symptoms and undesirable consequences [5]. Especially, it results in esophagitis or other esophageal symptoms or symptoms of the respiratory system.

2. Definition

Gastroesophageal reflux is a physiological condition that may occur in healthy infants, children, and adults. It usually occurs in very short episodes (<3 minutes) and in the postprandial period without any symptom, esophageal damage, or complications. If these reflux processes cause worrisome symptoms and unwanted conditions, GERD is in question [6, 7].

Regurgitation refers to reflux in the oropharynx, while vomiting refers to the gastric contents coming out of the mouth. There is no need to be with repetition and any coercion. The use of these terms is intertwined in clinical practice, and no definite distinction is made. They are perceived as different states of the same process. Symptoms occur for many reasons (**Table 1**).

Causes of vomiting		
Gastrointestinal obstruction	Neurological	Renal
Pyloric stenosis	Hydrocephalus	Obstructive uropathy
Malrotation	Subdural hematoma	Renal insufficiency
Intestinal duplication	Intracranial hemorrhage	Toxic
Hirschsprung's disease	Intracranial mass	The lead
Antral/duodenal web	Infant migraine	Iron
Foreign body	Chiari malformation	Vitamins A and D
Other gastrointestinal causes	Infectious	Cardiac
Achalasia	Sepsis	Congestive heart failure
Gastroparesis	Meningitis	Vascular ring
Gastroenteritis	Urinary infection	Metabolic/endocrine
Peptic ulcer	Pneumonia	Galactosemia
Eosinophilic esophagitis	Otitis media	Hereditary fructose intolerance
gastroenteritis		Urea cycle defects
Food allergy		Amino and organic acidemias
		Congenital adrenal hyperplasia

Table 1.
Differential diagnosis in vomiting infants.

3. Epidemiology

A study of 948 infants in the United States reported a prevalence of reflux in the 4–6 months of life as 67% which has decreased to 5% by 10–12 months of age. Similarly in the study with 602 babies in India, it showed that the prevalence of gastroesophageal reflux, which was 55% in the first 6 months of life, decreased to 4% at 1 year of age [8, 9]. Epidemiological studies suggest that gastroesophageal reflux in infancy with CHD can be seen from the first month of life and the frequency of occurrence reaches to the peak around the fourth month, most of them recover after the age of 1 year, almost all of them at the age of 2 [10].

There is also a genetic predisposition to GERD. In addition to known GERD symptoms in some families, the incidence of endoscopic esophagitis, hiatus hernia, Barrett's esophagus, and adenocarcinoma has been shown [11, 12]. Genetic factors

which the 9q22-9q31 gene was mapped with infantile gastroesophageal reflux were thought to play a role in the concordance of gastroesophageal reflux in monozygotic twins compared to dizygotic twins [13].

Regurgitation is common in infants. However, typically around 1 year of age, it decreases or completely recovers. Regurgitation usually occurs in late infancy, but there is a weak relationship with GERD that occurs later in life. For example, frequent regurgitation in infancy and GERD in the mother (not the father) are risk factors that increase the occurrence of reflux-related symptoms in childhood [14]. In addition, it has been shown in a recent study that the psychopathological personality traits of the mother negatively affect the baby's eating behavior and are effective in the development of reflux [15].

In a prospective study, it was found that babies with frequent vomiting more than 90 days in the first 2 years of life showed more adult symptoms of reflux at the age of 8–9 years [16].

4. Pathophysiology

The lower esophageal sphincter forms a functional barrier between the stomach and the esophagus and prevents the retrograde passage of stomach contents (acid, pepsin, sometimes bile) to the esophagus [17]. In addition, factors facilitating gastroesophageal reflux in CHD infants are the following:

1. Antireflux barrier dysfunction
2. Inadequate clearance mechanism of the esophagus
3. Impairment of esophageal mucosal resistance
4. Delay in gastric emptying

4.1 Antireflux barrier dysfunction

The physiological structure formed by the circular muscles, diaphragm crurae, and phrenoesophageal ligament in the esophagogastric junction forms the lower esophageal sphincter (LES) which acts as the primary barrier function for reflux. In addition, the His angle between the esophagus and fundus and the intraabdominal segment of the esophagogastric junction are other components of the antireflux barrier.

The main problem leading to primary gastroesophageal reflux is not the loose of the lower esophageal sphincter; it is known that there are transient relaxations lasting longer than 5 seconds, independent of swallowing [17, 18]. Also some hormones (cholecystokinin, glucagon, vasoactive intestinal peptide (VIP), nitric oxide (NO), dopamine, secretin, and estrogen), drugs (atropine), and nutrients (peppermint, and cocoa) may contribute to GERD by reducing LES pressure [17]. In addition, the presence of stress associated with intensive treatment periods and interventions in complicated CHD patients may lead to increased catecholamine levels. Therefore, it may increase the expression of acid secretion and cause reflux formation [19].

4.2 Inadequate clearance mechanism of the esophagus

Physiological reflux attacks return the secretions and nutrients that escaped from the stomach to the esophagus for a very short period of time with the effect of

normal esophageal peristalsis and gravity. In this way, acid, pepsin, and bile which may cause inflammation when it comes into contact with the esophageal mucosa are removed. However, the acid which has not been cleared from the esophageal mucosa is neutralized by swallowing saliva at the alkaline pH. The aim is to remove the gastric contents that will cause inflammation in the esophageal mucosa. Disruption of these natural mechanisms increases the exposure to reflux [20].

4.3 Impairment of esophageal mucosal resistance

The mucus layer and bicarbonate concentration covering the esophageal epithelium, the connections between epithelial cell membrane and cells, intra- and extracellular buffers, blood flow at the postepithelial level, and acid-base balance in the tissue are the factors that provide the resistance of the esophageal mucosa.

4.4 Delay in gastric emptying

Breast milk is known to have a healing effect on the intestinal mucosa and is well absorbed from the mucosa. However, it cannot provide sufficient energy support alone in infants with CHD. Therefore, high-energy density formulas used in patients receiving nutritional support due to increased energy support cause reflux by delaying gastric emptying. Increased fluid and sodium load, especially in patients with heart failure, increases the existing failure and therefore leads to malnutrition and increased metabolic consumption. In the presence of hepatomegaly and ascites, gastric emptying is delayed due to the compression of the stomach, and this delay causes gastroesophageal reflux [3, 21, 22].

Impaired gastrointestinal motility, the presence of protein-losing enteropathy, and the presence of mucosal atrophy secondary to decreased splanchnic blood flow significantly slow the frequency of food elimination and gastric emptying in infants with CHD [1, 4]. Heart failure, especially in infants with critical congenital heart disease, causes some gastrointestinal problems in addition to the findings of the present disease. It causes intestinal edema, malabsorption, steatorrhea, and protein-losing enteropathy, which cause malnutrition. If the clinical situation cannot be controlled and progresses, it forms the basis for gastroesophageal reflux disease [4, 10, 23].

Animasahun et al. reported in their study that cyanosis was the most common presentation of congenital heart disease in children [14]. In a survey based on the frequency of GERD in CHD infants, cyanosis was found to be more frequent in favor of reflux in the group with cyanotic CHD. However, it was stated that this finding is not specific for reflux in CHD infants because this may also be caused by disease [10].

As a result insufficiency of lower esophageal sphincter, transient LES loosening, deterioration of esophageal dysmotility and esophageal clearance, stress and hormonal factors that increase gastric acidity, as well as delayed emptying of the stomach and using high-energy density formulas play a role in reflux pathophysiology of CHD patients.

5. Clinical presentations

A thorough history, a detailed physical examination, and warning symptoms to exclude differential diagnoses are sufficient to make a clinical diagnosis of uncomplicated infant reflux. Regurgitation is the most frequent symptoms of infantile gastroesophageal reflux. In contrast to gastroesophageal reflux that occurs after birth, regurgitation may not be pronounced until the second or third week of life. The typical symptom of physiological reflux is effortless and painless regurgitation

Alarm symptoms in a vomiting baby	
Presence of bile	Diarrhea
Gastrointestinal bleeding	Fever
Presence of force vomiting	Lethargy
Failure to thrive	Hepatosplenomegaly
Presence of blood	Bulging fontanel
Abdominal distension	Macro/microcephaly
	Seizure
	Suspected genetic/metabolic syndrome

Table 2.
Alarm symptoms requiring further investigation in infants with regurgitation and vomiting.

which is called “happy spitter” [24]. A detailed nutritional history including the frequent amount of vomiting and regurgitation, feeding type (breastfeeding or formula), turning blue/purple in feeding time, hiccups, and behavior of the baby during feeding should be obtained.

In order to protect the airway from reflux during infancy, the dystonic posture formed by throwing back the baby’s head and sometimes the body can be mistakenly perceived as “seizure.” This condition, known as “Sandifer syndrome,” protects the airways from reflux or reduces abdominal pain caused by acid reflux. This position regresses with antireflux therapy [25, 26].

Unexplained crying attacks and restless behaviors during the day are associated with various conditions in infants. Healthy infants have crying attacks and restlessness on an average between 0 and 2 hours during the day. Excessive crying attacks and increased restlessness expressed by the family should be considered [27]. Feranchak and colleagues showed during video and pH monitoring study that infants had excessive crying attacks during reflux episodes [28].

Regurgitation, vomiting, irritability, and refusal of feeding which are common in infants may be clinical signs of reflux although food allergies that may develop with the same clinical presentation especially in infant children should be included in the differential diagnosis. Remember that vomiting/regurgitation during infancy may be the first sign of systemic infection, sepsis, or many metabolic diseases other than reflux [29]. Alarm symptoms should be questioned, especially in infants with vomiting under 1 year of age (**Table 2**).

6. Diagnosis

The first step in making a definitive diagnosis in gastroesophageal reflux disease is to suspect. The findings should be questioned with careful and detailed history. Anamnesis and physical examination are the basis of the treatment. A specific diagnostic test is not required to diagnose reflux in the presence of recurrent postprandial vomiting with typical history, especially in infants under 1 year of age. However, if symptoms are not typical or if reflux-related complications are suspected, specific methods should be used. Many methods are used for the diagnosis of GER. Each of these methods is important in obtaining different information [10, 30–32].

6.1 Surveys

The diagnosis of GERD in adults can generally be made by anamnesis and clinical history [33]. Since the complaints are difficult to identify in children under

12 years of age, the history is less reliable [34, 35]. The questionnaire forms are aimed at increasing the reliability of the history rather than making the diagnosis. It is widely accepted surveys that I-GERQ-R developed by Orenstein et al. and GSQ-I and GSQ-YC prepared by Deal et al. could be used in infants with gastroesophageal reflux [10, 35–37].

6.2 Barium contrast radiography

An upper gastrointestinal (GI) series are not sensitive and specific for the diagnosis of GERD. Especially in studies comparing esophageal pH studies, sensitivity, specificity, and positive predictive values were found to be very low [38, 39]. Therefore, radiological evaluation is not an appropriate method to confirm or exclude GERD. However, it can be used especially in the evaluation of selected cases with atypical or severe symptoms such as dysphagia or odynophagia. In these patients provides recognition of anatomical disorders such as achalasia, tracheoesophageal fistula, esophageal stricture, hiatal hernia, antral web, pyloric stenosis, intestinal malrotation or peptic strictures [33, 39].

6.3 Nuclear scintigraphy

Nuclear scintigraphy is a method of demonstrating the spread of isotope in the esophagus, stomach, and lung by ingestion of technetium-labeled food or food. The potential advantage when compared with the esophageal pH study is that it also shows reflux of nonacidic gastric contents and determines gastric emptying rate [40, 41]. However, its sensitivity and specificity are lower than the pH study. Therefore, its place in the diagnosis of GERD is limited and is not routinely recommended [24, 42].

6.4 Esophageal pH monitoring

The important advantages of 24 hr monitoring that can show the relationship between GERD and the patient's symptoms and allow the baby to be monitored for a long time (night, day, according to the position of the body) in the physiological environment [5]. It is used frequently in the diagnosis of patients with non-gastrointestinal symptoms (such as stridor, cough, hoarseness, chest pain) and in the evaluation of the response to medical treatment in patients with refractory gastroesophageal reflux [43, 44].

24 hr monitoring in esophagitis shows the duration, frequency of acidic reflux, and the degree of pH to which the esophagus is exposed [45]. Since it is a useful method in finding and evaluating reflux, it is widely accepted as the gold standard [43, 46, 47]. However, problems such as breast milk shifting the pH of the stomach to the alkaline side, the amount of reflux cannot be determined, and the pH probe cannot be fully inserted into the lower end of the esophagus are disadvantages of this method [45, 47].

6.5 Endoscopic evaluation

Esophageal endoscopy and biopsy are other valuable methods for the diagnosis of GERD. Endoscopy is used to diagnose complications such as erosive esophagitis, stricture, and Barrett's esophagus. Esophageal biopsy can be used in the histological diagnosis of reflux esophagitis in the absence of erosion and in the differentiation of allergic and infection-induced esophagitis. It also helps to exclude diseases such as allergic or infectious esophagitis.

The normal appearance of the esophagus on endoscopy does not exclude histopathological esophagitis. Minimal mucosal changes such as erythema and pallor may occur without esophagitis [48]. In one study, 87% of 62 patients with esophagitis had normal or mild mucosal changes endoscopically [49]. There are no eosinophils and neutrophils in the esophageal epithelium in healthy infants and children [50]. Intraepithelial eosinophilia, which is one of the diagnostic criteria for reflux esophagitis, shows that the esophagus is associated with long-term reflux injury [51].

7. Treatment

Physiological reflux should be considered in the approach to gastroesophageal reflux for infants with congenital heart disease, and patients should be followed up closely (1–2 month periods). Treatment decisions should be made according to the current clinical situation and follow-up [10]. GERD treatment in infants consists of three main topics.

1. Conservative measures
2. Pharmacological treatment
3. Surgical treatment

7.1 Conservative measures

7.1.1 Lifestyle changes

Lifestyle changes or regulation may vary according to age in infants, young children, and older children/adolescents. However, what is known is that lifestyle changes are effective in the prevention of GERD in infants as well as in adults. Education of parents and awareness raising of reflux, nutritional and positional changes are involved in the management of physiological reflux [52–54]. Lifestyle changes in non-pathological reflux should be made before aggressive treatment approaches in infants with CHD such as healthy infants [10].

7.1.2 Positioning

Antireflux conservative measures recommended during infancy are not to feed the baby in a supine position, to allow time to release gas for decompression of the stomach in the middle of the feeding, to place the baby in an anti-Trendelenburg position at 30° after feeding, and not to allow constipation [54, 55]. Many studies have shown that infants lying in the prone position significantly reduce acid reflux compared to the flat supine position [56]. Although keeping the head higher in the prone position was found to reduce reflux further, no such difference was found in the supine position. Despite its positive effect on prevention of reflux, finding a relationship between prone position and sudden infant death prevented this method to be recommended. However, if the child is still observed, this position can be applied after feeding [57, 58].

7.1.3 Dietary change

Since breast-fed infants are less likely to have GERD than infants who take formula, the importance of breastfeeding should be explained and encouraged

them. In this age group, cow's milk allergy symptoms (regurgitation, vomiting, sometimes refusal to feed, and restlessness) may not be distinguished from physiological reflux [59–61]. Therefore, in infants with persistent reflux symptoms, cow milk elimination should be performed for 2–3 weeks, and the patient should be followed up. The significant reduction in vomiting and other symptoms during this period and recurrence of symptoms when the diet is impaired suggest cow's milk allergy [62].

It has been shown that the thickening of formulas and nutrients prevents weight loss by reducing vomiting and regurgitation rather than reflux episodes. For this purpose, adding the products containing thickeners (rice cereal, corn or potato starch, and carob bean gum) to thickeners may reduce the frequency and volume of regurgitation [63].

7.2 Pharmacological treatment

Pharmacotherapy therapy is not indicated in infants with CHD who has uncomplicated gastroesophageal reflux because physiological reflux tends to improve over time. Pharmacotherapy should be considered in the treatment of gastroesophageal reflux disease in patients who do not respond despite thickened feedings, lifestyle changes, and nutritional recommendations [64, 65].

7.2.1 Proton pump inhibitors

This group prevents acid secretion by inhibiting $\text{Na}^+ - \text{K}^+$ ATPase, called proton pump, which is responsible for acid secretion in parietal cells. Proton pump inhibitors, which have a stronger acid suppressant and mucosal curative effect than H₂RAs, maintain gastric pH above 4 and inhibit food-borne acid secretion. It is also more effective in healing erosive esophagitis. Their efficacy is 24 hours, so they have the advantage of using a single dose per day. Proton pump inhibitors, omeprazole, lansoprazole, and esomeprazole, which can be used in the treatment of infants with gastroesophageal reflux, should be appropriately adjusted: omeprazole (infants: 3–<5 kg, 2.5 mg/day; 5–<10 kg, 5 mg/day; ≥10 kg, 10 mg/day), esomeprazole (infants: 3–<5 kg, 2.5 mg/day; 5–<10 kg, 5 mg/day; ≥10 kg, 10 mg/day), and lansoprazole (infants and children: 1 mg/kg/day [maximum 15 mg/day]) [38, 65].

There are potential risks of acid suppression due to PPI treatment in young children, which can be evaluated in four categories: idiosyncratic reactions, drug-drug interactions, drug-induced hypergastrinemia, and drug-induced hypochlorhydria [66]. The most common idiosyncratic reactions were detected in 14% of children receiving PPI and showed effects such as headache, diarrhea, constipation, and nausea. They can be improved by reducing the dose or replacing it with a different preparation [67, 68].

7.2.2 H₂ receptor antagonists

The mechanism of action of H₂ receptor antagonists, which is mainly used in children under 1 year of age, is to reduce acid secretion by inhibiting histamine 2 receptors in gastric parietal cells [53, 66]. Cimetidine, ranitidine, nizatidine, and famotidine are drugs in this group used in the treatment of reflux esophagitis. The frequency and dosage of use of these drugs in children are as follows: cimetidine (children: 30–40 mg/kg/day divided into four doses); ranitidine (children: 5–10 mg/kg/day divided into two to three doses), which is the most preferred drug in the treatment of infants and children; famotidine (children: 1 mg/kg/day divided

into two doses); and nizatidine (children: 10–20 mg/kg/day divided into two doses) [38]. Although H₂ receptor antagonists reduce pepsin and gastric acid secretion, they do not reduce the frequency of gastroesophageal reflux and are less effective than proton pump inhibitors.

If they are used in reflux treatment for a long time (>14 days), tachyphylaxis and hypochlorhydria which can lead to bacterial colonization may occur. Common adverse events include increased risk of enteritis infection, especially *C. difficile* enteritis, drowsiness, dizziness, headache, abdominal pain, and diarrhea [69–71].

7.2.3 Antacids

The mechanism of action of antacids containing a combination of magnesium, aluminum hydroxide, or calcium carbonate is shown by neutralizing gastric acid. The use of aluminum-containing antacids in infants can cause osteopenia, microcytic anemia, and neurotoxicity, so it is not suitable for use in infants [72].

7.2.4 Surface barrier agents

Alginate and sucralfate are used as surface protection agents in reflux treatment [24, 73]. According to the results of the meta-analysis in 2017, alginates have been shown to be less effective than H₂ receptor antagonists and proton pump inhibitors. Alginates are water-soluble salts of alginic acid and act as protective agents for the mucosal surface. Sodium and magnesium alginate preparations have been shown to significantly reduce vomiting symptoms even in preterm and term infants by pH/MMI studies [74]. Sucralfate, composed of sucrose sulfate aluminum, converts into a gel form with gastric acid and adheres to the mucosa, which is exposed to peptic erosion. Its efficacy has been shown in children in a limited number of studies, but there are not enough studies in terms of its efficacy and side effects and safety [75, 76].

7.2.5 Prokinetic agents

Metoclopramide, cisapride, domperidone, and baclofen are among the drugs in this group and can be used in the treatment of gastroesophageal reflux disease. However, cohort studies have shown that prokinetic drugs are not helpful in treatment of reflux [77]. In addition, these agents are not recommended for use in infants and children as they have important side effects such as lethargy, irritability, gynecomastia, galactorrhea, ventricular arrhythmias, QT prolongation, extrapyramidal reactions, and persistent tardive dyskinesia [78, 79].

7.3 Surgical treatment

Surgical procedures such as fundoplication (Nissen) are rarely performed under 1 year of age for indications such as recurrent pneumonia and life-threatening reactive airway disease. It is a method that can be applied in the case of cardiopulmonary insufficiency, which is unresponsive to medical treatment in patients with CHD [80, 81].

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