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DRAFT CLINICAL RECOMMENDATIONS FOR NEONATOLOGISTS AND PEDIATRICIANS ON THE DIAGNOSIS AND TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE IN NEWBORNS (FOR DISCUSSION BY SPECIALISTS)

© Dmitry O. Ivanov[1], Valeria P. Novikova[1], Margarita M. Gurova[1], Anna N. Zavyalova[1], Alexandra S. Panchenko[1], Valery F. Privorotsky[1], Larisa A. Fedorova[1], Ekaterina N. Balashova[2], Anatoly I. Khavkin[3]

[1] Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation
[2] National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov. 4 Academician Oparin str., Moscow 117997 Russian Federation
[3] Research Clinical Institute of Childhood. 62 Bolshaya Serpukhovskaya str., Moscow 115093 Russian Federation

Contact information:
Margarita M. Gurova — Doctor of Medical Sciences, Leading researcher of the laboratory of medical and social problems in pediatrics of the research center. E-mail: itely@mail.ru ORCID: https://orcid.org/0000-0002-2666-4759 SPIN: 8139-7866

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Abstract. Clinical recommendations are intended to optimize the tactics of managing newborns with gastroesophageal reflux disease and are offered for use by pediatricians working in outpatient and inpatient healthcare of the Russian Federation, aimed at providing information support pediatricians, neonatologists and gastroenterologists and all specialists interested in neonatology and medical clinical gastroenterology. These recommendations are offered for public discussion and are posted in full on the website (https://neonatology.pro).

Keywords: *newborns, gastroesophageal reflux disease, diagnostics, treatment, clinical recommendations*

ПРОЕКТ КЛИНИЧЕСКИХ РЕКОМЕНДАЦИЙ ДЛЯ НЕОНАТОЛОГОВ И ПЕДИАТРОВ ПО ДИАГНОСТИКЕ И ЛЕЧЕНИЮ ГАСТРОЭЗОФАГЕАЛЬНОЙ РЕФЛЮКСНОЙ БОЛЕЗНИ НОВОРОЖДЕННЫХ (ДЛЯ ОБСУЖДЕНИЯ СПЕЦИАЛИСТАМИ)

© Дмитрий Олегович Иванов[1], Валерия Павловна Новикова[1], Маргарита Михайловна Гурова[1], Анна Никитична Завьялова[1], Александра Сергеевна Панченко[1], Валерий Феликсович Приворотский[1], Лариса Арзумановна Федорова[1], Екатерина Николаевна Балашова[2], Анатолий Ильич Хавкин[3]

[1] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, д. 2
[2] Национальный медицинский исследовательский центр акушерства, гинекологии и перинатологии им. академика В.И. Кулакова. 117997, г. Москва, ул. Академика Опарина, д. 4
[3] Научно-исследовательский клинический институт детства. 115093, г. Москва, ул. Большая Серпуховская, д. 62

Контактная информация:
Маргарита Михайловна Гурова — д.м.н., ведущий научный сотрудник лаборатории медико-социальных проблем в педиатрии научно-исследовательского центра. E-mail: itely@mail.ru ORCID: https://orcid.org/0000-0002-2666-4759
SPIN: 8139-7866

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Резюме. Клинические рекомендации предназначены для оптимизации тактики ведения новорожденных с гастроэзофагеальной рефлюксной болезнью и предлагаются к использованию врачам-педиатрам,

работающим в амбулаторном и стационарном звеньях здравоохранения РФ, направлены на обеспечение информационной поддержки врачей-педиатров, неонатологов, гастроэнтерологов и всех специалистов, интересующихся вопросами неонатологии и врачебной клинической гастроэнтерологии. Настоящие рекомендации предлагаются к обсуждению общественности и в полном виде размещены на сайте Российского общества неонатологов (https://neonatology.pro).

***Ключевые слова*:** *новорожденные, гастроэзофагеальная рефлюксная болезнь, диагностика, лечение, клинические рекомендации*

DEFINITION

Gastresophageal reflux disease (GERD) is a pathological condition that develops when gastric contents are thrown into the esophagus resulting in bothersome symptoms and/or complications [1, 2].

Features of the International Statistical Classification of Diseases and Related Health Problems 10th revision coding of the disease are as follows:

P78.8 Other specified disorders of the digestive system in the perinatal period.

EPIDEMIOLOGY

The true incidence of GERD in neonates is unknown, as in most cases the disease occurs in a mild form under the mask of infantile regurgitation related to functional gastrointestinal (GI) disorders [3]. At the same time, GERD is detected among 1 in 10 newborns admitted to the neonatal intensive care unit (NICU). A confirmed diagnosis of GERD leads to increased duration and cost of hospitalization [3].

ETIOLOGY AND PATHOGENESIS OF DISEASE

GERD is a multifactorial disease resulted in the passage of gastric contents into the esophagus — gastresophageal reflux (GER) [2, 3], characterized by a pathologically high frequency and/or duration of episodes, resulting in disruption of the integrity of the esophageal mucosa (OM) or esophageal barrier. In most cases, GER is not accompanied by clinical symptoms and is considered physiological in newborn infants [4].

Maintaining the integrity of OM is determined by the balance between the factors of "aggression" and OM ability to resist damaging effects of gastric contents ingested during GER.

Traditional "aggression" factors include: hydrochloric acid, in case of duodenogastric reflux — lysolecithin, bile acids, pancreatic juice enzymes. However, these factors do not play such a role in the newborn period as they do in subsequent age periods, which is due to anatomic-physiological features [4].

Protective factors are represented by the anti-reflux barrier (lower esophageal sphincter and diaphragm legs), esophageal OM resistance (pre-epithelial, epithelial and post-epithelial levels), esophageal clearance (pH recovery in the distal esophagus after each reflux episode) and timely evacuation of gastric contents [5].

The neonatal period is characterized by a decrease in the effectiveness of defense factors with an unchanged level of aggression factors [3, 6].

Risk factors for the development of neonatal GERD are shown in Table 1 [3].

Main mechanisms in the pathogenesis of GERD development

1. Pathological transient relaxation of the lower esophageal sphincter (LOS), impairing the functioning of the anti-reflux barrier.

Intermittent relaxation of the LOS that occurs during swallowing is physiological and usually does not impair esophageal clearance. Pathological transient LOS relaxation (TLOSR), unrelated to swallowing, characterized by high frequency and/or duration of LOS relaxation episodes, underlies the development of neonatal GERD [7]. Triggers of pathological LOS relaxation are [7, 8]:

- abdominal bloating;
- tension of the anterior abdominal wall of the stomach;
- respiratory distress syndrome;
- therapy with xanthine derivatives (ATX code N06BC).

2. Changes in the abdominal-thoracic pressure gradient.

The lower pressure in the thoracic cavity compared to the abdominal cavity creates a pressure gradient that promotes retrograde flow of gastric contents from the stomach into the esophagus. Any conditions that increase this gradient increase the likelihood of GER [7, 9].

Among the conditions associated with GERD in the newborn period as triggers are:

1) apnea of premature neonates [10, 11];
2) bronchopulmonary dysplasia [12, 13].

Table 1. Risk factors for the development of GERD in the neonatal period

Таблица 1. Факторы риска развития ГЭРБ в периоде новорожденности

Краниофациальные аномалии / Craniofacial anomalies	Хейлосхизис / Cheiloschisis
Аномалии развития дыхательных путей / Anomalies of the respiratory tract	Трахеоэзофагеальная фистула / Tracheoesophageal fistula
Аномалии развития диафрагмы / Developmental abnormalities of the diaphragm	• Врожденная диафрагмальная грыжа / Congenital diaphragmatic hernia • Грыжа пищеводного отверстия диафрагмы / Hiatal hernia
Аномалии развития передней брюшной стенки / Developmental anomalies of the anterior abdominal wall	Дефекты брюшной стенки / Abdominal wall defects
Аномалии желудочно-кишечного тракта / Developmental and congenital anomalies of the gastrointestinal tract	• Атрезия пищевода / Esophageal atresia • Аномалии поворота кишечной трубки / Anomalies of intestinal malrotation • Стеноз пилорического отдела / Pyloric stenosis • Атрезия двенадцатиперстной кишки и других отделов тонкой кишки / Atresia of the duodenum and other parts of the small intestine • Стриктуры кишечника / Intestinal strictures • Кольцевидная поджелудочная железа / Annular pancreas
Патология нервной системы / Pathology of the central nervous system	• Внутрижелудочковые кровоизлияния / Intraventricular hemorrhages • Перивентрикулярная лейкомаляция / Periventricular leukomalacia • Гипоксически-ишемическая энцефалопатия / Hypoxic-ischemic encephalopathy

The causes of such a relationship may be due to chronic aspiration of gastric contents and increased intra-abdominal pressure as a result of respiratory distress, which in turn may lead to increased reflux. However, available studies aimed at identifying the relationship between the above conditions have a low evidence level [3].

CLASSIFICATION

A working classification of GERD in neonates is presented [14].

I–IV degrees of GERD with esophagitis are distinguished on the basis of the severity of endoscopic changes in EM:

I degree — moderately pronounced focal erythema and/or friability of the abdominal esophageal mucosa;

II degree — total hyperemia of the abdominal esophagus with focal fibrinous plaque and possible single superficial, non-adherent erosions within the abdominal esophagus;

III degree — spread of inflammation and erosions (non-adherent or adherent but not circular) to the thoracic esophagus; increased contact vulnerability of the mucosa is possible;

IV degree — esophageal ulcer/ulcers, esophageal stenosis.

CLINICAL PICTURE

The clinical presentation is variable and nonspecific. Most of the suspected symptoms of GERD in the newborn period are unreliable, making GERD a diagnosis of exclusion. The following symptoms help to suspect the disease [3, 15]:

1) general manifestations — prolonged episodes of crying and restlessness, including night, low weight gain;
2) digestive system — regurgitation, vomiting, restlessness during feeding, hematemesis, refusal to eat [2];
3) respiratory system — cough that increases during feeding, stridor, wheezing or aspiration episodes;
4) cardiovascular system — apnea, bradycardia, decreased blood saturation.

In most cases, mild or moderate severity of symptoms is characteristic, manifested as episodes of restlessness, crying and deterioration of the quality of night sleep [3, 15].

DISEASE DIAGNOSIS

Criteria for establishing a diagnosis/condition

The following data are considered to establish the diagnosis:

Identification of risk factors for the development of GERD.

1. Nature of complaints — attention is paid to the time of regurgitation/vomiting, frequency, relationship to food intake, other complaints, additional presence of bile, blood in the contents, the rate of change in physical development indicators.
2. Physical examination — assessment of physical development, detection of anxiety symptoms.
3. Instrumental examination (esophagogastroduodenoscopy (EGDS), intraesophageally pH-metry, pH-impedanceometry).

Due to the absence of specific symptoms that are characteristic for GERD, it is necessary to pay attention to the presence of anxiety symptoms for differential diagnosis and identification of diseases with a similar clinical picture to GERD (Table 2).

Complaints and history

When GERD is suspected in a neonate, it is **recommended to:**

- Study the course of the early neonatal period to identify risk factors for the development of GERD;
- Note the time of debut and the dynamics of complaints [1–3, 5, 14].

Grade of recommendation — C (evidence level — 5).

Comments. *See "Etiology and pathogenesis of the disease". When studying the history of a newborn with suspected GERD, attention should be paid to to certain groups of patients (see Table 1) [3]. The most characteristic complaints include frequent regurgitation/vomiting accompanied by marked restlessness, sleep disturbance and decreased weight gain.*

Physical examination

A visual physical examination **is recommended** for a newborn with suspected GERD [3].

Grade of recommendation — C (evidence level — 5).

Comments*. See "Clinical presentation of the disease". Due to the absence of pathognomonic symptoms, first of all, it is necessary to pay attention to anxiety symptoms (see Table 2). In order to detect them it is necessary to carry out differential diagnosis with other pathological conditions that are similar to GERD.*

Table 2. Complaints and symptoms of concern ("red flags"), the presence of which requires the exclusion of diseases that have a similar clinical picture to GERD [2]

Таблица 2. Жалобы и симптомы тревоги («красные флаги»), наличие которых требует исключения заболеваний, имеющих сходную с ГЭРБ клиническую картину [2]

Жалобы / Complaints	Симптомы, выявленные при осмотре / Symptoms revealed during examination
Время появления регургитации <2 недель жизни / Time of onset of regurgitation <2 weeks of age	Отклонения от нормы, выявленные при общем осмотре, со стороны пищеварительной, дыхательной и нервной системы / Deviations from the normal state, revealed during a general examination, of the digestive, respiratory and nervous systems
Рвота с примесью желчи, ночная или постоянная рвота / Vomiting with bile, nokturnal or constant vomiting	Выраженное вздутие живота / Severe abdominal distension
Хроническая диарея или диарея с кровью / Chronic diarrhea or bloody diarrhea	Лихорадка / Fever
Гематомезис / Hematemesis	Вялость или повышенное беспокойство / Weakness or increased restlessness
Дизурия / Dysuria	Плохие прибавки или отсутствие прибавок массы тела / Poor or no weight gain
Судороги / Cramps	Выбухание большого родничка или быстрый прирост окружности головы или микро/макроцефалия / Bulging of the anterior fontanelle or rapid increase in head circumference or micro/macrocephaly
Рецидивирующая пневмония / Recurrent pneumonia	Патологические изменения мышечного тонуса / Pathological changes in muscle tone
Дисфагия / Dysphagia	Отклонения в психомоторном развитии / Deviations in psychomotor development

Note. The appearance of regurgitation in the 1st-2nd week of life requires the exclusion of infectious diseases, anatomical anomalies, and metabolic disorders.

Примечание. Появление регургитации на 1-2-й неделе жизни требует исключения инфекционных заболеваний, анатомических аномалий, метаболических нарушений.

Laboratory diagnostic tests

- It is **recommended** that all newborn infants with suspected GERD and complaints of vomiting and poor weight gain should undergo a complete blood test to exclude the infectious nature of symptoms and to identify associated conditions/complications such as anemia [16].
  Grade of recommendation — C (evidence level — 5).
  Comments*. Exclusion of infectious diseases is necessary at the debut of symptoms which are typical for GERD in the first week of the child's life [2].*
- It is **recommended** that newborn infants with suspected GERD with complaints of intense vomiting and poor weight gain should undergo a study of acid-base status (ABS) and blood gas composition, determination of lactic acid and ammonia levels in the blood to identify signs of metabolic disorders for further diagnostic search [16].
  Grade of recommendation — C (evidence level — 5).
  Comments. *Exclusion of metabolic abnormalities is required at the onset of complaints which are typical for GERD in the first week of life [2].*

Instrumental diagnostic tests

- Esophagogastroduodenoscopy is **recommended** for neonates with suspected GERD in order to determine the degree of esophageal mucosa lesions, as well as to detect complications and to perform differential diagnosis [17].
  Grade of recommendation — C (evidence level — 5).
  Comments. *The study evaluates the condition of the esophageal mucosa, which is especially important if there are alarming symptoms such as hematemesis, dysphagia, delayed weight gain or anemia, in order to detect complications of GERD, such as erosive esophagitis [2, 17].*
  The examination allows diagnosing a number of congenital esophageal anomalies (atresia, stenosis, 'short esophagus', etc.), as well as acquired diseases of inflammatory and non-inflammatory genesis.
- Newborns with GERD **are recommended** to undergo esophageal biopsy by endoscopy followed by pathological and anatomical examination of esophageal biopsy (surgical) material in case there is no effect from the current therapy in order to exclude rare esophageal diseases, such as eosinophilic esophagitis [2, 3].
  Grade of recommendation — C (evidence level — 5).
  Comments*. It is important to note that even small deviations in biopsy technique affect the validity of histology as a diagnostic method identifying reflux esophagitis. At least two biopsy specimens (preferably four) should be taken at a distance of 2 cm or more above the Z-line for a reliable diagnosis [18].*
  The diagnostic value of biopsy is increased if there are alarm symptoms such as hematemesis, swallowing disorders, anemia. Biopsy is useful to detect complications of GERD such as erosive esophagitis, strictures, or to diagnose conditions that may mimic GERD such as eosinophilic esophagitis [2, 17].
- It is **recommended** that newborns with GERD undergo daily intraesophageally pH-metry in case current therapy is not effective [2, 3, 6, 14, 19].
  Grade of recommendation — C (evidence level — 5).
  Comments. *This method allows to accurately determine the acidic gastric content throwing into the esophagus and to estimate its duration. The study usually lasts from several hours to several days, after which the reflux index (RI) is calculated. The reflux index is defined as the percentage of pH recording time less than 4 to the total study time (in %) [14, 19]. Limitations of pH monitoring in neonates include the lack of reference pH values in this age group and the inability to detect weakly acidic refluxate, which makes up the majority of refluxates in infants (up to 73% of reflux episodes are weakly acidic and alkaline, with pH between 4 and 7, which is largely determined by nutritional characteristics — the alkaline pH of breast milk) [4, 6].*
- Daily pH-impedanceometry is **recommended** for newborns with GERD in case there is no effect on the therapy to correct it [3, 19].
  Grade of recommendation — C (evidence level — 5).
  Comments. *PH-impedanceometry allows to overcome the limitation of the daily pH-metry and to detect both acid and non-acid reflux. Additionally, the method can determine the height of refluxate throw into the esophagus and predict*

the risk of refluxate aspiration. Combined pH-impedance monitoring is promising as an objective method for diagnosing GERD, but more normative data are required before this method can be considered the 'gold standard' test [3, 19].

- It is **recommended** to perform esophageal fluoroscopy with contrast for differential diagnosis and exclusion of anatomical anomalies in newborns with GERD with suspected esophageal orifice hernia, diaphragmatic hernia, refractory course of GERD (absence of convincing clinical and endoscopic remission during 4–8 weeks of therapy) [2, 17].

  Grade of recommendation — C (evidence level — 5).

  Comments. *Barium examination of the esophagus and stomach is performed in straight and lateral projections and in Trendelenburg position with slight compression of the abdominal cavity. The permeability of suspension, the diameter of the esophagus, contours, elasticity of the walls, pathological constrictions, ampullary dilatations, peristalsis, relief of the mucosa are assessed during the study. In case of obvious reflux, the esophagus and stomach radiologically form the figure of "elephant with raised trunk". Delayed radiographs again show the contrast agent, which confirms the fact of reflux. This method is important in the diagnosis of sliding hernia of the esophageal aperture of the diaphragm (SHOAD), anomalies of esophageal development, assessment of consequences of trauma and surgical interventions. The method is also irreplaceable in the diagnosis of functional esophageal diseases. According to the literature, the specificity of radiological examination in the diagnosis of SHOAD is 94% [17].*

  Disadvantages of the method include the fact that radiography does not always allow fixation of hernias of small size, and also gives a high radiation load [2, 17].

Other diagnostic tests

Diagnosis of diseases associated with GERD is performed if there are indications [3].

TREATMENT

Taking into account the multicomponent nature of this pathophysiological phenomenon, GERD therapy is complex. It includes dietary therapy, postural, drug and non-drug therapy, surgical correction ('step therapy'). The choice of treatment method or their combination is carried out depending on the causes of reflux, its degree and spectrum of complications [2, 14].

Therapeutic measures in GERD are based on three main provisions:

1) a complex of non-pharmacological actions, mainly normalization of lifestyle, daily regime and diet;
2) conservative therapy;
3) surgical correction.

Conservative treatment

Diet therapy

- Postural therapy or treatment by changing the body position is **recommended** in newborns with GERD: when feeding, it is necessary to keep a child at an angle of 45–60°, which prevents regurgitation and aerophagia. At night, it is advisable to raise the head end of the bed by 10–15 cm [20]. Overfeeding of children with GERD is inadmissible [21].

  Grade of recommendation — C (evidence level — 5).

  Comments. *Abdominal and left-sided positions are not recommended for use at home because they increase the risk of sudden death syndrome [14, 22].*

- Dietary correction is **recommended,** when postural therapy is not effective. It includes anti-reflux milk mixtures with increased viscosity, they contain thickeners to reduce the frequency of regurgitation and vomiting [23].

  Grade of recommendations — C (evidence level- 5).

  Comments. *The use of specific foods enriched with complex carbohydrates to prevent backward movement of gastric contents and improve gastric emptying is a fundamental direction of dietary therapy of GERD in children. This nutritional approach is very effective for children with mild regurgitation and sufficient or slightly low rates of weight gain. When combined with postural therapy, its effectiveness reaches 90–95% [14, 23].*

  The best effect is achieved when anti-reflux mixtures are administered at the earliest stages of the disease.

  It should be remembered when prescribing mixtures with non-digestible polysaccharides (PS) (carob gum) as a thickener, that these mixtures are:

  - *therapeutic and should be prescribed by a doctor;*

- *require a clear calculation of the amount in the child's daily ration (1/2, 1/3 or 1/4);*
- *are prescribed for a limited period of time;*
- *are not recommended for healthy children who do not suffer from regurgitation;*
- *are only one component of a treatment program.*

Options for prescribing anti-reflux formulae:

- *At the end of each breast milk/adapted formula feeding, an anti-reflux (AR) formula is administered at 1/2–1/4 of the feeding volume;*
- *AR formula is administered 1–3 times a day in the volume of feedings, otherwise adapted formula is used;*
- *AR formula is administered in full daily volume for 2–4 weeks.*

- If dietary correction with anti-reflux milk mixtures is ineffective, it is **recommended** to use mixtures based on highly hydrolyzed protein or amino acid mixtures for two weeks [2, 23].
  Grade of recommendations — C (evidence level — 5).
  Comments. *Highly hydrolyzed protein-based mixtures are particularly indicated when a child has other symptoms that indicate atopic diseases, such as atopic dermatitis [2]. In case the clinical picture does not improve in two weeks, the chosen tactics of diet therapy is not effective. If there is a positive effect, it is recommended to continue taking the mixture for up to 12 months, but not less than 6 months [2, 24, 25].*

Pharmacological therapy

- Routine drug therapy **is not recommended** for newborns with uncomplicated GER because of insufficient efficacy and safety data; in most cases, infants' symptoms resolve on their own after 6 months of age [17].
  Grade of recommendation — C (evidence level — 5).
  Comments*. Available data do not support the efficacy of proton pump inhibitors (ATX code A02BC) for the treatment of GERD symptoms in neonates. Acid-suppressive therapy should not be used in preterm infants because of serious side effects [26, 27].*
- Therapy with proton pump inhibitors (code ATX A02BC) (IPN) — #esomeprazole** (code ATX A02BC05) is **recommended** for neonates with severe symptoms of GERD (restlessness, refusal to feed, poor weight gain) and moderate or severe esophagitis in case non-drugs methods of correction are not effective [3, 17].
  Grade of recommendation — C (evidence level — 5).
  Comments. *#Ezomeprazole** (ATX code A02BC05) is administered in a daily dose of 0.5 mg/kg for 1–2 intakes. The average duration of therapy is 4–6 weeks. Contraindications — individual intolerance to the drug [3, 17].*

Surgical treatment

- Neonates with GERD are **recommended** to undergo fundoplication / laparoscopic fundoplication (Nissen method, less frequently Tal, Dore, Toope methods) (open access fundoplication / laparoscopic fundoplication) in case of long-term persisting endoscopic picture of reflux esophagitis of III-IV degree on the background of repeated courses of therapy, in case of GERD complications (bleeding, strictures), in case of combination of GERD with SHOAD [28, 30].
  Grade of recommendation — C (evidence level — 5).
  Comments. *In the absence of contraindications, laparoscopic fundoplication is preferable [28].*

MEDICAL REHABILITATION AND HEALTH RESORT TREATMENT

Special methods of medical rehabilitation have not been developed.

PREVENTION AND MEDICAL FOLLOW-UP, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF PREVENTION METHODS

To prevent GERD, it is recommended to limit/avoid factors that provoke the development of GERD [14]:

1) to avoid overfeeding;
2) if possible, to limit the use of medications that relax the lower esophageal sphincter.

- It is **recommended** that newborns diagnosed with GERD are monitored by a gastroenterologist [14, 29].
  Grade of recommendation — C (evidence level — 5).
  Comments. *Subsequent follow-up of a patient with GERD is performed at least twice a year for three years from the last visit [29], and is determined by the severity of clinical symptoms and clinical and endoscopic findings.*

ORGANISATION OF MEDICAL CARE

Children with GERD are observed by a paediatrician and a gastroenterologist, if there is

a concomitant pathology — together with relevant specialists, including a paediatric surgeon.

Indications for hospital admission include the onset of symptoms requiring urgent intervention (dysphagia, weight loss, hematemesis or recurrent vomiting) [30].

Discharge of a patient with GERD is indicated if a patient is in satisfactory condition, symptoms of GERD have resolved, and an endoscopic picture has improved/normalized.

After discharge from hospital, children should undergo medical follow-up by a paediatrician and a gastroenterologist [14].

As a rule, children with GERD usually do not need treatment in a 24-hour hospital, except for a complicated course and indications for surgical intervention. Hospitalization in a day hospital (average duration is 10–14 days) is appropriate to establish the diagnosis and possible correction of therapy.

COMPLICATIONS

A formidable complication of GERD are strictures of the esophagus, which arise with the scarring of ulcer defects. This process involves deep layers of the esophageal wall and peri-esophageal tissues against the background of chronic inflammation, i.e. perioesophagitis occurs. The predominance of fibrosis leads to scar formation, as a result a peptic stricture of the esophagus develops.

Another serious complication of GERD is posthemorrhagic anemia, which can occur both in case of sliding hernia of the esophageal aperture of the diaphragm, the impingement of which traumatizes the mucous membrane of the diaphragmatic 'sac', and as a result of erosive and ulcerative lesions of the esophageal mucosa.

DIFFERENTIAL DIAGNOSTICS OF GERD

Differential diagnosis of GERD is differentiated with the following diseases and conditions:

1) achalasia of the cardia;
2) esophageal narrowing caused by pathological changes in the neighboring organs;
3) mediastinal tumors and cysts;
4) posterior mediastinitis;
5) pleuropulmonary fibrosis;
6) aortic aneurysm;
7) right-sided aorta;
8) vascular anomalies;
9) drug exposure;
10) *congenital metabolic disorders:*
    a) disorders of organic acid metabolism;
    b) disorders of amino acid metabolism;
    c) primary lactate acid acidosis;
    d) fatty acid oxidation disorders.

OUTCOMES AND PROGNOSIS

Most children with GERD have a favorable prognosis. A number of complications, such as Barrett's esophagus, may develop only at an older age [14, 17].

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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