MINISTRY OF HIGHER AND SECONDARY SPECIALIZED EDUCATION OF THE REPUBLIC OF UZBEKISTAN REPUBLIC OF UZBEKISTAN

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MONOGRAPH

"Modern aspects of clinical and immunological diagnostics of functional gastrointestinal disorders in children"

Bukhara 2025

CONTENTS

СОДЕРЖАНИЕ

MUNDARIJA

List of abbreviations

CD16 - Lymphocytes - natural killers

CD19 – B-lymphocyte

CD25 - T-, B-, TK-cells, thymocytes, activated macrophages

CD 3 - T-lymphocyte

CD 4 - T -lymphocyte (helper)

CD 8 - T -lymphocyte (cytotoxic)

CD 95 - cell apoptosis receptor

Ig - Immunoglobulin

TK - T-killer

AD - atopic dermatitis

ASRU– Academy of Sciences of the Republic of Uzbekistan

BRMMC – Bukhara Regional Multidisciplinary Medical Center

IBD – Inflammatory Bowel Disease

WHO - World Health Organization

GIT – Gastrointestinal tract

IL - interleukin

IFN - interferon

IFA – Immunoenzyme assay

ICD 10 - International Classification of Diseases, 10th Edition

NUC - nonspecific ulcerative colitis

AII - acute intestinal infections

CM - colon mucosa

IBS – Irritable Bowel Syndrome

FD - functional dyspepsia

FD - functional disorders

TNF - Tumour necrosis factor

CNS - central nervous system

INTRODUCTION

In recent years, the prevalence of pathologies of the digestive system in children has been steadily increasing. One of the most common reasons for seeking medical help is abdominal pain, and according to various sources, the frequency of gastrointestinal diseases among the pediatric population has increased from 20% to 50%. It is in this group that in 70-90% of cases, childhood pain is caused by functional causes and is an important component of the symptom complex of functional disorders of the gastrointestinal tract (FDGIT) [4].

Functional disorders of the gastrointestinal tract (FDGIT) occupy an important place in the general structure of the pathology of the digestive organs. According to many researchers, it is functional disorders that account for up to 90% of all forms of gastrointestinal pathology at an early age. Analyzing the publications of recent years, it can be noted that this problem is increasingly attracting the attention of researchers.

Definition: there have been repeated unsuccessful attempts to define various gastrointestinal disorders. According to the recommendations of the consensus meeting of the International Working Group on Improving Diagnostic Criteria for Functional Gastrointestinal Disorders, known as the "Rome II Criteria" (2000), gastrointestinal disorders are characterized as "... a variable combination of chronic or recurrent symptoms not explained by structural or biochemical changes...", i.e., functional disorders should not include well-known disorders that are essentially secondary to a structural base or diseases of the nervous system. According to them, the diagnosis of FD can be made if three mandatory conditions are met:

1) the patient has persistent or recurrent symptoms of dyspepsia that last longer than 12 weeks during a year;

2) an examination of the patient, including an endoscopic examination of the upper gastrointestinal tract, does not reveal organic diseases that could explain the symptoms;

3) there is no indication that the symptoms of dyspepsia disappear after defecation or are associated with changes in the frequency and nature of stool (i.e., there are no signs of IBS).

According to the definition given in the Rome criteria, FDs of the gastrointestinal tract include conditions in which it is impossible to identify morphological, genetic, metabolic, biochemical and structural changes that explain the observed clinical symptoms. In pediatric practice, the diagnosis of FDs of the gastrointestinal tract as a nosological entity is still carried out with certain difficulties. This is due to the lack of a unified approach to their interpretation and diagnosis. Therefore, the prevalence of diseases of the gastrointestinal tract in children has not yet been determined and requires further study. According to a number of authors, FDs account for 30-90% of all pathologies of the gastrointestinal tract in children of the first year of life. The first half of life deserves special attention as the initial and most important period for determining the child's health in the future [3].

In 1992, the International Working Group on Functional Disorders Criteria proposed the Rome criteria for IBS, updated in 2000 (Rome II criteria) [40].

A child who has consulted a doctor with abdominal or dyspeptic complaints should undergo a thorough medical examination, including: clinical, instrumental and morphological examination, as well as, if necessary, other examination methods, and then, if no signs of organic damage to the gastrointestinal tract are detected, a diagnostic test for functional dyspepsia is considered legitimate. In this case, it will be possible to exclude the diagnosis of functional dyspepsia .

In light of these facts , it is timely and relevant to address the above issues through planned research .

Functional disorders of the digestive tract are very common in pediatric practice, but they are difficult to diagnose. It is important to distinguish somatic complaints from true organic symptoms, which is of primary importance for making a correct diagnosis and choosing an optimal treatment plan. A distinctive feature of

this pathologies of this type, no clear morphological substrate is identified; rather, the abnormalities stem from disruptions in regulatory mechanisms—either neural or hormonal—impacting the function of the organs rather than their structure. Evaluating the prevalence of functional gastrointestinal disorders in early childhood, particularly among children under the age of three, presents significant challenges. These functional digestive issues in infants during their first year of life are intricately linked to feeding patterns and nutritional factors. During the early months, the gastrointestinal system is primarily attuned to processing breast milk (a lactotrophic mode of feeding), making it crucial to consider factors such as feeding intervals, frequency, the amount and composition of breast milk—all of which are directly influenced by the mother's diet.

According to the modern definition, dyspepsia syndrome is understood as a complex of functional disorders, including pain and / or discomfort in the epigastrium, a feeling of fullness in the epigastric region after eating, early satiety, nausea, vomiting, heartburn, belching, etc. A characteristic feature of dyspepsia in children is the predominant localization of pain in the umbilical region. The prevalence of the syndrome among the population is 25-50% and is approximately the same in all age groups.

After the birth of a child, his digestive system undergoes a number of changes due to the maturation of regulatory systems, the formation of neuromuscular response and enzyme-producing function, peristalsis and the formation of biocenosis. Despite the fact that these features are characteristic of all newborns without exception, complaints in some infants are of particular concern to parents, which forces them to consult a pediatrician or general practitioner, and therefore the need arises to correctly select symptomatic agents. Taking into account the fact that the appointment of any medication to a young child should be justified, it is absolutely appropriate to include the concept of "infantile colic" in the modern classification of functional diseases of the gastrointestinal tract.

The progression of functional gastrointestinal disorders (FGIDs) in pediatric patients demonstrates a wide range of clinical variability and remains insufficiently explored in the scientific literature. Current findings strongly suggest that the elevated incidence of these disorders in children is largely attributed to the anatomical and physiological peculiarities of their digestive systems. In evaluating the onset of functional abnormalities, clinicians must carefully consider several developmental characteristics of the esophagus, such as the relatively wide angle of His, the positioning of the cardiac sphincter at or below the level of the diaphragm, incomplete coverage of the esophagus by diaphragmatic ligaments, underdeveloped muscular layers, and immature innervation due to delayed development of intramural nerve ganglia. Additionally, the infant's stomach—characterized by its small size, spherical shape, and delayed peristaltic activity—contributes to reduced functional capacity of the cardiac region during early infancy.

These factors collectively explain the increased prevalence of regurgitation, pyloric spasms, and vomiting in this age group, with the enhanced development of the pyloric region playing a contributory role. Epidemiological data reveal that regurgitation is reported in nearly 50% of infants under three months, 20% at six months, and declines to about 5% by the age of one year. In newborns, bile reflux is common, whereas older children more frequently experience acid reflux. It is notable that more than 40% of gastroesophageal reflux (GER) cases in infants are associated with cow's milk protein allergy. Implementation of an elimination diet, especially formulas based on protein hydrolysates, has been shown to substantially alleviate GER symptoms.

Taken together, the findings underscore that a majority of the subjects studied exhibited a high incidence of functional gastrointestinal disturbances, complicating the differentiation of fibromyalgic manifestations. Importantly, psychological disturbances — particularly depressive and anxiety-related symptoms — play a crucial role in shaping the overall clinical profile of FD in children. The

leading one among them was depressive syndrome, which was diagnosed in almost 70% of cases (versus 4.44% in the control group). Depression was manifested by a depressed mood, a narrowing of the range of interests, a loss of a sense of pleasure, and a drop in the general level of activity. However, it should be noted that the overwhelming majority of these patients were individuals with a masked version of depressive state, while a clinically obvious version of depressive disorders was observed in only 1 patient. This, in turn, seriously complicated the timely and correct diagnosis of FD. About 1/3 of FD patients did not have reliable symptoms of depression.

When assessing the functional state of the digestive tract of a child, it is necessary to take into account that his intestines have a greater length and surface area than those of an adult, which is beneficial for the child's body, as it ensures maximum use of enzyme systems and participates in the processes of digestion, absorption and secretion. At the same time, it is known that the intestinal mucosa of a baby has a greater permeability and, accordingly, does not provide reliable adaptation of digestion to constant changes and adverse external influences [12].

Pain syndrome in intestinal colic is associated with increased gas filling of the intestines and impaired motor function (during eating and during digestion). In this case, the peristaltic wave covers not the entire intestinal tract, but only its individual sections, which leads to a sharp spasm in certain parts of the intestine (colic-like pain).

Etiology and pathogenesis

Despite the fact that the pathophysiology of functional syndromes of the digestive tract has been studied for many years, and an active search for their biological markers is underway, the origin of FGIDs remains largely unclear. According to V. T. Ivashkin, they represent "... a kind of "knot" in which various scientific directions are intertwined and which to some extent reflects the progress achieved in the study of intestinal diseases" [24]. Until now, the question of their exclusively inorganic origin remains open, since, according to some researchers, a

purely functional pathology cannot exist in principle, since the function is a reflection of structural changes [27], and the possibilities of their detection are determined, first of all, by the temporary development of the relevant technologies. Thus, there are enough works that show that dystrophic changes in the mucous membrane of the gastrointestinal tract, detected during endoscopic and histological studies in individuals with FGID, although they do not lead to the development of a clinical picture of the disease, are capable of causing changes in other functions, for example, the absorption function and permeability of the digestive tract. Perhaps this calls into question the exclusively functional origin of these diseases. Their opponents rely on the assumption that such changes do not cause clinical manifestations of the disease and can be detected in most practically healthy individuals, for example, endoscopically verified superficial gastritis occurs in almost 100% of cases during gastroscopy [19]. In this regard, a legitimate question arises: could this be a "physiological inflammation" of the intestine or does everything depend on the time and conditions of taking the biopsy? E.A. Poluektova et al. found changes in the mucous membrane of the colon in patients with IBS that fit into the picture of productive inflammation [15, 16]. They also found changes in the vessels of the submucosal layer of all calibers in the form of sclerosis and thickening of the walls, narrowing and obliteration of the lumen, which were multifocal in nature, which was consistent with the sonographic data of the intestinal loops.

The activity of the digestive system, intestinal motility, secretion and absorption are regulated by a complex system of nervous and humoral mechanisms. There are three main mechanisms for regulating the activity of the digestive system. They are divided into central reflex, humoral and local. Functional bowel diseases include such clinical manifestations as irritable bowel syndrome, functional constipation, functional diarrhea, functional bloating of the abdominal cavity and non-specific functional bowel diseases. In our study, we surveyed parents using a questionnaire and general clinical examinations developed by us to develop a

predictive scale for the formation of risk factors for the gastrointestinal tract in young children. All selected patients underwent general clinical, laboratory, functional and biochemical examinations. In order to develop an optimal method for assessing risk factors for the development of complications of functional constipation in children with the subsequent decision on the tactics of patient treatment, we carefully analyzed the results of the study, risk factors, biochemical indicators, as well as immunological blood parameters. Reflex control mechanisms exert their strongest influence on the upper segments of the gastrointestinal tract, particularly near the oral cavity. As one moves further along the digestive system, the impact of reflex responses gradually diminishes, while humoral regulatory processes become increasingly dominant. These humoral influences play a significant role in modulating the functions of the stomach, duodenum, pancreas, and in the processes of bile synthesis and secretion. In contrast, within the small and especially the large intestines, regulation is primarily governed by local mechanisms that respond to mechanical distension and chemical stimuli present within the intestinal lumen. In approximately 25% of children with moderate or severe symptoms of intestinal colic , the cause is food allergy, namely intolerance to cow's milk protein, which may be the first manifestation of atopy.

Chapter I. GENERAL INFORMATION ON LITERATURE SOURCES; LITERATURE REVIEW. MODERN CONCEPTS OF FUNCTIONAL DISEASES OF THE GASTROINTESTINAL TRACT IN CHILDREN

1.1 Some aspects of the study of the prevalence, etiopathogenesis and clinical course of functional disorders of the gastrointestinal tract.

In recent years, the prevalence of digestive system pathologies in children has been steadily increasing. Abdominal pain represents one of the leading complaints prompting pediatric medical consultations. According to different studies, its prevalence among children ranges from 20% to 50%. Notably, in approximately 70% to 90% of cases, such pain is attributed to functional rather than organic causes. It is frequently considered a key clinical manifestation within the broader spectrum of functional gastrointestinal tract disorders (FGIDs) in the pediatric population.

Functional gastrointestinal syndromes encompass a range of chronic or recurrent symptoms that lack identifiable systemic, structural, or biochemical abnormalities. The Rome 2006 criteria categorize patients by age groups—specifically, “Newborns and Infants” and “Children and Adolescents,” with the latter group comprising individuals aged four years and older.

Abdominal discomfort or pain that persists for a minimum of 12 weeks within the previous 12 months—though not necessarily occurring consecutively—is considered clinically significant when it exhibits at least two of the following three features:

- symptom relief following defecation;
- symptom onset correlated with a change in bowel movement frequency;
- symptom onset associated with an alteration in stool consistency or form.

Despite its clinical utility, this definition has several limitations that warrant further refinement and clarification in future diagnostic frameworks. It should be recognized that the current definitions of functional gastrointestinal disorders have serious shortcomings. First, they do not clearly

distinguish between functional disorders of different organs due to the fact that they often overlap. Secondly, the above definitions do not allow us to distinguish clinical variants of each gastrointestinal disorder based on the proposed diagnostic criteria. Thirdly, the sensitivity of diagnostic criteria for gastrointestinal disorders varies between males and females. In addition, the definition of functional disorders cannot be considered indisputable also because a rather paradoxical situation has arisen today in the issue of the final clinical diagnosis in patients with gastrointestinal disorders. Despite the consistency of the definition of these disorders, several narrow specialists recognize them as "their own". In our country, gastrointestinal disorders have essentially become an interdisciplinary problem. Thus, various variants of gastrointestinal disorders of functional genesis are considered by psychiatrists as somatoform disorders, i.e. conditions in the clinical picture of which "somatic" or pseudo-somatic complaints come to the fore, and the actual mental disorders are hidden behind "somatic" manifestations and are not noticed by either patients or doctors. On the other hand, neurologists recognize the existence of functional gastralgia and the syndrome of the celiac and superior mesenteric plexus, neurosis of the digestive tract with clearly defined diagnostic criteria [3, 4]. Gynecologists often diagnose women with these disorders with "chronic pelvic pain". General practitioners mean by gastrointestinal diseases such popular "nosologies" as "intestinal dysbacteriosis" and "chronic enterocolitis", which are not included in the 10th revision of the ICD at all. A kind of vicious circle of narrowly specialized views on the same problem is being formed, which must be broken in the coming years.

Moreover, soon after the practical use of the Rome criteria, some of their shortcomings and inaccuracies were discovered. An analysis of diagnostic errors using IBS as an example showed the following: 1. The biggest shortcoming of the diagnostic criteria is that they are non-specific and can occur in a wide variety of diseases, not only organic but also functional. 2. Individual symptoms of the diagnostic criteria for FGIDs are not clearly defined (for example, the concept of

"discomfort" in the abdomen, which almost always accompanies diarrhea and constipation of various etiologies), which prevents, for example, from distinguishing between the concepts of IBS and functional constipation, IBS and functional diarrhea. 3. On the contrary, other symptoms that are not very specific for functional GIT disorders are considered to be frequently encountered in this pathology. For example, the sensation of incomplete emptying of the rectum was often interpreted as a manifestation of IBS. However, in practice, this symptom is a characteristic sign of pathology of the proctoanal zone and pathology of the pelvic organs.

4. An important role in the differential diagnosis of patients with FGID is played by the modern identification of "alarm symptoms" or "red flags". However, their absence often does not mean anything. Every doctor with even a little clinical experience can cite many examples when various serious diseases proceeded outwardly quite favorably, without changes in laboratory parameters and objective examination data.

5. Often, diagnostic criteria do not reflect the characteristic connection in many patients of the appearance of the main symptoms of FGID with food intake. However, as practice shows, abdominal pain associated with a change in the frequency of stool, bloating in such patients, as a rule, are postprandial in nature.

6. Not all specific symptoms of FGID are included in the diagnostic criteria, for example, when diagnosing IBS, urgent uncontrolled acts of defecation are not taken into account as an extreme degree of severity of imperative urges.

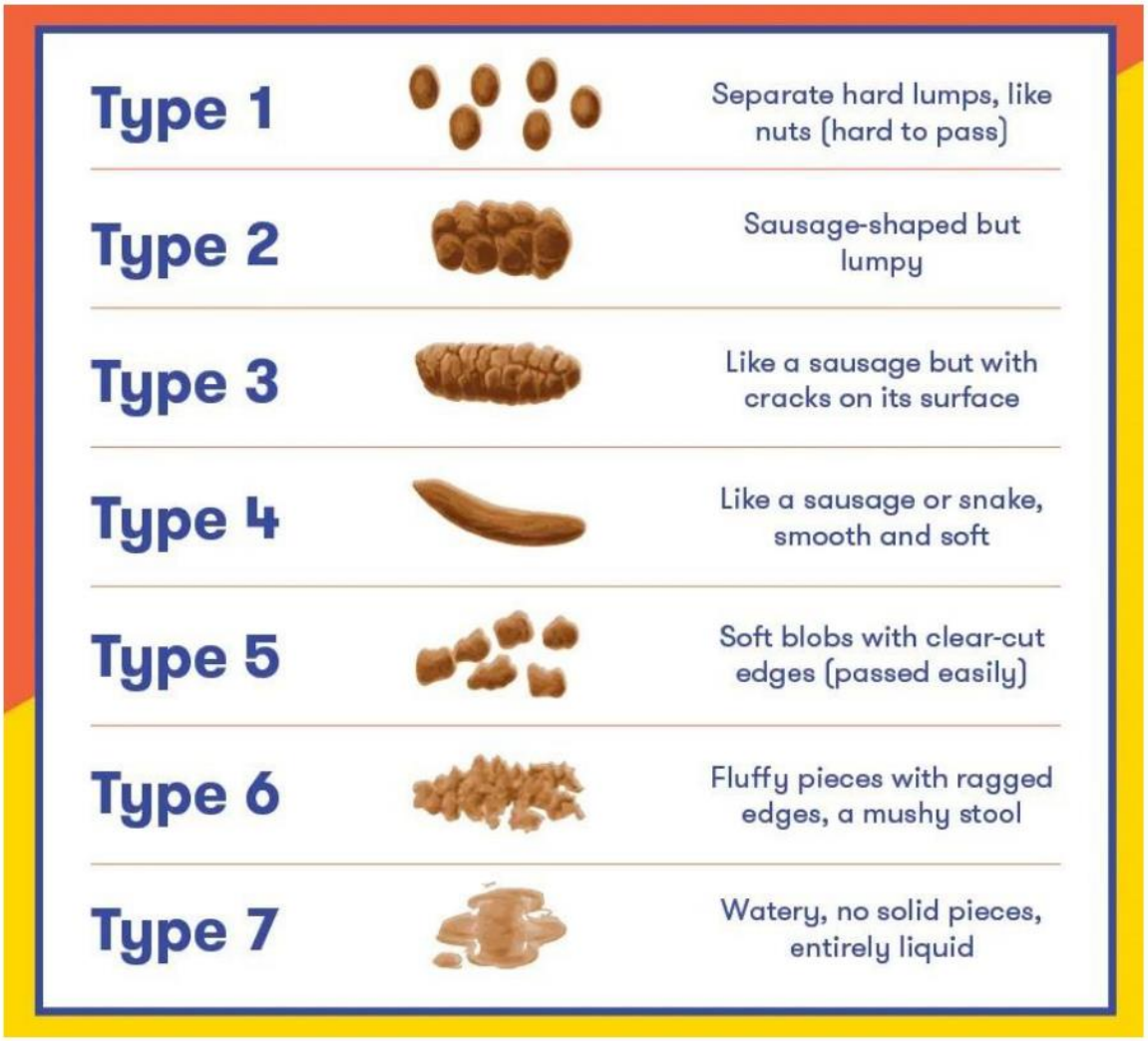
7. The patient's subjectivity in accurately describing complaints and the doctor's subjectivity in their correct interpretation acquire, based on the proposed criteria, great importance.

Diagnostic Features: The non-specificity of clinical manifestations of FGID makes it extremely difficult to establish a diagnosis at the nosological level. Since the symptom complex characteristic of a separate clinical variant of FGID is not specific, its diagnosis involves, first of all, excluding organic diseases that occur with similar symptoms. This requires a large volume of laboratory and instrumental

studies within the framework of the approved algorithm for establishing a specific diagnosis. Choosing the easier path of syndromic diagnosis is fraught with gross diagnostic errors and an increased risk of untimely diagnosis of an organic disease. However, such an algorithm for diagnosing FGID is extremely complex and takes a long time. For example, the diagnosis of IBS is established in five stages, after which a primary course of treatment of at least 6 weeks is prescribed, based on the results of which the diagnosis is assessed again. If the treatment is effective, a final diagnosis of IBS can be made; if it is ineffective, additional examination is carried out. Often, the use of expensive invasive procedures is recommended (serial enterography, intestinal manometry, balloon dilation test, lactose tolerance test, aspiration of the contents of the small intestine to study the bacterial flora, radioisotope transit study, study of anorectal functions, etc.), which are inaccessible to most hospitals and clinics in large cities. Moreover, different approaches to the fundamental question of whether it is possible to diagnose a gastrointestinal disorder, and if so, after which instrumental methods, have led to the fact that these diseases are overdiagnosed (and, thus, more serious pathology is not recognized), and this pathology is not established in other people who actually suffer from functional disorders (Picture 1)

Classification:

A difficult situation has arisen in the issue of classifying gastrointestinal disorders. All existing classifications of functional disorders can be divided into two groups: topical (by the affected organ) and clinical (by the leading symptom). (Picture-1)



Pic.1 – Determination of functional disorders by stool forms

Second Rome Classification of Functional Gastrointestinal Disorders

1. Esophageal disorders:
   1) globus;
   2) ruminant syndrome;
   3) functional chest pain, presumably of esophageal origin;
   4) functional heartburn;
   5) functional dysphagia;
   6) nonspecific functional disorders of the esophagus.
2. Gastroduodenal disorders:
   1) functional dyspepsia:

a) ulcer-like dyspepsia;

b) dysmotility-like dyspepsia;

c) nonspecific dyspepsia;

2) aerophagia;

3) functional vomiting.

3. Intestinal disorders:

1) irritable bowel syndrome;

2) functional bloating;

3) functional constipation;

4) functional diarrhea;

5) non-specific functional bowel disorders.

4. Functional abdominal pain:

1) functional abdominal pain syndrome;

2) non-specific functional abdominal pain.

5. Biliary disorders:

1) gallbladder dysfunction;

2) sphincter of Oddi dysfunction.

6. Anorectal disorders:

1) functional fecal incontinence;

2) functional anorectal pain:

a) levator ani syndrome;

b) proctalgia;

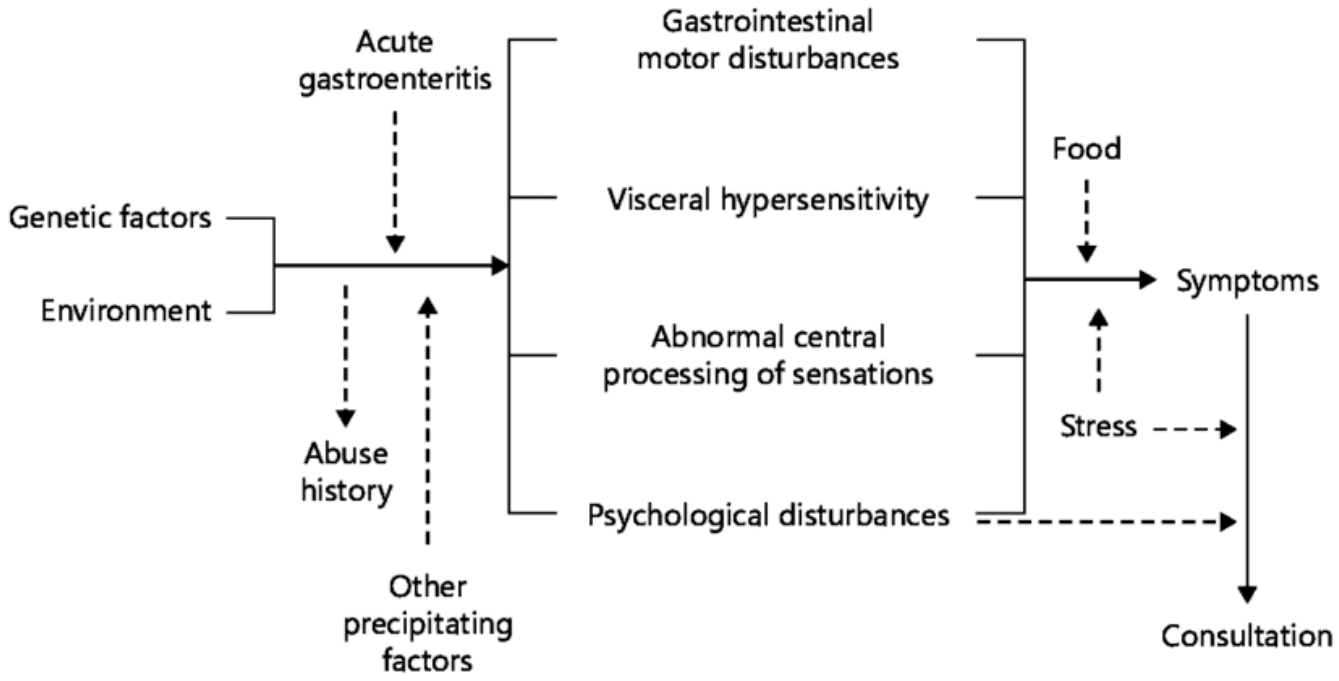
3) pelvic floor dyssynergia.

The Rome IV revised criteria for the diagnosis and treatment of functional disorders of the gastrointestinal tract in children and adolescents are based on the absence of any organic clinical manifestations against the background of intestinal disorders in the form of periodic exacerbations of abdominal pain, flatulence, diarrhea, a tendency to constipation, changes in the gastrointestinal tract are considered as manifestations of irritable bowel syndrome. The main intestinal

immunoglobulin is IgA, which is produced locally by plasma cells located in the lamina propria of the intestine. When deciding on the onset of functional disorders, the doctor should take into account the anatomical and physiological characteristics of the esophagus (large size of the angle of Hiss; the location of the cardiac sphincter under or at the level of the diaphragm; the diaphragmatic ligaments do not completely cover the esophagus; the muscular layer of the esophagus is weak, usually not completely covered; its innervation is not fully provided due to the immaturity of the intramural nerve ganglia), as well as the small size of the stomach, its spherical shape and delayed peristalsis of the movement are the causes of functional weakness of the cardia in infancy. Secretory IgA binds antigens of viruses and bacteria (neutralizes viruses, agglutinates bacteria), blocks the adhesion of viruses and bacteria to mucous membranes, stimulates the antibacterial activity of phagocytes and lymphocytes against pathogenic bacteria, binds food antigens and allergens that cause allergies. Functional disorders of the gastrointestinal tract in infants and young children are particularly emphasized, among which: regurgitation, colic, functional diarrhea, functional constipation, etc. [16].

The group of functional disorders that manifest as abdominal pain includes: functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine, and functional abdominal pain (FAP)(Picure-2). However, the Rome criteria stipulate that these diagnoses can only be made in children over four years of age. Thus, the age range from 1 to 3 years remains open. There is no doubt about the polyetiology of gastrointestinal risk factors in children. The main factors in their pathogenesis are impaired motor function and visceral sensitivity, but they are often accompanied by changes in secretory and absorptive functions, gastrointestinal microflora, and inflammatory potential of the mucosa [20].

Pediatricians often use a symptomatic approach in their work, trying to eliminate the immediate manifestations, rather than the causes of gastroenterological diseases. In



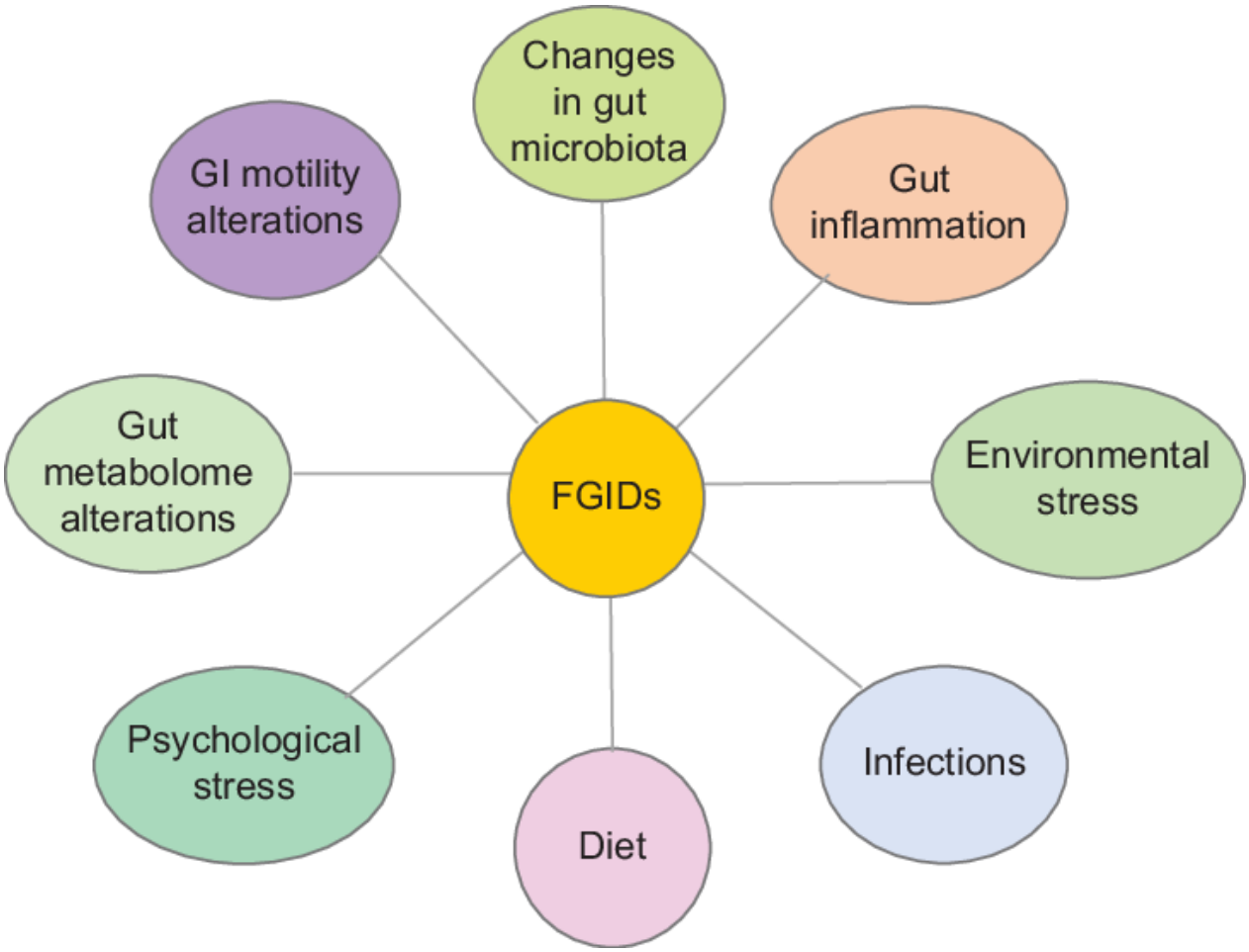
Pic.2 Systemic developing mechanism of gastrointestinal disorders

many cases, they do not take into account the neurological psychological and behavioral aspects, which often form the basis of gastrointestinal risk factors, which leads to the development of the stereotype of the "gastroenterological patient".

Increased gastrointestinal reactivity influenced by hereditary factors may contribute to the development of functional dyspepsia (FD). Specifically, polymorphisms in the GN-β3 gene have been linked to this condition. Individuals carrying the GN-β3 CC genotype exhibit a twofold higher risk of developing dyspepsia, particularly the dyskinetic subtype, compared to those with TT or TC genotypes. The presence of the GN-β3 CC genotype may impair receptor sensitivity to neurotransmitters that regulate gastric motility, such as serotonin 5-HT4 receptors, potentially leading to delayed gastric emptying. Moreover, children may manifest symptoms by mimicking parental behaviors. Among children with gastrointestinal risk factors, their parents more frequently suffer from functional gastrointestinal disorders than parents of unaffected children, with considerable overlap in risk factors between parents and offspring. Motor and emotional

disturbances can result from perinatal complications. Stressful influences on the developing brain of the fetus and newborn can lead to long-lasting adaptations, which later manifest as functional gastrointestinal disorders in childhood. Psychotraumatic and stressful experiences often present as pathological symptoms in children with adverse perinatal histories, including neonatal medication exposure, autonomic dysfunction, and allergies.

Functional gastrointestinal disorders (FGIDs) are classified as those with no organic cause and those not attributable to structural or biochemical abnormalities. FGIDs are also defined as 'Disorders of Gut–Brain Interaction'. The etiology of FGID is multifactorial and may include altered brain–gut interactions, genetic predisposition, dysbiosis, dysregulation of the intestinal barrier, and environmental factors (Picture-3). FGIDs are characterized by chronic gastrointestinal symptoms and occur in a high proportion of children. FGIDs account for approximately 5% of presentations to primary care physicians and are the cause of many referrals to tertiary care services for further investigation or to exclude serious organic disease. Pediatric FGIDs are now considered to be a global health problem associated with high healthcare utilization and psycho-socioeconomic burden for families. Children with FGIDs have been shown to have lower health-related quality of life (HRQoL) and experience interference with sleep, school, and social activities, thereby representing significant symptom burden as well as other sequelae. There are many facets of ongoing research into pediatric FGIDs, and the aim of this Special Issue is to gather evidence of the challenges in diagnosing and treating FGIDs in children and to add to the growing body of evidence advancing the topic.



Pic.3 Groups of hastroinrtestinal disoerders

An important aspect of assessing the burden of any condition in a population is to study the epidemiology, either as the incidence of new diagnoses during a time period, or the prevalence of those who are assessed as having the condition. The standardization of these assessments is vital to gain a true representation of the burden of FGIDs throughout the world and to compare epidemiology over time or between regions. The most widely known and implemented of the FGID tools are the Rome IV assessments—symptom based criteria with versions available for neonates/toddlers and children/adolescents. The broad adoption of the Rome criteria has enabled more consistent comparisons of epidemiological patterns. Studies indicate that around 22% of children across both age groups—neonates and toddlers, as well as older children and adolescents—are affected by at least one functional gastrointestinal disorder (FGID), with some of the highest rates reported

in the Americas. There is little published epidemiological data available worldwide. In this Special Issue, Vernon-Roberts et al. addressed this gap in New Zealand by measuring the prevalence of FGID in a cohort of New Zealand children attending a tertiary care hospital while concurrently measuring HRQoL. This research showed that 29% of the children aged four years of age or more, within the population studied, had FGID, with the most common being functional constipation and functional dyspepsia. The presence of FGID was not found to be related to HRQoL overall, but within the domain of 'feeling sad, worried or unhappy', there was an association between having FGID and scoring lower in this domain than those without FGID. Of note was that associations were also seen between having an FGID and being of Māori ethnicity, the indigenous population of New Zealand who have known health disparities compared to other ethnic groups. Having a parent with self-reported FGID was also associated with children having FGID.

The management of FGID in children can be challenging, as there is considerable variation in the diagnostic categories, thereby preventing a universal approach. Based on the Rome IV criteria for children under 12 months old, infant regurgitation and functional constipation are identified as the most prevalent functional gastrointestinal disorders (FGIDs). Among toddlers aged 13 to 48 months, functional constipation remains the most common condition. Approximately 22% of children in both age categories are affected by at least one FGID. Infants experiencing FGID are shown to have a lower weight, shorter breast-feeding duration, and are more likely to be formula-fed or have been introduced to cow's milk before those without FGID. Infants with FGID are also more likely to have behavioral or developmental problems, migraines, and future GI disorders. Given that these sequalae are deleterious to infant health and longitudinal outcomes, effective symptom management is vital. In this Special Issue, Rishanghan et al. provide a comprehensive overview of the management of FGID in infancy. For each infant FGID, the paper summarizes the possible organic differential diagnoses, outlines the indicative symptoms, and provides a literature review of treatment and

management strategies. The findings highlight the importance of clear education and guidelines for parents/families of infants presenting with FGID and summarizes that the management approach is predominantly based around providing parental reassurance.

Pediatric feeding disorders are another common group of problems facing children, parents, and clinicians. While no direct link has been established between the presence of FGID and feeding disorders, many children with FGID have symptoms induced by eating specific foods and may subsequently practice food avoidance or meal modification. Pediatric feeding disorders are characterized by difficulties in oral intake linked to medical issues, feeding skills deficits, nutritional problems, and/or psychosocial dysfunctions. These disorders often arise from a combination of factors, including medical conditions, nutritional challenges, behavioral aspects, psychological influences, and environmental contributors. Feeding disorders among children are common, with the reported prevalence being 25% in all children, and 80% in children with developmental disabilities. Between 3 and 10% of children will go on to develop chronic feeding issues that may be associated with a number of negative medical and developmental outcomes. In this Special Issue, Dharmaraj et al. provide a guideline for the evaluation and management of pediatric feeding disorders, with overviews of associated medical conditions, diagnostic criteria, and initial evaluation and assessment methods. They provide a multifactorial management approach with the aim to increase oral intake, reduce tube feeding, improve eating behaviors, and reduce parental stress through interdisciplinary intervention.

With the high prevalence of FGID in the pediatric population, effective interventions that may help us to ameliorate symptoms are required. However, intervention studies have been hampered by small sample sizes and limited effect sizes. Pharmacological treatments such as anti-depressants, anti- or synbiotics, anti-spasmodics, and anti-emetics have shown limited benefits. There is also a lack of high quality nutritional intervention trials in children for diets such as the low

fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet, the fructose- or lactose-restricted diet (FRD/LRD), and the gluten-free diet. For this reason, and due to the risk of nutritional inadequacy or disorder eating behaviors, these have been stated as having no or limited place in daily clinical practice for FGID in children [22,23]. Showing greater promise are non-pharmacological interventions such as hypnotherapy, cognitive behavioral therapy (CBT), probiotics, and fiber supplements [24]. Specifically within the FGID of functional abdominal pain (FAP), pharmacological intervention studies have been hampered by small sample sizes and minimal effects [25]. Some patients, specifically those with irritable bowel syndrome (IBS) and FAP, may experience some benefit from low FODMAP or FRD/LRD [22]. However, CBT has shown more promise in reducing symptoms and improving HRQoL, among other outcomes [26,27]. Group education among adults with IBS has also been shown to be effective at reducing symptoms and increasing HRQoL, but this has not been trialed in children [28]. To address this gap in knowledge, in this Special Issue, Löfgren et al. reported on a feasibility study of group education for children and adolescents with FAP. Twenty-three parent/child dyads participated in the intervention that consisted of two lecture sessions delivered by a pediatric gastroenterologist, a psychologist, and a dietitian. This group education was shown to be feasible and acceptable to participants and was effective at increasing knowledge and HRQoL, and reducing symptoms and food avoidance behavior.

A diagnosis of FGID requires an appropriate medical evaluation to ensure that symptoms cannot be attributed to another medical condition [12]. With a number of cross-over symptoms between FGID and organic GI conditions, and the co-existence of FGID and some medical conditions such as inflammatory bowel disease [29], alarm symptoms that may be indicative of organic conditions warrant particular attention. While the latest Rome IV criteria advocate for selective or no testing to support a positive diagnosis of an FGID [12], children and adolescents presenting with alarm symptoms of organic conditions may undergo invasive

clinical investigations as part of the elimination process. In particular, for children with FAPDs, the most common of which are IBS and functional dyspepsia (FD), investigations such as upper endoscopy may be utilized to exclude Helicobacter pylori infection, and to assess for inflammation, although the presence of inflammation or eosinophilia does not rule out FD [10,11]. One alarm symptom that has been historically used to predict diagnostic yield on endoscopy for children with symptoms indicative of FD is nocturnal pain. However, the evidence in support of this being an indication to support performing an upper endoscopy is limited [23]. The symptom of nocturnal pain was further investigated by Cindrich et al. in this Special Issue, with the finding that this particular alarm symptom was not associated with esophageal, gastric, or duodenal histologic inflammation. Nocturnal pain was, however, associated with increased social stress, depression, disordered sleep, excessive daytime sleepiness, and night sweats. The study conclusion was that nocturnal pain is not useful to predict upper gastrointestinal inflammation but that this symptom should be used to facilitate the further exploration of psychosocial well-being and sleep disturbances.

While work continues in the realm of identifying and managing pediatric FGID, a focus has also been drawn on identifying causes and risk factors to try and identify those more likely to develop FGID in order to develop preventative strategies [7]. One area of particular interest is the gut microbiota, with disruption of the microbial equilibrium (known as dysbiosis) known to play a role in the development of FGID [24]. The gut microbiota in children with FGID has been reported to differ from healthy controls [5] and modulation of the microbiota using pre- and pro-biotics may lead to improved HRQoL for those with FGID [3]. While dysbiosis in children may be caused by a number of factors, such as gastrointestinal infections, organic disease, and treatment with antibiotics [16,17], dysbiosis may also occur in neonates due to factors such as maternal diet during pregnancy, delivery mode, prematurity, breast feeding, and antibiotic exposure [10]. Although the uterine/placental microbiome does not seem to be associated with the neonatal

microbiome, in this Special Issue, Smith et al. have provided a thorough review of the inheritance of the maternal microbiome and the opportunities for early identification and intervention to prevent future childhood FGIDs. In this paper, the importance of the initial 'handshaking' between the maternal and neonatal microbiome is explained as being vital to the proper development of the brain–gut axis and causes of disruption in this process have been outlined. While the optimal microbiome components for neonates at birth are yet to be elucidated, this paper proposes that, once identified, a 'birth probiotic' could be developed and could provide neonates with the essential microbes that may be preventative of later FGID.

The work presented in this Special Issue has contributed to the ever-growing body of literature on pediatric FGID from many facets. The ongoing collection of epidemiological data will allow the global burden of FGID to be assessed and updated, thus allowing for increased awareness to facilitate research on both effective management and preventative strategies. Outlining management strategies for FGID among infants and for those with feeding disorders may help to ameliorate symptoms and reduce the associated negative child and parental health and psychosocial outcomes. Further research to identifying effective interventions and reduce invasive investigations should be prioritized to reduce healthcare utilization. Preventative strategies such as identifying the essential neonatal microbes for future health will be essential in reducing the global burden of pediatric FGID. A large proportion of children with FGID are known to have symptoms that persist into adulthood, in particular FAP and early-life risk factor identification and prevention must be prioritized.

Functional disorders of the digestive tract are very common in pediatric practice, but they are difficult to diagnose. A crucial step in establishing an accurate diagnosis and selecting the most appropriate treatment strategy is differentiating somatic complaints from genuine organic symptoms. A hallmark of functional gastrointestinal tract (GIT) pathology is the absence of a morphological substrate;

that is, pathological changes occur outside the affected organ and are linked to dysregulation of nervous or humoral functions. Investigating the prevalence of functional gastrointestinal disorders in early childhood, particularly among children under three years of age, presents significant challenges.

In infants during their first year, functional digestive disorders are closely associated with nutritional patterns. The unique structural and functional characteristics of the infant's digestive system play a pivotal role in these disorders. During the initial months of life, the gastrointestinal tract is predominantly adapted to absorb breast milk (lactotrophic nutrition), making it essential to monitor feeding rhythm, frequency, volume, and composition, all of which directly depend on maternal nutrition.

Researching the prevalence of digestive dysfunctions and their relationship with nutritional and other risk factors remains a priority in pediatric gastroenterology, especially in regions such as Siberia, where data on functional digestive disorders (FD) and associated risk factors are scarce. According to the World Health Organization, elevated body weight in breastfed infants "may not be a cause for concern, as it is unlikely to persist into adulthood." However, overweight and obesity in children older than three to five years represent significant health concerns.

Regurgitation is defined as the abrupt expulsion of a small quantity of gastric contents into the pharynx and oral cavity, occurring without noticeable effort following feeding. Pathophysiologically, regurgitation is considered a manifestation of the gag reflex and is closely related to age-dependent cardiac sphincter insufficiency, gastroesophageal reflux, and improper feeding techniques.

The absence of statistically significant differences in regurgitation incidence among children fed with different methods may be attributed to common causative factors such as excessive feeding volume, inappropriate feeding practices that do not consider individual infant needs, and aerophagia, the swallowing of air during feeding.

According to the literature, functional delay in defecation is one of the most common problems in children in the first months of life, especially those who are bottle-fed.

Nutritional factors contribute indirectly to the development of functional dyspepsia (FD) in the gastrointestinal tract, primarily by triggering visceral hypersensitivity to dietary stimuli. The digestive process stimulates the release of various gastrointestinal hormones, such as cholecystokinin and peptide YY, which may act as triggers for dyspeptic symptoms in individuals with heightened nutrient sensitivity.

Currently, the biopsychosocial model is considered the most comprehensive explanation for FD pathogenesis. According to this model, symptoms arise from the interplay of several physiological factors, including impaired gastrointestinal motility, visceral hypersensitivity, alterations in mucosal immunity and inflammatory responses, changes in gut microbiota, and modulation of the enteric nervous system (ENS) influenced by psychological and sociocultural conditions.

A subtype of FD linked to infectious causes has been identified and termed "post-infectious functional dyspepsia" (PI-FD). Research tracking patients who experienced acute Salmonella gastroenteritis revealed that approximately one in seven developed PI-FD within a year. Similarly, infection with Giardia intestinalis has been associated with an increased risk of PI-FD onset.

Although the precise mechanisms underlying PI-FD remain unclear, gastric mucosal biopsies from affected individuals demonstrate activation of immune cells, including T-lymphocytes and CD8+ cells, alongside neuroendocrine alterations characterized by elevated release of tryptase and histamine. These changes are believed to contribute indirectly to delayed gastric emptying.

In infants, prolonged gastroesophageal reflux may lead to secondary complications such as bacterial overgrowth and fermentative disturbances, which can provoke inflammatory responses in the intestinal mucosa. In 87% of children

with a long-term and persistent course of gastrointestinal reflux, as well as taking into account individual characteristics, a gradual pathogenetic correction of these conditions, organic pathology of the digestive system is formed. Therefore, the need for prediction, timely diagnosis and prevention of risk factors of the gastrointestinal tract, as well as gradual pathogenetic correction of these conditions, taking into account the individual characteristics of the child, is undeniable [24].

1.2. Risk factors for the development of functional gastrointestinal diseases in children

Gastrointestinal RFs play an important role in the overall structure of the pathology of the digestive system. According to many researchers, these are functional disorders that account for up to 90% of all forms of gastrointestinal pathology at an early age. Analyzing the publications of recent years, it can be noted that this problem is increasingly attracting the attention of researchers [16].

According to the definition given in the Rome criteria, FD of the gastrointestinal tract includes cases in which it is impossible to identify morphological, genetic, metabolic, biochemical and structural changes that explain the observed clinical symptoms [18]. In pediatric practice, the diagnosis of FD of the gastrointestinal tract as a nosological entity is still carried out with certain difficulties. This is due to the lack of a unified approach to their interpretation and diagnosis. Therefore, the prevalence of FD of the gastrointestinal tract in children has not yet been determined and requires further study [13].

According to a number of authors, FD accounts for 30-90% of all pathologies of the gastrointestinal tract in children of the first year of life [14, 22]. The first half of life deserves special attention as the initial and most important period for determining the health of the future child. The mechanisms of development of RF remain a subject of debate. The main reasons for the appearance of FD at an early age may be morphological and functional immaturity of the gastrointestinal tract,

imperfect central and vegetative regulation, late onset of enzymatic activity, and peculiarities of the formation of intestinal microflora [17, 19]. Due to the subjectivity of assessment and increased anxiety of parents, as well as attempts at self-treatment, the child's symptoms are often misinterpreted.

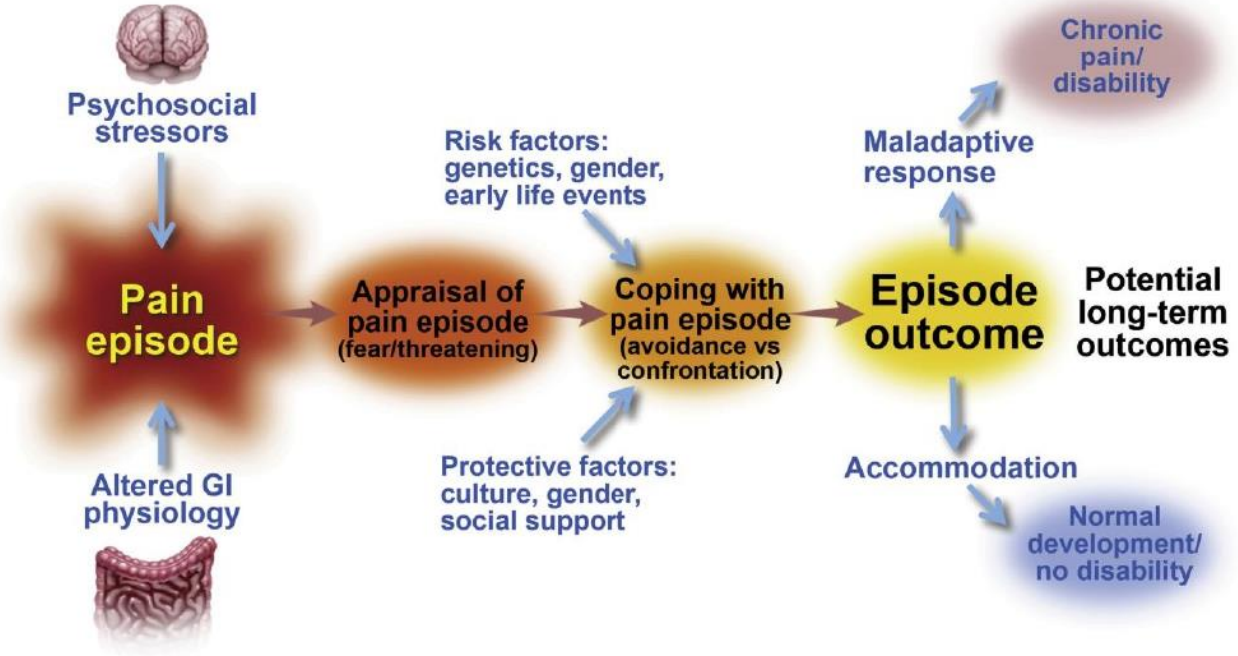
According to the modern classification proposed by the Rome III criteria, the following variants of FD of the gastrointestinal tract in children in the first six months of life are distinguished: infantile regurgitation, infantile colic, functional constipation [10]. Not only the diagnosis, but also the correction of risk factors of the gastrointestinal tract remain imperfect: this is due to incorrect diagnosis and a misunderstanding of the nature of risk factors and the mechanisms of their development, which leads to simplified symptomatic treatment [25] and is usually expressed only in a temporary improvement in the patient's condition, or it turns out to be completely ineffective and sometimes requires long-term and not always justified prescription of various medications [23].

Functional bowel disorders (FDGIT) occupy a leading position in the group of pathologies of the digestive system in children; they account for 30% of hospitalizations with complaints of digestive disorders. A significant part of gastrointestinal diseases in children is associated not with organic lesions of the digestive organs, but with a violation of one or another of their functions (picture-4). In 90-95% of children, recurrent (recurrent) abdominal pain is of a functional nature, and only in 5-10% is it associated with organic pathology [3].

In recent years, chronic constipation has become one of the urgent problems not only in adults, but also in pediatric gastroenterology. According to some data, the prevalence of constipation in pediatrics is 1-30%, which accounts for 3-5% of all outpatient visits, and in the composition of visits to a pediatric gastroenterologist - from 25 to 40% [17]. According to American scientists, constipation affects from 5 to 20% of children in the general population. Constipation as a main complaint occurs in 3-5% of outpatients in pediatric practice, and in 25% in

gastroenterological practice. At the same time, 35% of girls and 55% of boys with constipation have encopresis [20].

FNK may be accompanied by functional diarrhea associated with impaired intestinal motility. Functional diarrhea is a persistent or periodic disorder of intestinal function, manifested by an increase in bowel movements ≥3 times a day with the passage of liquid or pasty stools. There is no abdominal pain. There may be frequent urgency in the stool, noise, flatulence, and a feeling of incomplete bowel movement; However, if the diet is adequate in calories, there is no growth retardation in children. There are no reliable statistics on the prevalence of functional diarrhea in childhood [6-7].



Pic.4 *The appraisal of any pain episode experienced by a child may have significant impact on the child's ability to cope effectively and accommodate to the pain, and consequently his or her normal function and development. In the presence of risk factors or when protective factors are less effective, the child may develop a maladaptive response leading to a state of chronic pain.*

Approximately one-third of patients have gastric distention (postprandial fundal relaxation). Patients with FNK often have gastric and duodenal distension, as well as hypersensitivity to hydrochloric acid and lipids. The Rome IV criteria also include a number of new pathophysiological factors not present in the previous

criteria: past infections, low-grade inflammation of the duodenal mucosa, increased duodenal permeability, and increased eosinophils in the indicated area (duodenal eosinophilia).

FNC in children may be associated with the characteristics of pregnancy, childbirth and the postpartum period [16]. FNC is often diagnosed in children whose mothers grew up in families with high levels of anxiety during pregnancy, malnutrition and an unfavorable emotional climate [14]. The risk group also includes children of mothers who were overweight or underweight at the time of conception. Smoking of the parents during pregnancy and after childbirth also increases the risk of developing functional anomalies in the child. A separate risk group is children of mothers who were born by cesarean section. Antibacterial therapy taken by a woman in the perinatal period can change or disrupt the process of intestinal biocenosis [9].

Premature and premature infants weighing less than 2500 g are at increased risk of developing FNK, since they produce intestinal hormones more slowly, the duration of the central nervous system's response to pain impulses increases, and the motility of the stomach and duodenum is not coordinated. [6]. The causes of the development of functional disorders of the digestive tract are anatomical and physiological features, the child's growth, nervous regulation and gradual maturation of the motor function of the digestive tract and sphincters, its morphofunctional maturity, in combination with motor-evacuation disorders and damage to the nervous system (usually of a hypoxic nature), in most cases are the cause of abdominal distension and dyspeptic disorders [17].

Infant regurgitation. Involuntary movement of gastric contents into the mouth, nose, or esophagus is common in infants between three weeks and 12 months of age. It should occur at least twice per day for at least three weeks without any retching, failure to thrive, apnea, feeding difficulty, or posturing. The estimated prevalence is 41–67%.

Infant rumination syndrome. This condition is rare compared to regurgitation. It involves effortless regurgitation of food, which is chewed and re-swallowed, accompanied by repetitive contractions of abdominal muscles, lasting for at least two months. Its estimated prevalence is 1.9%. The onset is between three to eight months of age, without any distress, and usually does not occur during sleep. It has been considered a self-stimulatory mechanism in a child with maternal emotional and sensory deprivation or neglect.

Cyclic vomiting syndrome. This condition involves stereotypical and repetitive episodes of vomiting lasting hours to days, with episodes separated by weeks to months of return to baseline. For diagnosis, it must occur at least twice within six months. The estimated prevalence is 3.4%. Although it has a wide range of onset ages, an onset before two years of age might warrant metabolic, neurological, or anatomical testing for more serious conditions.

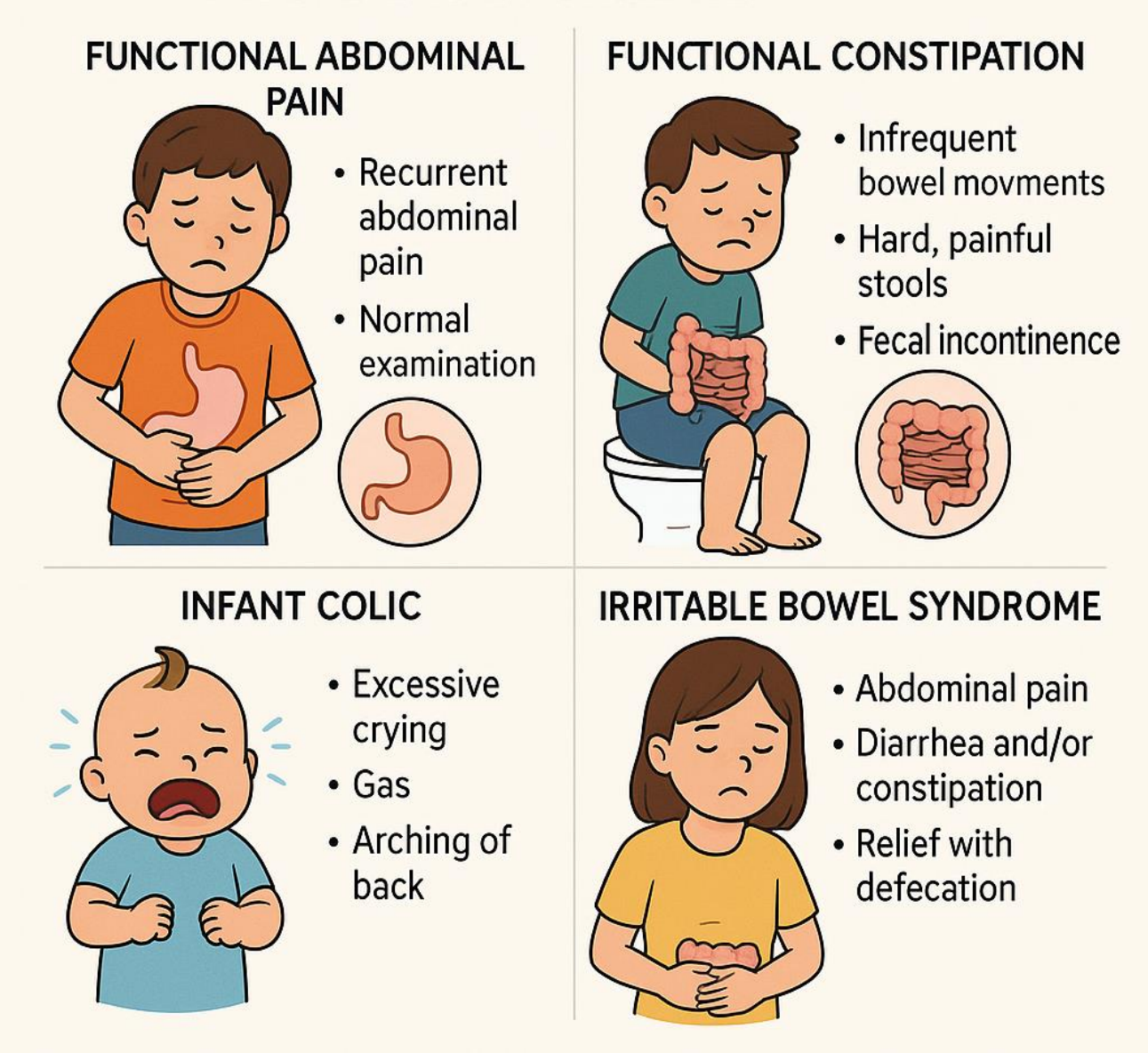
Infant colic. This condition has an onset before five months of age and is characterized by recurrent and prolonged irritability, fussing, and crying without any obvious cause and no evidence of failure to thrive. These episodes should last for at least 3 h a day, three days a week, or in a 24-hour behavior diary record of 3 h of crying with fussing. About 5–19% of infants are thought to have infant colic.

Functional diarrhea. Painless and recurrent passage of four or more well-formed stools, lasting for a minimum of four weeks without any failure to thrive in a child aged six months to 60 months, constitutes functional diarrhea. About 6–7% of infants have functional diarrhea.

Infant dyschezia. This condition has an onset before nine months of age, without any other red flag signs, and involves at least 10 m of crying and straining before the passage of soft stools. The estimated prevalence is about 2.4%.

Functional constipation. A child who is afraid of the unpleasant evacuation of the rectum voluntarily withholds feces, leading to overabsorption of water and hard stools that further cause painful defecation. This condition is called functional constipation. For children up to four years of age, it should include at least two of

the following features: history of stool retention, hard painful bowel movements, larger diameter stools, fecal mass in the rectum, with two or fewer defecations per week. For a toilet-trained child, it can involve at least one episode of incontinence or large stools clogging the toilet. About 3–27% of children are found to have functional constipation (Picture – 5).



Pic.5 *Functional gastrointestinal disorders' common types include: pain, constipation, colic, irritable bowel syndrome*

Child/Adolescent FGID

Cyclical vomiting. Diagnosing cyclical vomiting in older children is similar to that in younger children, with an emphasis on ruling out other medical conditions. The estimated prevalence is 0.2–1.0%.

Rumination syndrome. One significant change for older children is that it can occur secretly without the parents' knowledge. It does not occur during sleep and involves no retching, but begins as soon as food is taken. Eating disorders and other medical conditions need to be ruled out.

Functional nausea and vomiting. Pediatric data is rare. It is characterized by bothersome nausea at least twice a week or one episode of non-self-induced vomiting per week, not explainable by any other medical condition.

Aerophagia. Excessive air swallowing leading to belching, flatus, and abdominal distension lasting for at least two months and not explainable by another medical condition constitutes a diagnosis of aerophagia. It occurs in about 4.2–7.5% of children.

Functional dyspepsia. Postprandial fullness, early satiety, or epigastric pain, all not explainable by other medical conditions, must be present for at least four days a month for two months. This can be further subclassified as postprandial distress syndrome or epigastric pain syndrome based on predominant symptoms. The estimated prevalence is about 1.4% in children and ranges from 5 to 10% in adolescents.

IBS. IBS is classified as IBS with diarrhea, IBS with constipation, or IBS unspecified. Symptoms must include abdominal pain related to defecation, a change in stool frequency, or stool consistency, lasting for at least four days a month for a minimum of two months, and not explained by other medical conditions. About 1.2–5.4% of children are thought to have IBS.1 The presence of red flag signs like blood in stools or failure to thrive should prompt a thorough search for organic causes like celiac disease and inflammatory bowel disease.

Abdominal migraine. It is characterized by paroxysmal episodes of severe and diffuse abdominal pain that last for a minimum of 1 hour, interfering with normal daily activities, and presenting a stereotypical pattern with at least two of the following six features: anorexia, nausea, vomiting, headache, photophobia, and pallor. there must be a minimum of two episodes separated by weeks or months within a 6-month period and possible medical conditions must be ruled out. The estimated prevalence is up to 23%. Cyclical vomiting, abdominal migraine, and migraine headache are all episodic, stereotypical conditions with symptom-free periods in between, often triggered by stress, fatigue, or travel, and likely share a common pathophysiology. These abdominal conditions can develop into migraine headaches in adulthood.

Functional abdominal pain not otherwise specified. This group includes conditions that involve abdominal pain for four days a month for at least two months without the classic features of IBS, dyspepsia, or abdominal migraine, and not explained by other medical conditions. An estimated 1.2–4% of children have this disorder.

Functional constipation. As discussed in the toilet-trained children category above, the only change for older children is that constipation should last for at least one month, should not fulfill IBS criteria, and should not be explained by other medical conditions. The estimated prevalence is about 14%. In the absence of any red flag signs, routine testing for celiac disease, hypothyroidism, cow milk allergy, or radiography is not recommended. An X-ray can be considered if fecal impaction is suspected.

Non retentive fecal incontinence. A child older than four years should have at least a one-month history of defecation in inappropriate places with no evidence of fecal retention or other medical conditions. Around 0.8–4.1% of the children may have this disorder. It has been postulated to occur as a result of emotional disturbance and even sexual abuse in childhood

Children with FNC often have helminthiasis, proteosis, and allergic diseases [21]. Post-infectious FNCs occur in 10-20% of patients with acute intestinal infections. Genetic factors and the specific characteristics of the infectious agent predispose to their development. It is known that the central nervous system regulates the activity of all organs and systems, including the digestive system. If the child's nervous system is overloaded, this affects the functioning of the digestive system. When these factors are eliminated, the child's condition completely normalizes without any consequences, including long-term ones. If the necessary measures are not taken to eliminate these functional disorders, they can develop into organic pathologies [22].

Nevertheless, among the most possible causes and mechanisms contributing to the development of FGID, a number of the following factors are considered [5, 24, 27]:

1) gastric and intestinal motility disorders;

2) psychosomatic disorders;

3) Helicobacter pylori infection;

4) visceral hyperalgesia;

5) neurohumoral regulation disorders;

6) imbalance of mediators and intestinal hormones.

For several decades, primary intestinal motility disorder was considered as the pathophysiological basis of FGID, and clinical symptoms (pain, discomfort, flatulence, constipation, diarrhea) – as a consequence of gastric and intestinal dyskinesia. However, it was not possible to identify movement disorders that are characteristic only of functional disorders - the observed movement changes were recorded in a wide range of organic diseases and even in healthy people, and they also correlated poorly with clinical symptoms. The current stage of studying the problem of FDGIT, according to foreign authors, is characterized by a shift in focus

from the primary disorder of the motor activity of the digestive tract to the phenomenon of visceral hypersensitivity associated with the enteric nervous system. In patients with FDGIT, two types of impaired visceral sensitivity have been identified: a decrease in the threshold of pain perception or a more intense sensation of pain with a normal threshold of perception. Using the IBS model as an example, it was shown that hypersensitivity to visceral stimulation can be caused by pathology of the receptors of the mucous membrane, internal receptors of the intestinal wall, spinal afferentation, impaired signal processing in the central nervous system (CNS), or mood changes. In this case, the condition for the formation of visceral hypersensitivity is, possibly, the impact of so-called sensitizing factors, among which are gastrointestinal infection (helicobacter pylori, previous dysentery and salmonellosis), psychosocial stress and physical trauma. According to the results of our studies, when studying the H. pylori status of the oral cavity using a rapid urease test, helicobacter infection was detected in 76.74% of patients with FD, although PCR diagnostics demonstrated a significantly lower frequency of its persistence - 42.42%. At the same time, helicobacter pylori was most often associated with the ulcer-like variant of FD. After the phenomenon of visceral hypersensitivity was identified, the debate about its clinical significance has not ceased. Some experts consider it an absolute pathophysiological marker of FGID [26], while others claim that it is absent in patients with a typical clinical picture of FGID.

The following facts support the involvement of the central nervous system:

1) centrally acting drugs (antidepressants) and psychotherapeutic methods (psychotherapy, hypnosis) are quite effective in the treatment of gastrointestinal disorders;

2) symptoms of gastrointestinal disorders are absent during sleep, when central nervous system activity is minimal;

3) patients suffering from gastrointestinal disorders often have other functional and psychosomatic disorders, in the development of which the central nervous system is involved [8].

Serotonergic mechanisms have recently been studied to explain the causes of visceral hypersensitivity and impaired motility. The theory of relative independence of the enterochromaffin cells of the gastrointestinal mucosa, containing serotonin, is currently relevant. Its release from cells is stimulated by an increase in pressure in the lumen of the stomach or intestine or by a change in the chemical composition of the contents of the organ. It has been established that in individuals with symptoms of IBS, for example, the number of enterochromaffin cells exceeds the normal value, but the question of a direct relationship between the number of these cells and the amount of secreted serotonin remains open [12]. The released serotonin interacts with the internal and external primary afferent neurons located in the submucosal layer by paracrine secretion. Receptors activated in the internal primary afferent neurons belong to the subtype 1P and, possibly, to 4P, and in the external ones - to 3P. Activation of the first receptor subtype leads to the initiation of peristalsis and secretion, and the third to an increase in anxiety, unstable mood, and increased aggression. Interaction with different types of serotonin receptors helps explain why, for example, 5HP3 receptor antagonists do not block peristalsis and why the 5HP4 receptor agonist tegaserod enhances motility. Thus, a violation of serotonin synthesis or reuptake may also be responsible for the occurrence of disease symptoms.

Certain significance in the occurrence of gastrointestinal tract diseases is attributed to infection, in particular acute intestinal infection [13, 24]. Spanish scientists conducted a prospective cohort study among patients who had acute gastroenterocolitis caused by Salmonella enteritidis, in order to assess the incidence of FD and IBS within 1 year after infection [25]. It was found that previous salmonella gastroenteritis is a significant risk factor for the development of not only IBS, but also FD. Within a year after acute gastroenteritis, FD and IBS developed in

every seventh and every tenth patient, respectively. An opinion has been expressed about the possible involvement of Helicobacter pylori persistence in the body in the pathogenesis of IBS [11].

1.3. Gut-related immune system

The gastrointestinal tract (GI) is not only an organ of digestion, but also an important part of the immune system. The specificity of its functioning is associated with the presence of a large number of environmental antigens (food components, bacteria, viruses, parasites), a large area of contact with them (about 200 m2 for children), and the need to develop protective reactions against pathogenic microorganisms and many inorganic substances [5].

The intestine is the largest immune organ in humans. Approximately 25% of its mucosa consists of immunologically active tissue, where about 80% of immunocompetent cells are localized [1, 9].

The immune system of the stomach and intestines includes cellular elements: lymphoid cells (B and T lymphocytes), intraepithelial and lamina propria; plasma cells; myeloid cells (macrophages, neutrophils, eosinophils, mast cells); enterocytes; special epithelial cells associated with follicles (M cells).

Structural elements: Peyer's patch, solitary lymphofolliculocytes, appendix, mesenteric lymph nodes [1, 20].

Lymphocytes play a key role in the following immune-based processes: antigen recognition, clearance, and antigen-contact memory. The innate defense system of the gastrointestinal tract, in addition to the immune system, the intestinal epithelium, and the mucosal barrier, is also represented by the intestinal microflora, which provides a strong barrier effect [24].

The main intestinal immunoglobulin is IgA, which is produced locally by plasma cells located in the lamina propria of the intestine. When deciding on the onset of functional disorders, the doctor must take into account the anatomical and

physiological features of the esophagus (large size of the angle of Hiss; the location of the cardiac sphincter under or at the level of the diaphragm; the diaphragmatic ligaments do not completely cover the esophagus; the muscular layer of the esophagus is weak, usually not completely covered; its innervation is not fully provided due to the immaturity of the intramural nerve ganglia), as well as the small size of the stomach, its spherical shape and delayed peristalsis of the movement are the causes of functional weakness of the cardia in infancy. Secretory IgA binds antigens of viruses and bacteria (neutralizing viruses, agglutinating bacteria), blocks the adhesion of viruses and bacteria to mucous membranes, stimulates the antibacterial activity of phagocytes and lymphocytes against pathogenic bacteria, and binds food antigens and allergens that cause allergies [4].

Microbes, including micromycetes and viruses: • can adhere to epithelial cells, penetrate them, and leave epithelial cells from the basal side; • destroy intercellular cytoplasmic bridges and penetrate between intestinal epithelial cells into the body; • their water-soluble antigens can be pinocytosed by epithelial cells and transepithelially penetrate into the lamina propria; • water-soluble and corpuscular antigens are captured by M-cells of the mucous membranes, transferred by the cell to the basal side and secreted subepithelially into the M-pocket; M-cells located in the epithelial layer above the follicles of Peyer's patches cover ~ 10% of the surface of the epithelium associated with the follicles; • are fixed by interepithelial and subepithelial dendritic cell (DH) processes localized between epithelial cells in the intestinal lumen; Through such processes, microbes and other antigens are attracted to the DH body, where the antigens are processed and then presented to lymphocytes and TK cells. Infected enterocytes may die by apoptosis, and apoptotic cells and apoptotic bodies are captured by dendritic cells along with the infection and transported to the sites of immune response or effector sites [44].

In newborns, transepithelial transfer of antigens from the intestinal microflora is carried out using IgG receptors of epithelial cells; on the basal side of the enterocyte, Fcy Rneon is loaded with IgG molecules, and such a complex is

transported through the cell and embedded in the cell membrane on the apical side of the enterocyte; IgG complexes can interact with antigens, and the resulting immune complex is retained by Fcy Rneon - a receptor that is transported in the opposite direction through the epithelial cell and expressed by the cell in the lamina propria, which activates dendritic cells. Immunobiological activity of epithelial cells - intestinal mucosa • Barrier, transport, excretory functions (water, inorganic salts and food components); • Production of mucus and its antimicrobial components (lactoferrin , lysozyme, peroxidases, etc.); • Digestion of internalized substances by epithelial cells; • Trans-epithelial transport of macromolecules from the intestinal lumen to the lamina propria; • Transepithelial transfer of IgA into the intestinal lumen; participation in the formation of sIgA and their secretion from the intestinal wall; • IgA - mediates the transfer of antigens from the lamina propria of the intestinal wall; • Presentation of antigens to resident and recruited lymphocytes and dendritic cells of the mucosa using HLA class 1 and class 2 proteins expressed on the basolateral cell surfaces; • On the basal - lateral surfaces of enterocytes are Toll-like Bacterial flagellin receptors (TLR-5 receptors) and intracellular TLR-4 receptors for lipopolysaccharides and other microbial products; TLR-2 - for yeast zymosan; cryptococcal xyloglucromannan (XGM) interacts with TLR-4 and CD-14; XGM is internalized in neutrophils and macrophages (more in the latter); Activation of enterocytes through these receptors stimulates the production of chemokines (IL-8, CCL20), cytokines (IL-6), and adhesion molecules, and promotes mucosal infiltration by neutrophils, dendritic cells, and monocytes [59, 66].

Regulation of the local antigen-specific immune response by epithelial cells of the intestinal mucosa: a) presentation of the antigen to lymphocytes in conjunction with HLA class 1 and 2 proteins; b) presentation of the antigen to resident dendritic cells (maintenance of tolerance) or obtained from the blood and activated dendritic cells (induction of the immune response); c) TSLP products (Thymic Stromal Lymphopoietin), capable of dose-dependently regulating the production of IL-12 by dendritic cells (IL-12 synthesis occurs with an increase or

decrease in the content of TSLP); under normal conditions, the level of constitutively synthesized TSLP provides inhibition of IL-12 synthesis by resident dendritic cells; d) maintenance of epithelial cells (they are a source of TGF-β) in the mucous membranes, suppressing IgA production and lymphocyte activation (maintenance of immunological tolerance); e) formation of IL-7 and SCF (St Cell Factor), which are activation signals for immature γ / δ T cells.

Regulation of the local antigen-specific humoral immune response by epithelial cells of the intestinal mucosa is achieved by: a) production of CCL28, a ligand for the CCR10 receptor on sIgA-secreting cells (which ensures the distribution of IgA cells along the mucosa); b) local production of CCL25, a ligand for CCR9, also expressed by IgA-secreting cells [14].

The chronic course of functional disorders, numerous extraorgan manifestations of the disease allowed us to put forward a hypothesis about the participation of immune mechanisms and non-specific defense factors in the development of FGID, primarily cytokines. Since it is cytokines at the body level that establish a connection between the immune, nervous, endocrine, hematopoietic and other systems and serve to involve them in the organization and regulation of defense reactions [7], it is of particular interest to study the cytokine status in the formation of various models of FGID. It is no secret that most cytokines are not synthesized by cells outside of the inflammatory reaction and immune response. Expression of cytokine genes begins in response to the penetration of pathogens into the body, antigenic irritation or tissue damage. That is why the involvement of the immune system in the pathogenesis of FGID has not been discussed for a long time. Nevertheless, recent advances in immunology demonstrate that many organs, including the gastrointestinal mucosa, are normally in a state of "controlled" inflammation - the content of cellular subpopulations and, accordingly, the ratio of proinflammatory and anti-inflammatory, regulatory cytokines is balanced, which ensures an adequate immune response to antigenic irritation [12, 17]. It has been found that in a healthy person, only 0.2% of the lymphocytes of the lamina propria

of the intestinal mucosa and intraepithelial lymphocytes produce cytokines, while CD4+ lymphocytes of the peripheral blood practically do not synthesize them [8]. That is why the involvement of the immune system in the pathogenesis of gastrointestinal diseases has not been discussed for a long time. It is possible that peripheral hypersensitivity or hypermotility may be due to the induction of inflammatory cytokines. These assumptions are supported by the fact that about 1/3 of patients with IBS indicate the onset of symptoms after an acute intestinal infection; 1/3 of patients with acute intestinal infection subsequently develop IBS; 1/3 of patients with IBS demonstrate extraintestinal manifestations, which usually indicate the involvement of nerve structures located outside the intestinal wall in the process [6]. The results of a histological examination of a biopsy of the intestinal mucosa in such patients are also characterized by excessive cellular infiltration and increased expression of some cytokines, including IL-1, which also indicates the role of the inflammatory reaction in the development of FGID. However, these facts contradict the main postulate of their development - an exclusively functional origin. In addition, in individual studies [6] it was shown that the level of individual anti-inflammatory cytokines (IL-10 and IL-12) in patients with IBS was lower than in healthy people. These phenomena have not yet been scientifically substantiated, but it is assumed that their deficiency may indicate suppression of non-specific protection, which contributes to the chronicity of the process. In addition, it is unclear whether the identified changes occur primarily or secondarily. To understand these aspects of pathogenesis, studies performed at the preclinical stage of FGID, as well as in first-degree relatives, would be very important.

Immunobiological activity of dendritic cells (DCs) of the intestinal mucosa: • DCs are located mainly in the lamina propria of the mucosa and form a network of cells that interact with each other and with other cells of the mucosa; • Among the DCs of the mucosa, DCs of myeloid (mDCs) and lymphoid (plasmacytoid, pDCs) origin are identified; • The residence time of DCs in the intestinal mucosa is 2-4 days; • When interepithelial cytoplasmic bridges are damaged, DCs produce

proteins that form cytoplasmic bridges between DCs and enterocytes at the sites of rupture (damage repair); • DCs process antigens captured by them along the intestinal surface or delivered subepithelially by M cells and enterocytes; • Antigens processed by dendritic cells to activate NKT cells and lymphocytes of antigen-specific clonal epitopes are presented on the DC membrane in a complex with HLA class 1 and class 2 proteins or CD-1 proteins; • DHs are sources of costimulatory signals, through which they regulate the proliferation and differentiation of interacting immunocompetent cells.

Normally, DH of Peyer's patches stimulates the differentiation of activated "naïve" T cells, mainly into TH-2 lymphocytes; • In the areas of induction of the immune response in the mucous membranes, unactivated (unactivated) DH and plasma DH stimulate mainly T- reg lymphocytes and activate the synthesis of IL-10 and TGF-β, which in turn ensures the local production of IgA and the formation of immunological tolerance to antigenic agents; • Resident and blood-collected DH, activated during inflammation, stimulate the differentiation and accumulation of TH-1 and TH-2 lymphocytes and the "cellular" and "humoral" immune responses mediated by them.

Lactose and gluten-free diet. Lactose intolerance and non-celiac gluten sensitivity symptoms might mimic those of IBS. The role of lactose elimination in FGID is controversial. Several randomized controlled trials (RCTs) have not shown promising results with lactose-restricted diets.49,50 Pediatric studies are lacking in the prevalence of non-celiac gluten sensitivity. Although a recent RCT showed promising results in reducing abdominal pain symptoms, the overall evidence is still not concrete.

Fiber supplementation. Soluble dietary fibers that are viscous and moderately fermented improve IBS symptoms via laxative effect, increasing stool bulk and forming a gel-like covering. They also promote a beneficial gut microenvironment via short-chain fatty acids like butyrate and help regulate the gut-brain axis.53 Meta-analyses on predominantly adult populations have shown a

proven role of soluble dietary fibers in IBS.54 Pediatric RCTs have also shown a greater reduction in pain and IBS severity scores with the use of psyllium.

Probiotics. Probiotics, beneficial organisms that inhabit the gut, have a proven role in antibiotic-associated diarrhea, ulcerative colitis, and celiac. A systematic review in 2018 showed Lactobacillus rhamnosus GG reduces the intensity and frequency of IBS-related abdominal pain in children though evidence is unsatisfactory for functional constipation and functional abdominal pain disorder. An RCT on infants showed a 50% reduction in infant colic with L. reutreri.

Nutraceuticals. Peppermint oil has shown some efficacy in relieving abdominal pain symptoms, though quality studies are lacking. Fennel, a medicinal herb with potential antioxidant, antispasmodic, and anti-inflammatory properties, seemed to reduce crying episodes in infants with colic. A meta-analysis on the role of vitamin D in IBS showed poor quality evidence for improvement in IBS severity scores but not in quality of life.

In Peyer's patches and regional mesenteric lymph nodes, DHs, presenting antigens to "naïve" CD4+ and CD8+ T lymphocytes, induce the synthesis of surface molecules (α4β7 integrin and chemokine receptor CCR9) in them, through which circulating clones activate antigen-presenting cells. recognition and recruitment of lymphoid tissues associated with the mucosa (mucosal imprinting phenomenon); The counterpart partners of these molecules are, respectively, MadCAM-1 molecules of vascular endothelial cells of Peyer's patches and TESK molecules of enterocytes . T-lymphocytes of the intestinal mucosa • T-lymphocytes in the intestinal mucosa: • In Peyer's patches (inductive zone); • In the lamina propria and epithelial layer (effector zone); • In Peyer's patches, α/β CD4+ T lymphocytes and relatively many CD45Rα+ cells predominate; • In the lamina propria, α/β CD4+ T lymphocytes predominate, but also express CD45 phenotype, which also expresses CD-69; • Among intraepithelial lymphocytes (IEL), CD-8+ cells are abundant, and γ/δ T lymphocytes have a relatively high content compared to other areas of the mucosa. Features of the humoral antigen-specific immune response in the intestinal

mucosa • B-1 and B-2 lymphocytes participate in the response; B-1 cell progenitors are localized in the lamina propria of the mucosa and are activated and differentiate locally into plasma cells; B-1 cell differentiation is T-independent; Plasma cells from B-1 lymphocytes are short-lived cells specialized to secrete natural antibodies of the IgM, IgA and IgG3 classes; • B-2 lymphocyte progenitors are located in the follicles of Peyer's patches and require the cooperation of TH lymphocytes to differentiate into plasma cells; • Progeny of B-2 lymphocytes can migrate to lymph nodes and spleen; short- and long-term subpopulations are expressed among the antibody-producing progeny of B-2 lymphocytes [14].

Among the antibody-secreting cells of the intestinal mucosa, 80% of the cells synthesize IgA, as well as the γ-protein required for the polymerization of Ig molecules [13].

In adults, IgA is synthesized daily at a rate of 66 mg/kg body weight, and sIgA is secreted at ~30 mg/kg body weight (more than IgG is synthesized per day); • Specific IgA in the lamina propria of the intestine can interact with antigens that have entered it, and the resulting immune complexes are secreted by intestinal epithelial cells; • sIgA secreted into the intestinal lumen interacts with antigens there, preventing the penetration of antigens through the epithelial lining of the mucosa [15].

Normally, inactive resident DHs under the control of epithelial cells provide homeostasis and tolerance of immune Tunica cells. mucosa ; Accumulated DH precursors during inflammation are activated, differentiated and present antigen to lymphocytes, causing the development of an immune response mediated by TH-1 cells; IgA secreted by enterocytes is the most important humoral factor of immune protection of mucous membranes from microbes and molecules inhabiting the intestinal microflora, especially those with which the mucosal surfaces are constantly in contact; Dendritic cells of the mucous membranes interact with "naïve" T-lymphocytes in the inductive zones of the intestine, forming a "mucosal footprint" in the latter, which allows them to recognize and selectively recruit

subsequent “immune T-memory cells” lymphoid tissues of the mucous membrane of the digestive tract and respiratory tract (systemic response of the mucosal lymphoid tissues).

To date, there is no clearly formulated concept of possible immune status disorders in FGID. It is anticipated that a deeper insight into the role of cytokines in the pathogenesis of functional gastrointestinal disorders (FGIDs) will undoubtedly enhance their clinical relevance. While the importance of immune alterations in organic intestinal diseases remains clear, one of the most promising and crucial avenues of research lies in investigating cytokine production within FGIDs and clarifying how these molecules contribute to the development of such conditions.

Chapter II. CHARACTERISTICS OF CLINICAL MATERIALS AND RESEARCH METHODS

§ 2.1. Clinical characteristics of the examined children

Work was carried out at the clinical base of the Bukhara State Medical Institute - the regional children's multidisciplinary medical center.

To study the frequency of FD of the gastrointestinal tract in children, official medical statistics from the Bukhara regional health department for 2021-2024 were used**.**

To assess the impact of risk factors in the development of gastroesophageal reflux disease, medical records of 3,150 pediatric patients (2,142 boys and 1,008 girls) as well as 439 hospitalized children (233 boys and 206 girls) at the Children's Medical Center for Gastrointestinal Diseases were analyzed. Girls were retrospectively studied for gastrointestinal diseases from 2021 to 2023.

The findings of the retrospective analysis revealed that between 2021 and 2023, a total of 2,363,905 children under the age of 18 were registered in the Bukhara region, averaging 590,976 children per year. Among them, 3,150 children (0.87%) were admitted to hospitals due to gastrointestinal conditions. This corresponds to an average annual prevalence of 2.17 cases per 1,000 children. Within the same period, 439 children (0.07%) were hospitalized specifically for gastroesophageal reflux, yielding an average prevalence of 0.18 cases per 1,000 pediatric individuals in the region. (Table 2.1.1).

Table 2.1.1.

Prevalence of all gastrointestinal diseases and gastrointestinal risk factors in children

Study date (in years)	Total number of children under 18 years old (abs)	Number of gastrointestinal diseases in children (abs)	Incidence of gastrointestinal diseases per 1000 children	FD number of the gastrointestinal tract (abs)	Frequency of gastrointestinal FD in children per 1000 children

2021	571887	1082	2.24	127	0.22
2022	606160	1094	2.29	111	0.18
2023	625051	974	2.0	82	0.13
Total	2363905	3150	2.17	439	0.18

Among all patients hospitalized with gastrointestinal reflux, 183 patients had functional diarrhea, which is an average of 56.7% (Table 2.1.2).

Table 2.1.2.

Frequency of gastrointestinal FD and gastrointestinal allergies in children (m ± M)

Study date (in years)	FD number of the gastrointestinal tract (abs)	Number of GIA cases in children (abs)	IN %
20 21	127	50	39.4 ± 3.6
20 22	111	45	40.5 ±3.62
2023	82	40	48.8 ± 3.68
Total	439	183	41.7 ± 2.3

It was found that 156 (35.5%) of all risk factors for gastrointestinal diseases in children.

The distribution of sick children hospitalized with gastrointestinal infarction revealed a higher number of boys - 233 (53%) than girls - 206 (47%). Analysis by age showed that children aged 1 to 3 years were more often hospitalized - 221 (50.4%) (Table 2.1.3).

Table 2.1.3.

Age distribution of children with gastrointestinal infarction (m ± M)

No.	**Age distribution**	**Abs**	**%**
1	Up to 1 year	41	9.4
2	1-3 years	221	50.3

3	3-7 years	57	13.0
4	7-12 years	52	11.8
5	12-18 years old	68	15.5
	Total	439	100%

The identification of comorbid forms in children is of interest. Given the presence of contraindications to invasive diagnostic procedures during the period of exacerbation of the disease and limited possibilities, in order to identify possible causative factors of functional disorders, we limited ourselves to a complete collection of anamnesis and the identification of the relationship between the development of the disease and previous diseases.

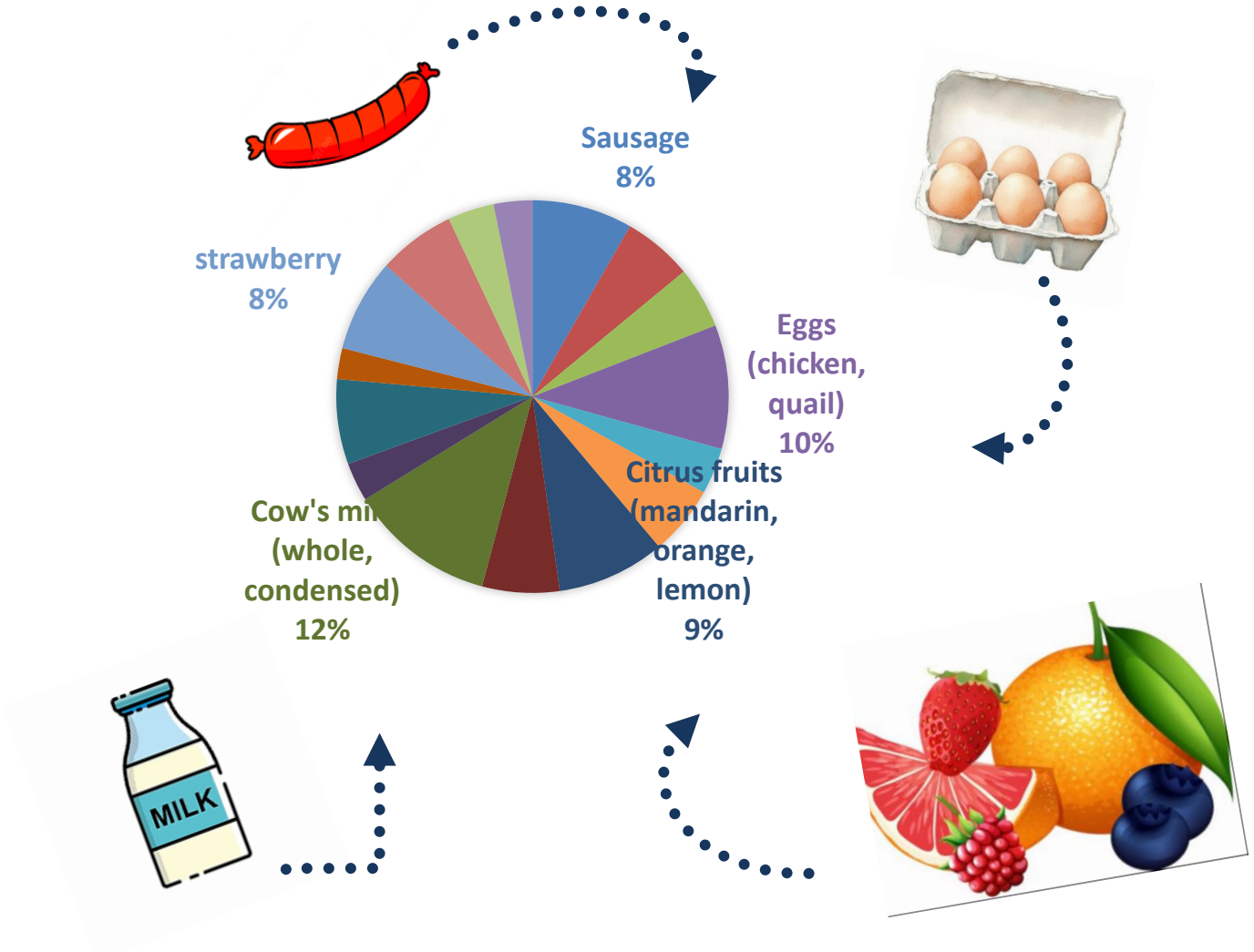
The study of the anamnesis allowed to identify the causes of gastrointestinal allergies in children with gastrointestinal reflux (Picture-6), (Table 2.1.4).

Table 2.1.4.

Causal factors in the formation of gastrointestinal allergies in children (m ± M)

No.	**Allergen**	**N**	**%**
1	Chocolate	9	5.8±1.3
2	Sausage	13	8.3±2.7
3	Mutton	8	5.1±1.3
4	Eggs (chicken, quail)	16	10.3±1.2
5	Watermelon melon	6	3.8±1.0
6	Peach	9	5.8±1.0
7	Citrus fruits (mandarin, orange, lemon)	14	9.0±1.0
8	Peanut	10	6.4±0.9
9	Cow's milk (whole, condensed)	19	12.2±0.8
10	Chicken meat	5	3.2±0.8

11	Fish	11	7.0±0.8
12	Carbonated drinks and juices	4	2.6±0.8
13	Strawberry	12	7.7±0.7
14	Honey	10	6.4±0.7
15	Eggplant	6	2.28±0.7
16	Tomatoes	5	3.8±0.5
	Total	156	100



Pic.6 *Causal factors in the formation of gastrointestinal allergies in children*

The identified provoking food products, for example, cow's milk - 12.2%, chicken and quail eggs - 10.3%, citrus fruits - 9.0%, allow us to characterize the regional characteristics of the causative structures of allergies in children aged 1 to 3

years. It should be noted that in the study there was a combined sensitization to several food products, and patients with polysensitization to food products amounted to 44 (28.0%). Autonomic or vagal neuropathy is most prominent in cases of post-surgical gastroparesis, and is generally irreversible in the setting of complete vagal nerve injury or vagotomy, as seen in fundoplication or lung transplant. In diabetic gastroparesis, autonomic neuropathy disrupts vagal nerve function, leading to impaired coordination between gastric contractions and pyloric relaxation. Hyperglycemia, a hallmark of diabetic gastroparesis, exacerbates motility dysfunction by impairing vagal activity and reducing antral contractions. An open-label pilot study on patients with idiopathic gastroparesis demonstrated that noninvasive vagal nerve stimulators can modulate gastroparesis symptoms and gastric emptying, further corroborating the contribution of vagal neuropathy to disease. Dysautonomia seen in POTS, Parkinson's disease, and some post-viral syndromes is also associated with gastroparesis. Post-viral gastroparesis conditions are thought to originate from direct damage to systemic neurons, and have poorer prognosis when associated with acute autonomic dysfunction such as cases of norovirus, EBV, and CMV.

The clinical form of FD manifestations of the gastrointestinal tract was diverse. Functional diarrhea prevailed in its structure (Table 2.1.5).

Table 2.1.5.

Clinical forms of the gastrointestinal tract in children (m ± M)

No.	**Clinical presentation of RF**	N	%
1	Functional diarrhea	249	56.7±2.3
2	Functional constipation	1 90	43.3±0.6
	Total	439	100

166 (60.6%) of all hospitalized patients had concomitant gastrointestinal disease (Table 2.1.6), which affected the course of the underlying disease. Clinically, functional gastrointestinal diseases are most often manifested in the form

of functional constipation - 43.3% and functional diarrhea - 56.7%, anemia (46.6%) and gastrointestinal allergies (35.5%).

Table 2.1.6.

Frequency of comorbidities in the gastrointestinal tract RF (m ± M)

No.	Nosology	Abs	%
1	Iron deficiency anemia	41	15.4±1.8
2	ARD / obstructive bronchitis	20	7.5±0.7
3	PPCNS	13	4.9±0.9
4	Gastrointestinal allergy	156	58.6±1.5
5	Helminthiasis	36	13.5±1.2
	Total	266	100%

Among all identified concomitant pathologies, anemia - 41 (15.4%), helminthiasis - 36 (13.5%) and gastrointestinal allergies - 156 (58.6%) (Figure 2.1.1).

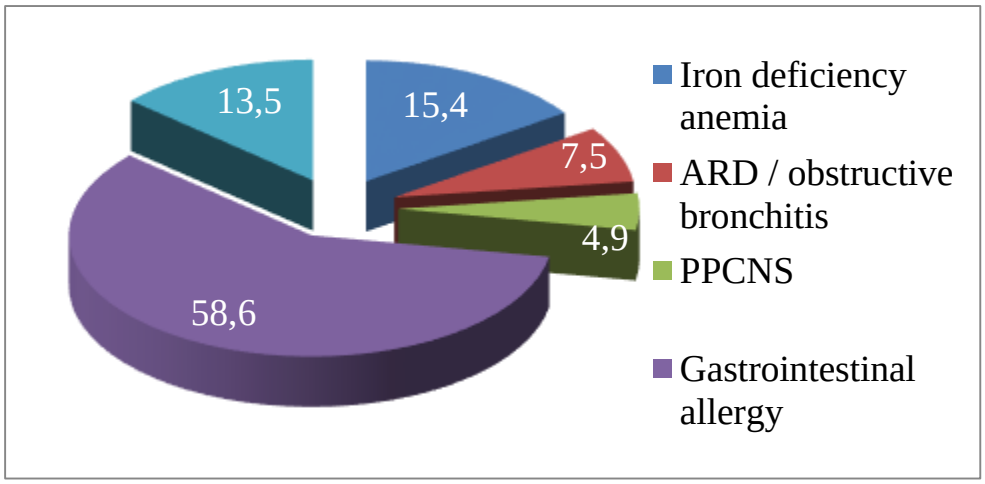


Figure 2.1.1. Pathology accompanying gastrointestinal reflux in children (%)

Consequently, the established data confirm the need for an individual approach to the diagnosis and management of this category of patients.

A prospective study was conducted at the Children's Medical Center in 2023. We selected a total of 63 pediatric patients with gastrointestinal reflux who were hospitalized at the BRMCMC. Of these, 38 (60.3%) were boys and 25 (39.7%) were girls aged 1 to 3 years. The control group consisted of 30 healthy peers, of whom 11 (6 girls, 5 boys) and 19 (7 girls and 12 boys) were children aged 1 to 3 years.

The study utilized a custom-designed questionnaire comprising five main sections: (1) demographic data; (2) the child’s health status at the time of the interview, as reported by the mother (assessed through 33 questions); (3) parental background information (10 questions across two subsections); (4) a targeted set of 27 questions addressed specifically to the mother; and (5) survey outcomes along with supplementary details. Inflammatory and immune-mediated mechanisms are increasingly recognized as contributing factors in gastroparesis. In idiopathic cases, inflammatory infiltration of the gastric muscularis propria has been observed, with associated loss of ICCs and neuronal elements. Immunohistochemical stains have suggested an increased number of macrophages and other phagocytic cells in the gastric body of patients with gastroparesis. In the muscular and myenteric plexus layers of the gastric antrum of patients with gastroparesis, anti-inflammatory CD206+ M2 macrophage cells were found to be significantly reduced, which also correlated with ICC counts. The gene HMOX1 encodes the heme oxygenase 1 (HO1) enzyme, expressed in CD206+ macrophages, whose loss leads to loss of ICC in animal models. The mechanisms underlying this loss may therefore have causal implications in the pathogenesis of disease. Deep transcriptome analysis of the gastric body and proteomic analysis of the gastric antrum revealed molecular changes in pathways involving macrophages, fibroblasts, and endothelial cells; some molecules related to inflammation, such as prostaglandins and complement pathway proteins, appeared to be related to gastric emptying delay. Neuroimmune processes targeting neural and interstitial cells are also implicated, particularly in post-infectious gastroparesis. Post-viral gastroparesis is caused by viral triggering of neuroimmune pathology and/or autoimmunity due to immune-mediated damage of

the enteric nervous system. Approximately 50–70% will have serologic evidence of neural autoantibodies, such as acetylcholine receptor (AChR) and glutamic acid decarboxylase 65 (GAD65). Some patients with autoimmune GI dysmotility will have overlapping autoimmune conditions including type I diabetes, Grave's disease, Celiac disease, and lupus, or, in rare cases, a paraneoplastic etiology. The diagnosis was established based on a thorough medical history, physical examination, and consultations with relevant specialists. The questionnaire was completed using information provided by the mother, as well as data obtained through clinical evaluation, laboratory tests, and objective examination. It also included details on primary and secondary diagnoses, pregnancy and childbirth history, breastfeeding practices, potential triggers or contributing factors for the onset or exacerbation of the condition, and the child's living environment, among other relevant factors.

FD is thought to be caused by a combination of motor and sensory disturbances, similar to gastroparesis. An increased number of duodenal eosinophils and mast cells seen on biopsies may suggest an immunoinflammatory mediated pathway in FD as well. The "leaky gut" theory proposes that the impaired intestinal mucosal barrier integrity seen in FD may be related to microbiome alterations. Increased intestinal permeability is associated with mucosal immune activation and FD symptoms; however, the role of the microbiome in this process is not yet fully understood. The shared neuropathology underlying gastroparesis and FD, including loss of ICC and CD206+ macrophages in full-thickness stomach biopsies, emphasizes the lack of distinction between them. Additionally, central and peripheral nervous system dysfunction contributes to both conditions. Central sensitization may enhance visceral hypersensitivity, amplifying pain and discomfort associated with gastric distension in both disorders. Abnormalities in brain–gut communication pathways, including altered neurotransmitter signaling, may further exacerbate symptoms. The symptoms and clinical course were also indistinguishable between groups with and without delayed gastric emptying on long-term follow-up, and gastric emptying was found to transition between normal

and delayed in the same patient over time without a corresponding change in symptoms. These commonalities underscore the shared neuropathology and symptomatology of the two disorders, which corroborates the notion of FD and gastroparesis or gastroparesis-like symptoms as part of a larger entity of GNDs without attention to gastric emptying status.

The diagnosis of the underlying condition was made in accordance with the 2016 Rome IV criteria, as referenced in the International Classification of Diseases (ICD-10). During the diagnostic process, potential triggering factors were carefully evaluated, including genetic predisposition, previous intestinal infections, allergic conditions, parental lifestyle habits, dietary patterns, psychosocial influences, environmental exposures, and the presence of comorbidities.

All participants underwent a comprehensive set of clinical, immunological, and instrumental assessments. These included abdominal ultrasonography, standard laboratory analyses, and biochemical evaluations. Blood tests assessed levels of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, and diastase. Urine tests comprised general urinalysis and urine diastase measurements.

Depending on the form of gastrointestinal FD, sick children are divided into 2 groups (Table 2.1.7), (Figure 2.1.2):

Group 1: 32 children with functional diarrhea;

Group 2: 31 pediatric patients with functional constipation.

Table 2.1.7.

Distribution of patients with gastrointestinal FD by gender

Gender	number	%
Boys	38	60.3
Girls	25	39.7
Total:	63	100

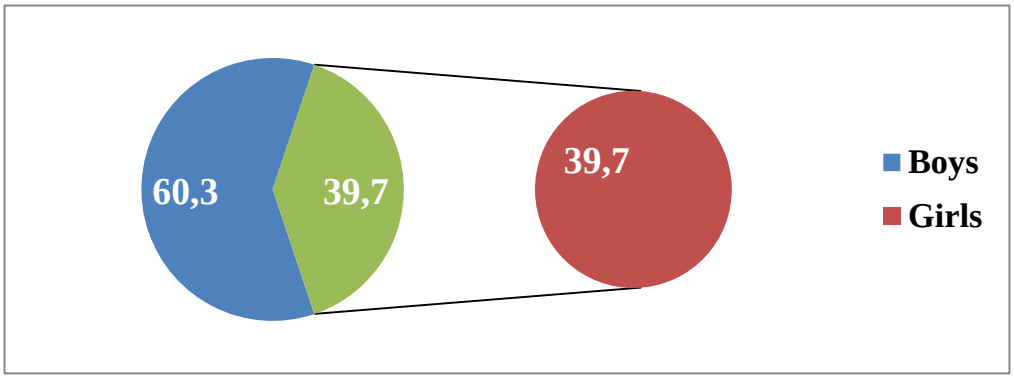


Figure 2.1.2 Distribution of children by gender (%)

As can be seen from Table 2.1.7, 60.3% of the respondents were boys, 39.7% were girls. It is noteworthy that in all age groups studied, the number of boys prevails over the total number of children by gender. This pattern is very difficult to explain, apparently, the reason lies in the biological sexual characteristics of the child's body, which are still incomprehensible to us (Figure 2.1.2.).

It should be noted that the frequency of gastrointestinal diseases in this age group can be explained both by the anatomical, physiological and pathomorphological local and general characteristics of the body, and by the expansion of the nutritional spectrum.

62% of affected children live in cities. Analysis of the frequency by place of residence and gender showed a predominance in boys permanently residing in cities.

§ 2.2. Immunological research methods

Assessment of the immune status according to modern concepts implies a comprehensive study of the immune system, including an examination of its most important functional connections. This is a description of the cellular and humoral components of immunity.

Immunological analyses of blood and saliva samples from the affected children were performed at the Laboratory of the Institute of Human Immunology and Genomics, Academy of Sciences of the Republic of Uzbekistan.

A variety of physiological processes may lead to GI symptoms and, when more prevalent, to functional GI disorders.

Abnormal motility. Disturbed gastrointestinal motility can generate symptoms of nausea, vomiting, diarrhea, acute abdominal pain, incontinence, and others. Furthermore, in healthy subjects, and more so in patients with FGIDs, strong emotion or environmental stress via the brain–gut axis can lead to dysmotility throughout the GI tract. FGIDs have an even greater motility response to stressors when compared with normal subjects. However, these motor responses only partially are correlated with symptoms, and are not sufficient to explain reports of chronic or recurrent abdominal pain.

Visceral hypersensitivity. The poor association of pain with GI motility with many functional GI disorders (eg, functional chest pain, functional dyspepsia–epigastric pain syndrome, IBS, and so forth) is explained by the concept of visceral hypersensitivity.84 These patients have a lower pain threshold with balloon distension of the bowel (visceral hyperalgesia), or they have increased sensitivity even to normal intestinal function (eg, allodynia). Visceral hypersensitivity may be amplified in patients with FGIDs: repetitive balloon inflations in the colon lead to a progressive although transient increase in pain intensity in healthy subjects and for a longer period in patients with FGIDs. Hypersensitivity and sensitization may be amplified at all levels of the brain–gut axis such as by factors listed later.

Immune dysregulation, inflammation, and barrier dysfunction

The work on postinfection IBS and dyspepsia have been associated with increased interest in mucosal membrane permeability via alteration of tight junctions,85 the intestinal flora, and altered mucosal immune function.86 These associations increase the access of intraluminal antigens into the submucosa associated with low-grade activation of mast cells and increased inflammatory cytokine release.87 These actions alter receptor sensitivity at the gut mucosa and myenteric plexus, producing visceral hypersensitivity. Factors contributing to this

occurrence include genetics, psychological stress via mast cell activation, and altered receptor sensitivity at the gut mucosa and myenteric plexus. This is enhanced by alteration of the bacterial environment or outright infection.

Microbiome. The microbiome represents the collection of microorganisms, which is shaped by host factors such as genetics and nutrients, but in turn is able to influence host biology in health and disease. It has become a major area for research in gut functioning in the FGIDs, and there is also an emerging concept of the microbiome–gut–brain axis.69,88 Differences among IBS patients in the bacterial composition of the gut (eg, increased firmicutes and reduced bacteroidetes and bifidobacter), and also reduced fecal microbial diversity relative to healthy individuals, have implied a causative role in the onset and maintenance of IBS. This is supported by the modest effect of probiotics and more substantive benefit of periodic antibiotic treatment in improving IBS symptoms.45 However, further research is needed to fully understand the place of the bacterial flora in the pathogenesis of FGIDs.

Food, diet, and intraluminal factors

A recent addition to understanding FGIDs relates to food and diet46 and also their relationship to intestinal microbiota.89 Certain specific alterations in diet such as low fermentable oligo-, di-, and monosaccharides and polyols, or gluten restriction in some patients, may provide benefit as a result of reduced osmotic effects or alterations in gut mucosa. However, no one diet is of specific value and treatment must be individualized. In addition, the diet provides substrates for microbial fermentation, and because the composition of the intestinal microbiota is altered in IBS, the link between food and diet, microbiota composition, and fermentation products may play an important role in IBS pathogenesis. This is noteworthy because there has been a discrepancy between patients' and physicians' attributions to the effect of food on FGID symptoms, with patients believing the effect was more relevant.90 Further study is needed to define the subsets of patients who are more likely to respond to alterations in diet.

Another recent area of interest relates to the effect of intraluminal factors in addition to maldigested nutrients on gut function. This includes microflora alterations in short-chain fatty acids; the products of enteroendocrine cells including granins and their effect on nervous, endocrine, and immune cells; and the proportion of secondary to primary bile acids, possibly affecting gut-transit rates.83 For example, the prevalence and role of cholerheic enteropathy likely has been underestimated previously in conditions such as diarrhea-predominant IBS, and when recognized can lead to a more specific treatment using bile acid binders.

Brain–gut axis

The brain-gut axis is the neuroanatomic substrate in which the psychosocial factors just described influence the GI tract and vice versa. The hardwiring between the brain and gut is a complex integrated circuitry that communicates information from emotional and cognitive centers (subserving thoughts, feelings, memories, and pain regulation) of the brain via neurotransmitters (software) to the peripheral functioning of the GI tract and vice versa.91 Structurally, there are direct connections between the CNS and myenteric plexus to the visceral muscles and other end-organ structures that affect sensory, motor, endocrine, autonomic, immune, and inflammatory function.92 Thus, emotions such as fear, anger, anxiety, painful stimuli, and physical stress can delay gastric emptying and intestinal transit. They also can stimulate colonic motor function, reflected by decreased colonic transit time, increased contractile activity, the induction of defecation, and symptoms of diarrhea. Also, psychological stress can disrupt the gut-pain threshold and impair mucosal secretory and barrier functions, and this is associated with transmigration of bacterial cell products leading to GI pain and diarrhea, as with IBS. Conversely, enhanced motility, visceral inflammation, and injury can amplify ascending visceral pathways and affect brain areas, leading to greater pain and contributing to altered mental functioning including anxiety and depression. In effect, the reciprocal relationships that we call the brain–gut axis is the

neuroanatomic and neurophysiologic substrate for the clinical application of the systems or biopsychosocial model.

With regard to pain regulation, the relationships between psychosocial distress and painful symptoms appears mediated through impairment in the ability of various brain networks such as the cingulate cortex to process bodily pain. In effect, the brain's pain control system can act as a filter to enhance or block pain by up-regulating or down-regulating the incoming neural signals affecting symptom perception through this gate control mechanism. Down-regulation, which increases the pain threshold, seems not to occur as well in patients with functional GI pain. The anterior cingulate cortex, involved in the motivational and affective components of the emotional arousal and salience network, is dysfunctional with IBS and other functional GI pain, fibromyalgia, and other functional somatic symptoms. When this system is influenced by psychosocial distress, the gate is open and the pain threshold is decreased. Conversely, improvement in pain control can be enabled by cognitive or emotional factors such as focused attention, hypnosis, psychological treatment, and certain antidepressants. These effects may be more than physiological based on growing evidence for their role in enhancing neurogenesis as well, thus possibly contributing to more lasting effects for these treatments.94 A more recent understanding expands upon the complexity of multiple brain network operating systems including emotional arousal, salience and executive functions, sensorimotor and autonomic functions related to FGIDs.93 In sum, the clinical phenotype that we understand as FGIDs emerges from the interactions of multiple systems in the periphery (microbiome, altered mucosal inflammation, visceral hypersensitivity) and in the brain (brain network systems of emotional arousal, sensorimotor function, central autonomic function) interacting with each other in bidirectional ways that lead to the FGID phenotype

Indicators of active and humoral immunity (Ig A , Ig G , Ig M , Ig E) in the blood. Blood tests were performed during periods of increased gastrointestinal risk factors.

§ 2.3. Statistical processing of results

Statistical processing of data was carried out in two stages:

1) preparation for statistical analysis;

2) real statistical analysis.

Relative risk is often used in statistical analysis of paired outcomes when the outcome of interest has a relatively low probability. The inherent appeal of relative risk is its ease of calculation for simple cases.

In a simple comparison between the study and control groups:

- yellow color - relative risk 1 means there is no difference in risk between the two groups;

Indicates that *HP is in the main group* infected GIA develops less frequently than the control group;

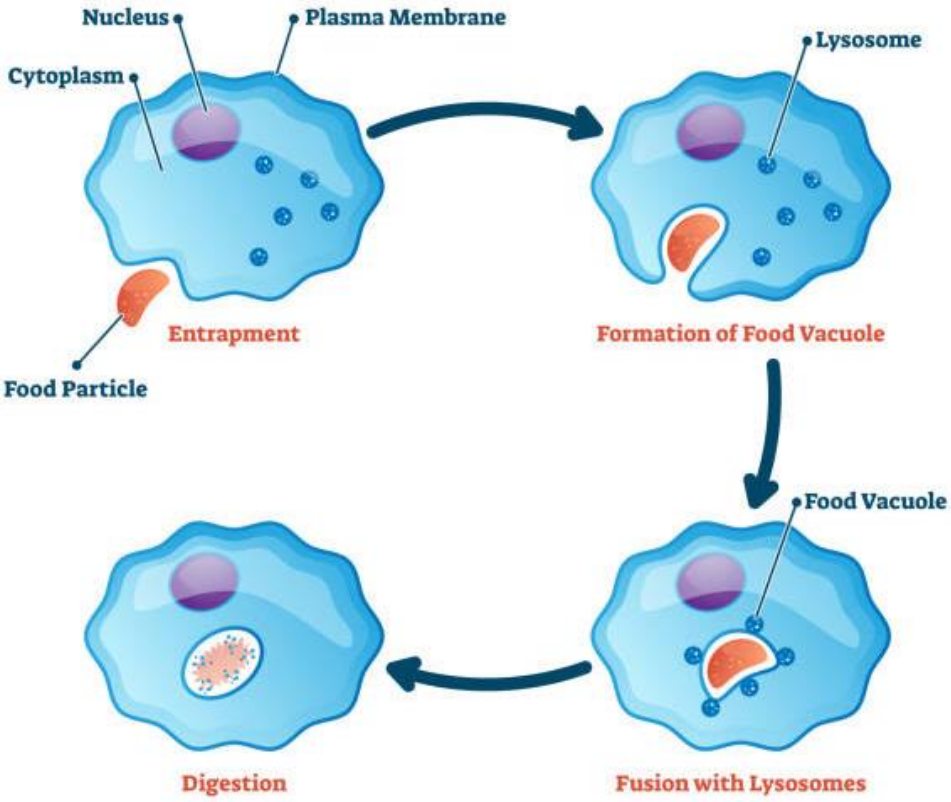
-Red color - relative risk > 1 *Nr* -related allergy develops more often in the main group than in the control group.

Determination of the content of immunoglobulins of classes G, A, M in blood serum

The immunoglobulin content was determined by the Manchini radial immunodiffusion method using monospecific sera against immunoglobulins G, A and M produced by the N.F. Gamaleya Moscow Institute of Microbiology and Epidemiology. The method is based on the reaction of formation of an insoluble complex of the immunoglobulin being detected with specific antibodies to it in a thin layer of agar. This precipitate has the form of a visually visible ring, the diameter of which is proportional to the logarithm of the concentration of the immunoglobulin being determined. Reaction setup. Standard serum is dissolved in 1 ml of distilled water, then three two-fold dilutions are prepared from it in veronal-medinal buffer (1:2, 1:4, 1:8 - 25 μl each). The prepared immunodiffusion plate is placed on a flat horizontal surface and 2 μl of the standard serum diluted 1:8 are

added to the first well, and the standard serum diluted 1:4, 1:2 and undiluted standard serum are added to the next 3 wells. 2 µl of the samples to be tested are added to all other wells of the plate. The dish is covered with a lid and left for incubation at room temperature. When determining IgG and IgA, the incubation period is 24 hours, and when determining IgM, 48 hours. The diameters of the precipitation rings are measured. Based on the results of measuring the rings formed in the corresponding dilutions of the standard serum, a calibration curve is plotted in semi-logarithmic coordinates. The immunoglobulin level of each sample to be tested is determined using the calibration curve and expressed as mg/%.

The phagocytic activity of leukocytes was determined using the Kudryavtseva method by incubating a mixture of leukocytes and latex particles in a thermostat at 37°C for 30 min. The number of neutrophils that had absorbed the latex particles was counted. The results were expressed as %. Melamine-formaldehyde latex with a diameter of 1.5 microns was used in the work (Picture – 7).



Pic.7 *Mechanism of phagocytic activation in intestine*

Determination of cytokinin levels using the IFA method

To determine cytokines, test systems developed in the State Research Institute and produced by the company "Cytokine" were used. The “elisa” kit uses a "sandwich" version of solid-phase enzyme immunoassay using horseradish peroxidase as an indicator enzyme. To implement this version, two monoclonal antibodies with different etiotropic specificity to IL were used. One of them is immobilized on the solid phase of a 96-well plate and has the ability to capture an antigen (cytokine) from a solution. Biotinylated polyclonal antibodies conjugated with horseradish peroxidase are used as the second antibodies. When the test sample and the anti-IL-peroxidase conjugate are added to the wells, immobilization of the cytokine contained in the test sample and its binding to the conjugate simultaneously occur during incubation. The amount of bound conjugate is directly proportional to the amount of cytokine in the test sample. During incubation with TMB, the solution in the wells is colored. After measuring the optical density of the solution in the wells, the concentration of cytokines in the samples under study is calculated based on the calibration graph.

The main objective of this study was to highlight the prevalence of FGIDs and the accompanying differences in food and lifestyle patterns among millennials and generation Z. A key novel finding is that functional constipation was the most common FGID among the two generations and that type of consumed beverages affected the prevalence of FGIDs most in generation Z. Twenty percent of millennials and 33.5% of individuals in generation Z were classified as having FGIDs. These findings are in line with reports in the literature, which showed that the prevalence of FGIDs in Saudi Arabia ranged between 9% and 40%. The variation of prevalence rates from different parts of the country suggests a multifactorial etiology. In the present study, the prevalence of FGIDs was strongly associated with some food and lifestyle patterns, such as commonly consumed meals (homemade vs. ready meals), number of takeout meals per day, and type of commonly consumed beverages. Takeout food, ready meals, and sugary beverages

are generally energy dense, high in fats, added salts, and sugars, and low in fiber, vitamins, and minerals, all of which contribute to disease mortality and morbidity. In the context of FGIDs, there have been limited reports of a link between the prevalence of FGIDs and negative dietary habits. In Kundur et al. study, individuals who regularly consumed fatty meals and fast food had a higher prevalence of FGIDs compared with the healthy group. This finding is in line with similar observations regarding fried foods. The link can be related to the fact that consumption of a lot of fatty and fast foods triggers the development of reflux symptoms by reducing esophageal sphincter pressure, increasing exposure of

the esophagus to gastric juices and, thus, increasing gut sensitivity and irritation and causing functional upper gastrointestinal disorders. Moreover, previous research has highlighted the influence of high energy meals on gastrointestinal transit time, causing disturbances and deregulation of proper digestion and leading to constipation. These associations were found to be significant in generation Z but not millennials. A similar trend was seen previously, with higher prevalence of FGIDs in the younger group when compared with the older group, which is to be expected logically, as such negative lifestyle habits are known to be common among younger generations. On the other hand, the incidence of FGIDs among millennials, although lower when compared with generation Z, suggests a different association that was not intended to be studied currently. Kundur et al. found a link between age and the incidence of FGIDs, which can be explained physiologically. For instance, acid reflux and gas formation increase with age. Addressing these associations in different age groups is important, as it can direct both the health care provider and patients on how to manage symptoms and inform the role of dietetics on what nutritional advice should be followed. Of note in the present study is the finding that functional constipation was among the most prevalent FGID in both generations and that commonly consuming sugary drinks was the only lifestyle habit that contributed significantly to the prevalence of FGIDs. It is well documented in the literature that functional constipation is highly prevalent among people of different age groups in

Saudi Arabia, due to a variety of discussed contributing causes. Moreover, a positive association between many gastrointestinal problems, such as constipation, and sugary dietary items, specifically refined sugars, has been established previously. Sugary drinks are mostly rich in refined sugars and energy and low in fiber. There have been hypotheses discussing the complex relationship between functional constipation and the gut microbiota, which, in this case, can be affected by lifestyle habits, stressors, and diet. Dysbiosis, which often refers to disruption in the gut microbiota, has been linked to increased rates of FGIDs including functional constipation. Indeed, data from animal models have supported the interplay between regulation of gastrointestinal motility and the gut microbiome through complex metabolic and neuroendocrine mechanisms that are driven by dietary metabolites, such as short-chain fatty acids. These hypotheses support the link between low fiber intake and, consequently, high sugar intake, and functional constipation, which explains the results of the present study and others. However, whether there is a cause-and effect relationship is still not fully understood given the inherent risk of bias related to the observational study design. Observations have shown that the incidence of FGIDs was higher among GID patients when compared with healthy controls. Some of the reports suggested "post-infectious" mechanisms, including direct viral invasion of the gastrointestinal tract, increased fecal calprotectin, presence of viral RNA in feces, altered intestinal permeability, gut microbiota dysbiosis, mucosal damage on gastrointestinal endoscopy, and involvement of enteric nervous system mechanisms that lead to FGID development. However, the present findings showed no difference in FGID prevalence before and after the pandemic or before and after participants were infected with gastrointestinal infections. In fact, the participants reported having FGIDs before being infected with GII, which explains the discrepancy with the literature. More research is needed to clarify the nature of this relationship. Out of interest, the authors were keen to examine differences between the two generations in how important they regarded CAM, which is commonly practiced among people in Saudi Arabia and

other countries. In the present study, 82.9% of millennials and 67.4% of participants in generation Z practiced CAM to prevent diseases and enhance immunity. Moreover, 50.7% of millennials and 29.0% of those in generation Z reported practicing CAM in response to COVID-19. However, no significant relationship was found between practicing CAM and FGID symptom alleviation. This result comes contrary to theories in the literature, as recent review articles concluded that significant benefits were shown in patients with FGIDs following the use of some herbal therapies. Future studies focusing on testing this link are required.

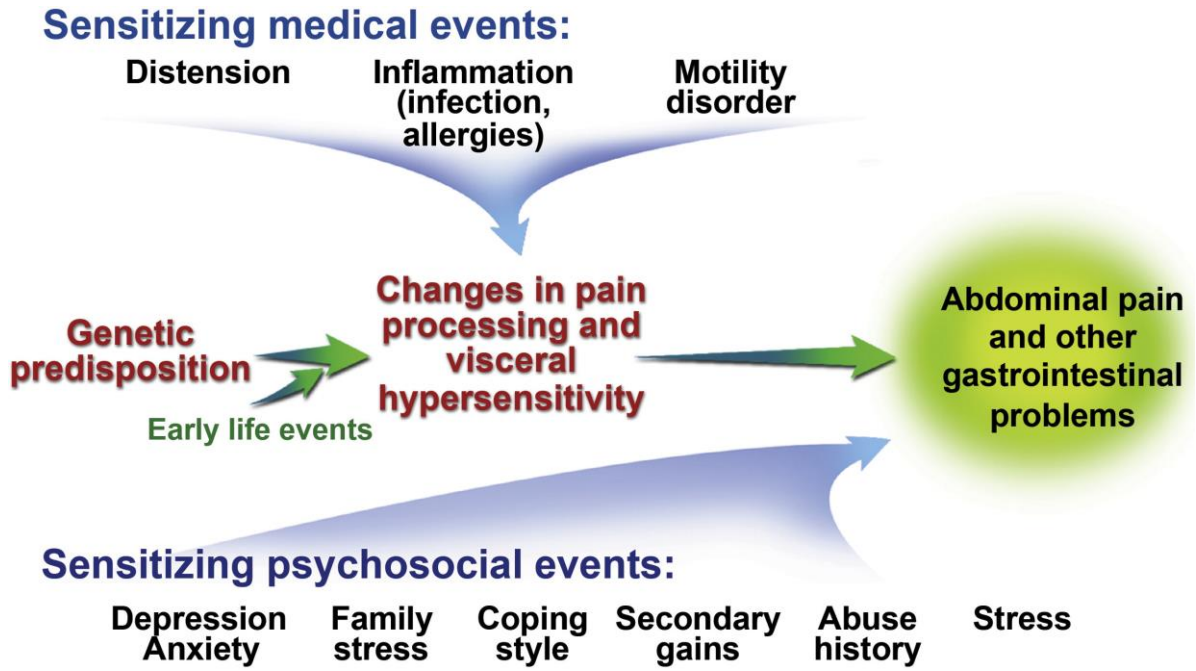
The key novelty in this study is exploring the generational difference in prevalence of FGIDs and related risk factors including food habits, lifestyle in both men and women. The use of the validated ROME IV DQ has made identification of FGIDs in larger samples much easier and more reliable. Nevertheless, data collection was carried out by inviting the students directly and their parents indirectly. Hence, participation was greater from the students than the parents. Nevertheless, limitations of this study include reliance on self-reporting at a single point in time to assess dietary and lifestyle behaviors and the use of an online and anonymous questionnaire. Moreover, it would be interesting for future research to consider the use of public toilets while at school, since the current results showed that functional constipation was the most common FGID.

Chapter III. RESULTS OF PERSONAL RESEARCH

3.1. Risk factors and clinical features of functional gastrointestinal diseases in children

Functional bowel disorders (FDGIT) are a large group of disorders associated with functional pathology of the gastrointestinal tract and are very common worldwide. These disorders affect all segments of society, regardless of gender, age, race, religion, skin color, or socioeconomic status.

The relevance of the ongoing active process of studying these nosological forms in recent decades is due not only to the significant decrease in the quality of life of patients, but also to the significant damage to the global healthcare system due to the direct and indirect costs of their treatment. The achievements of fundamental and clinical science over the past 10 years in the study of the epidemiology, etiology, pathophysiology, diagnosis and therapy of FCD have necessitated a revision of the Rome III criteria, which have been in place since 2006. (Picture – 8)



Pic.8 *The pathophysiology of functional abdominal pain disorders involves visceral hypersensitivity as a central mechanism, which may progress to disability. This heightened pain perception typically results from the interaction of sensitizing medical influences layered upon a foundation of genetic susceptibility and adverse early-life experiences.*

The gastrointestinal tract (GIT) serves not only as a site of digestion and nutrient absorption but also functions as a crucial component of the immune system. Its immunological role is largely influenced by constant exposure to a vast array of external antigens—including dietary elements, bacteria, viruses, and parasites—alongside an extensive mucosal surface area, estimated to be approximately 200 m^2 in children. This extensive exposure necessitates the activation of defense mechanisms against pathogenic microbes and various non-organic substances.

The intestine is recognized as the largest immune organ in the human body. Approximately 25% of its mucosal lining is comprised of immunologically active tissue, and around 80% of all immunocompetent cells reside within it. On average, each meter of intestinal length contains approximately 10^{10} lymphocytes.

The gastrointestinal immune system encompasses both cellular and structural elements. The cellular components include B and T lymphocytes located intraepithelially and in the lamina propria, plasma cells, and myeloid cells such as macrophages, neutrophils, eosinophils, and mast cells. Additionally, enterocytes and specialized M cells associated with lymphoid follicles contribute to immune function. Structural components include Peyer's patches, isolated lymphoid follicles, the appendix, and mesenteric lymph nodes.

Lymphocytes are fundamental to core immune processes such as antigen recognition, elimination, and immune memory. Beyond cellular immunity, the GIT's natural defense is bolstered by the mucosal epithelium, mucus barrier, and the resident intestinal microbiota. The microbiota forms a stable biocenosis that promotes colonization resistance—an essential form of non-specific defense—thereby inhibiting the growth of pathogenic microorganisms.

In May 2016, the global gastroenterological community was introduced to the Rome IV criteria at American Gastroenterology Week, with the main provisions of the consensus already published.

The gut–brain interaction involves the central, autonomic, and enteral nervous

systems, as well as the neuro-endocrine and neuro-immune systems. The neuroendocrine stress response is controlled by the paraventricular hypothalamic nucleus through the hypothalamic–pituitary–adrenal axis. Stress induces an increase in corticotropin releasing factor. Corticotropin-releasing hormone increases colonic motility and pain in adult patients with IBS. A possible impairment of gut–brain communication, mediated by the hypothalamic–pituitary–adrenal axis and the autonomic nervous system in functional gastrointestinal disorders associated with abdominal pain, such as IBS, has been studied in children. Gulewitsch et al.'s study showed that children with functional abdominal pain disorders seem to have a downregulated hypothalamic–pituitary–adrenal axis capacity, probably as a consequence of chronic stress. There was no evidence in that study for parasympathetic withdrawal during stress. In their study, Sjolund et al. support the idea of a bidirectional gut–brain interaction that leads to symptoms of IBS and other abdominal pain-related functional gastrointestinal disorders. Abnormalities in the levels and signalling of serotonin (5-hydroxytryptamine-5-HT), an essential neurotransmitter in the enteral nervous system, lead to both intestinal and extraintestinal symptoms, including diarrhea, constipation, bloating, nausea, vomiting, altered pain perception, anxiety, obsessive-compulsive disorders, depression, and phobias. Studies in adult patients with IBS show that visceral hypersensitivity may play a role in the pathophysiological mechanisms of this disease. Elsenbruch et al. aimed to describe the role of anxiety and depression in pain processing in adult patients with IBS. They found that anxiety and depression alter the perception of pain. Dorn et al. document an increased tendency to report pain in adults with IBS-associated anxiety and depression. In post-infectious IBS adult patients, Sundin et al. report that a reduced fecal microbiota in both the mucosa and intestinal lumen was found in patients with anxiety and/or depression.

Brain imaging studies like MRI and functional MRI have shown structural changes in the hypothalamus, grey matter density, volume, and cortical thickness in regions involved in emotional modulation or pain modulation in patients with IBS.

Pediatric patients with IBS have lower cortical thinning in the dorsomedial and dorsolateral prefrontal cortex and posterior parietal cortex, and they show cortical thickening in the posterior cingulate cortex. A study was conducted by Hubbard et al. in 19 adolescents diagnosed with IBS based on Rome III criteria, compared with a healthy control group. In these patients, functional disability was positively correlated with total anxiety scores. Cortical thickening in the left posterior parietal cortex, supramarginal gyrus, the right inferior temporal, and fusiform gyri was associated with greater anxiety scores. The authors also noted a strong negative correlation between cortical thickness in the right dorsolateral prefrontal cortex and pain catastrophizing. It is undetermined whether these structural and functional brain changes precede or follow the symptoms of IBS. The authors conclude that these brain changes may have long-term consequences on psychosocial functioning, anxiety and depression. Bhatt et al. aimed to find structural differences in the grey matter volume in the brain, and its associated resting-state abnormalities in functional connectivity, in girls with IBS, compared to healthy controls. They also wanted to correlate these changes with anxiety levels, pain-related anxiety, and pain levels. The study included 32 girls aged between 7 and 17 years diagnosed with IBS based on Rome III criteria. The participants of the study with IBS had a lower grey matter volume in the prefrontal cortex, basal ganglia, and anterior mid-cingulate, altered functional connectivity between multiple brain networks, and showed altered relationships between pain sensitivity and brain structure. A recent review by Mayer et al. gathered growing evidence from both clinical and preclinical studies in support of a common genetic, structural, and functional background for gastrointestinal and psychological disorders. In addition to these shared factors, environmental influences, especially during childhood, play an important role.

Anxiety and Depression in high school patiens with IBS

Correlations between anxiety and depression and different subtypes of IBS; connections between psychological factors and other symptoms of IBS besides

abdominal pain or changes in bowel pattern, like bloating; and the influences of psychological factors in different ethnic groups, and dietary and cultural influences, are not well studied in children with IBS. In adult patients, however, a more recent meta-analysis by Hu et al. explored the prevalence of anxiety and depression in adult patients with different IBS subtypes and in healthy controls. IBS with mixed symptoms, both diarrhea and constipation, was associated with the highest levels of anxiety and depression, followed by IBS manifested as constipation and IBS manifested as diarrhea. Patients with IBS manifested predominantly by constipation had the highest prevalence of anxiety and depression (40% and 38%, respectively). In a systematic review and meta-analysis that aimed to compare depression and anxiety levels in adult patients with IBS of different subtypes, both depression and anxiety levels were found to be higher in adult patients with IBS compared with healthy controls. This difference was also noted in the subgroup analysis of IBS subtypes. The translation of English questionnaires into different languages and cross-cultural validation would improve global epidemiological studies in both IBS and psychological disorders.

One of the most bothersome symptoms in patients with IBS is bloating. Hod et al. found a significant correlation between bloating severity and both depression and somatization in a study of adult patients with IBS. Anxiety scores were higher in IBS patients with bloating as compared with IBS patients without boating, but these differences did not reach statistical significance. Ryu et al. also report an association between depression and bloating. The question remains as to the association of abdominal pain and psychological symptoms, and whether the gastrointestinal symptoms precede or follow the psychological ones.

Childhood Psychological Events with Impact on teenagers with IBS

About 50% of adult patients with IBS report mental symptoms like anxiety or depression. Illness anxiety is considered a risk factor for the development of IBS in adults. A question that has not been answered is whether symptoms like anxiety or depression trigger gastrointestinal symptoms or abdominal pain, and whether

changes in stool patterns lead to psychological distress. Answering this question would optimize treatment options in patients with IBS. Studies performed in teenager patients with IBS reveal a strong link between events with psychological impact, taking place in childhood or later in life, and the development of gastrointestinal symptoms. In a systematic review, Chitkara et al. state that symptoms related to functional gastrointestinal disorders experienced in childhood are likely to persist into adulthood. Factors that may contribute to this situation are socioeconomic status, traumatic events during infancy or childhood, such as hysical, emotional, or sexual abuse, and parental separation or divorce. Park et al., in a study performed on adults with IBS, found that early life events like incarceration or mental illness in a member of the household and emotional abuse are significant predictors of IBS. IBS is also linked to post-traumatic distress syndrome in adult patients. Berens et al.'s study suggest that adverse childhood experiences and illness anxiety are significantly increased in patients with IBS, with significant correlations for women. Howell et al. conclude in their study that chronic abdominal pain in children progresses into adulthood gastrointestinal disorders, particularly in children aged between 7 and 9 years. However, emotional distress was not correlated with this finding. Anxiety and depression are more likely to be associated in children diagnosed with IBS who have a family history of this disease. A study from a group with significant research experience in clustering functional gastrointestinal disorders within families found a positive correlation between mothers and children for somatization. Multiple independent factors and behaviours are transmitted from one generation to another, influencing a child's response to somatic sensations [13]. Ramchandani et al. showed that in children aged between 2 and 6 years, recurrent abdominal pain was associated with higher scores for anxiety and depressive disorders in the mothers. Reaserches et al. showed that anxiety disorders seem to be diagnosed in adults who had functional abdominal pain associated with anxiety in childhood. Later, a study from the same group found that an anxiety disorder was diagnosed in almost 80% of children with recurrent abdominal pain, with separation

anxiety being the most frequent. Almost 43% of children exhibited a depression disorder.

Functional Gastrointestinal and Psychological Disorders in Children. Zia et al., in a systematic review, found that anxiety and depression are associated with abdominal pain-related disorders of the gut–brain interaction in children. Anxiety and depression were associated with a two-fold increased risk of abdominal pain-related disorders of the gut–brain interaction. Also, these two psychological factors are associated with the persistence and chronicity of abdominal pain-related disorders of the gut–brain interaction. Waters et al. found that the incidence of functional gastrointestinal disorders was significantly higher in children with anxiety disorders in comparison with non-anxious children (40% versus 6%). The severity of symptoms was also higher. Yacob et al. report a prevalence of 51.5% of anxiety or depression in children with pain-predominant functional gastrointestinal disorders (including IBS), as compared with controls (8.8%). Most of the studies in children focus on finding a relationship between psychological factors, like anxiety and depression, and functional gastrointestinal disorders manifested as abdominal pain, in general, and not specifically IBS. However, Rutten et al. found no differences in anxiety and depression scores in children with IBS compared with children with functional abdominal pain syndrome. Further, 28% of children with IBS were greatly anxious, and 34.8% had depression. The authors support the idea that IBS and functional abdominal pain syndrome are one underlying functional disorder with different expressions if psychological characteristics are considered. The overlap in symptoms of gastroesophageal reflux disease, functional dyspepsia, and IBS is also noted by Gastroenterologists of central Asia et al., who find that children with IBS or functional dyspepsia who report heartburn have increased anxiety, depression, and sleep disturbances [11].

A study regarding chronic pain in children reported that 55% of the children had more than one pain diagnosis simultaneously. Chronic abdominal pain-related diagnoses were found in 22.3% of the children enrolled in the study. Further, 31.6%

of the children with chronic abdominal pain had significant scores for anxiety, and this was 26.7% for depression. Machnes-Maayan et al. found that of 19 children with recurrent abdominal pain (medium age 12.8 Ґ} 3.267 years), 52.6% had psychiatric comorbidities such as different types of anxiety or depressive disorders, obsessive-compulsive, post-traumatic stress, or attention deficit hyperactivity disorders, or phobias. However, the prevalence of associated depressive disorders was lower than in other studies (5.3%). A study conducted by regional multidisciplinary central hospitals of Uzbekistan prospectively followed children with functional abdominal pain into adolescence and young adulthood to investigate if these patients have a higher risk of anxiety and depressive disorders compared to children without these associations. IBS was diagnosed in 27.4% of the children included in the study. In this study, 51.2% of patients had at least one lifetime anxiety disorder. Social anxiety was the most common disorder, diagnosed in 25.9% of patients with functional abdominal pain. Depressive disorders were diagnosed in 40.1% of participants in the functional abdominal pain group. In a significant number of patients, anxiety disorders continued into adolescence and adulthood.
Saps et al. found a seasonal link between functional abdominal pain disorders and anxiety and depression. Consultation rates for abdominal pain decreased by 20-to-25% in the summer months. The same trend was noted for consultations for anxiety and depression (a decrease of 5-to-20% in the consultation rates). A valid explanation was not found, but the authors speculate that school-related stress could be a cause [15].

Anxiety and Depression in Children with IBS. A case–control study that included patients with both IBS and recurrent abdominal pain found lower thresholds for visceral perception in patients with IBS compared to controls. Higher scores for anxiety were found in 45% of the total number of patients. Yamamoto et al. evaluated the symptoms and associated factors in a large number of children diagnosed with IBS. Depression or anxiety were strongly associated with IBS,

especially in correlation with constipation. Dong et al. prospectively studied risk factors in children diagnosed with IBS. The authors found that, among other factors, anxiety and depression are significant risk factors for IBS in children. In a more recently published prospective study, Hollier et al. tried to see if pain catastrophizing and somatization mediate the relationship between pain severity and anxiety or depression. The authors analyzed children diagnosed with IBS. The study suggests that the association between psychological factors like anxiety and depression and pain severity in children with IBS is mediated by somatization and pain catastrophizing. These two factors might be better treatment targets than anxiety and depression.

A retrospective study published by association of gastroenterologist of country enrolled children fulfilling Rome IV criteria for IBS. The study focused on family history of IBS, a factor which increased the risk of a child developing anxiety and depression and having psychological counselling and antidepressant treatment.

The total mass of microorganisms reaches 1–1.5 kg in children and up to 3–4 kg in adults, accounting for 50–60% of the dry residue of feces. The intestinal flora is represented by more than 500 species of microbes, the total number of which reaches 1015, which is almost two orders of magnitude greater than the number of all cells in the human body. "The skin and mucous membranes of a person are covered in a glove-like biofilm, consisting of hundreds of species of microbes" (Mechnikov I.I., 1907) [5, 6].

The main functions of normal intestinal microflora:

• protective (antagonistic) — parietal microflora, increasing the colonization resistance of the intestinal wall, prevents its colonization by pathogenic and opportunistic microflora;

• enzyme-producing — hydrolysis of fiber, proteins, fats, starch, deconjugation of bile acids;

• metabolic — synthesis of vitamins B, C, K, amino acids, cholesterol, uric acid, organic acids, absorption of Ca salts, vitamin D;

• immunomodulatory — normal flora, which performs the following functions:

— maintains the synthesis of immunoglobulins, mediates the maturation and functioning of immunocompetent organs;

— stimulates the formation of B lymphocytes, plasma cells;

— regulates the content of lysozyme, properdin, complement and its fractions;

— promotes the development and maturation of the intestinal immune system;

- increases the protective properties of the intestinal mucosa, stimulates the immune response, increases phagocytic activity, increases the content of IgA, T helpers.

Intestinal microflora provides key signals for the maturation of the immune system and actively controls intestinal-related immune homeostasis. It has been proven that the full maturation of the largest human immune organ requires exposure not so much to food antigens as to normal flora antigens. The main mechanism by which normal microflora acts on the body's immune system is the "homing effect", which results in an increase in the number of plasma cells synthesizing secretory IgA throughout the body in the mucous membranes of the body, including the gastrointestinal tract, and an increase in both local and general immunity. The mechanism of lymphocyte recirculation is the process of their continuous movement from the body into the lymph and bloodstream and back. Lymphocyte migration is an important process for the functioning of the central link of the immune system [2–8]. The main immunoglobulin of the intestine is IgA, which is produced locally by plasma cells located in the intestinal lamina propria. Secretory IgA binds antigens of viruses and bacteria (neutralization of viruses, agglutination of bacteria), blocks the adhesion of viruses and bacteria to mucous membranes, stimulates the antibacterial activity of phagocytes and lymphocytes against pathogenic bacteria, binds food antigens and allergens that can provoke allergic reactions [1, 4, 6]. A pronounced negative relationship between the level of bifidobacteria and the concentration of secretory IgA in human feces has been

proven, which has given grounds for considering the determination of the concentration of secretory IgA in feces as an additional method for diagnosing dysbacteriosis.

The main tasks of the intestinal immune system:

• recognition of one's own antigens and formation of immunological tolerance to them;

• protection of the body from the introduction and toxic effects of foreign antigens that can disrupt the structure and function of one's own tissues;

• formation of tolerance to antigens that do not have a harmful effect on one's own tissues

(normal microflora, food).

In daily practice, a specialist constantly encounters such factors that weaken and disorganize the body's immune system as poor nutrition, hypovitaminosis, frequent colds, chronic gastrointestinal pathology, iatrogeny (prescription of antibiotics, sulfanilamide drugs, corticosteroids, immunosuppressants, laxatives, etc.), environmental problems, stress, physical overload, food allergies, etc. On the other hand, a decrease in the immunobiological reactivity of the body, i.e. the system of differentiated protection and regulation of the constancy of the internal environment, is of great importance in the development of chronic diseases. At the same time, the mucous membrane of the gastrointestinal tract is a powerful barrier that prevents the penetration of foreign antigens into the internal environment of the body. The most significant role in this process is played by the local immune system, which is involved in the inactivation of bacterial, viral, alimentary, medicinal and other antigens, the elimination of immune complexes, and the synthesis of immunoglobulins. Naturally, lesions of the gastrointestinal tract of various etiologies are accompanied by changes in the activity of the immune system [9]. Long-term chronic gastrointestinal processes reliably disrupt the microecological balance, reduce colonization resistance, lead to damage to the functions of the intestinal normal flora, and worsen the immune status. In the

development of chronic gastrointestinal pathology, due to the cyclical nature of the process, the most pressing issue is prolonging remission and preventing exacerbation of the disease. This goal is achievable provided that the immune function of normal microflora is restored by effectively correcting the disturbed microbiocenosis. In this regard, it is important to search for new approaches to the treatment of chronic intestinal diseases in children that simultaneously provide relief of abdominal syndrome, restoration of local immunity of the digestive system and a general immunomodulatory effect.

Functional bowel disorders include clinical manifestations such as irritable bowel syndrome, functional constipation, functional diarrhea, functional abdominal distension, and nonspecific functional bowel disorders.

In our study, we surveyed parents using a questionnaire we developed and general clinical research to develop a predictive scale for the formation of gastrointestinal risk factors in young children.

85 patients with functional constipation , 85 patients with functional diarrhea , and 170 children with no gastrointestinal symptoms were selected. All selected patients underwent general clinical, laboratory, functional, and biochemical examinations.

In order to develop an optimal method for assessing risk factors for the development of complications of functional constipation in children with the subsequent decision on the tactics of treating the patient, we carefully analyzed the results of the study, risk factors, biochemical indicators, as well as immunological blood parameters used in the diagnosis of gastrointestinal diseases.

A Xi^2 test was calculated to assess the significance of differences in outcomes depending on exposure and/or the presence of a risk factor. At the same time, a four-area table was constructed to analyze the study data and compare the percentages of symptoms in the two study groups. All patients were divided into 4 groups: A, B, C, D.

At the same time, group A includes children with functional constipation and the presence of a risk factor; group B includes children without gastrointestinal risk factors, but with a risk factor ; group C includes children with functional diarrhea and the presence of a risk factor ; group D includes children without gastrointestinal risk factors , not exposed to a risk factor.

The groups of patients selected for the study were divided according to the main clinical, laboratory and functional indicators . A four-field prognostic table was constructed to determine the risk of developing gastrointestinal FD and determine patient management tactics.

A total of 15 features were studied and calculated using Excel .

To compare the reliability, sensitivity, and specificity of the effect of a risk factor on the formation of gastrointestinal risk factors, the relative risk (RR) with a 95% confidence interval was studied (Table 3.1.1) (Figure 3.1.1).

Table 3.1.1.

Scale of predictors of the formation of risk factors for the gastrointestinal tract in children depending on the influence of risk factors

Risk factor	A		C		B		D		DI	OP
	abs	%	abs	%	abs	%	abs	%	95%	RR
Frequent acute respiratory infections	60	71.2	25	28.8	51	60.5	33	39.5	1.001 - 1.633	1279
Artificial and mixed feeding	37	42.9	48	57.1	24	28.8	60	71.2	1.093 - 1.655	1.345
Inherited predisposition	46	54.2	39	45.8	19	22.4	66	77.6	1.548 - 2.345	1.905
Exudative-catarrhal anomaly of the child's constitution	48	56.5	37	43.5	29	34.2	56	65.8	1.263 - 1.943	1.567

Anemia	64	74.7	21	25.3	12	14.7	73	85.3	2.784 - 4.794	3.653
Lymphatic-hypoplastic anomaly of the child's constitution	70	82.4	15	17.6	30	35.3	55	64.7	2.349 - 4.543	3.267
Behavioral disorders of various etiologies	44	51.7	41	48.3	23	26.5	63	73.5	1.357 - 2.055	1.670
Irrational introduction of complementary foods	68	79.4	17	20.6	19	22.4	66	77.6	2.745 - 5.051	3.723
Perinatal central nervous system damage	55	65.3	30	34.7	27	32.4	57	67.6	1.561 - 2.491	1.972
Intrauterine growth restriction	64	74.7	21	25.3	22	25.8	63	74.2	2.222 - 3.834	2.919
Post-puberty period	15	17.1	70	82.9	34	39.4	51	60.6	0.379 - 0.722	0.523
Premature birth	38	44.2	47	55.8	19	22.4	66	77.6	1.296 - 1.941	1.586
Passed intestines new infections	33	39.4	52	60.6	22	25.8	63	74.2	1.090 - 1.652	1.342
Food allergies	50	59.4	35	40.6	33	39.4	52	60.6	1.202 - 1.868	1.499

Alimentary main factors	27	32.4	58	67.6	14	16.5	71	83.5	1.206 - 1.818	1.481

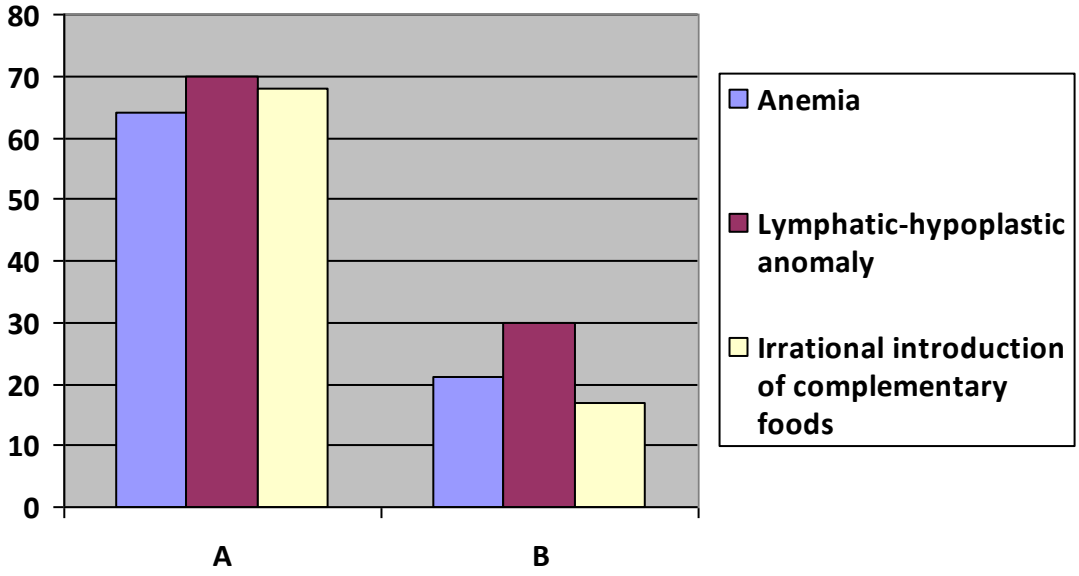


Figure 3.1.1. *predictors of the formation of risk factors for the gastrointestinal tract in children*

As a result of the calculation, the following was determined:

- The risk of functional diarrhea increases by 3.2-3.7 times in children with lymphatic-hypoplastic constitutional anomalies and irrational introduction of complementary foods ;
- The RR for the development of functional constipation in children with intrauterine growth retardation, hereditary predisposition to gastrointestinal risk factors and perinatal damage to the central nervous system is 1.9-2.9 times higher than in others ;
- Children born prematurely, with exudative-catarrhal constitutional anomaly, food allergy, nutritional risk factors, and behavioral disorders of various etiologies have a 1.4-1.6 times higher risk of developing functional diarrhea than others;

The risk of developing functional diarrhea is also 1.2-1.3 times higher in children with acute intestinal infections, who are on artificial and mixed feeding, and who often suffer from acute respiratory infections.(Figure 3.1.2)

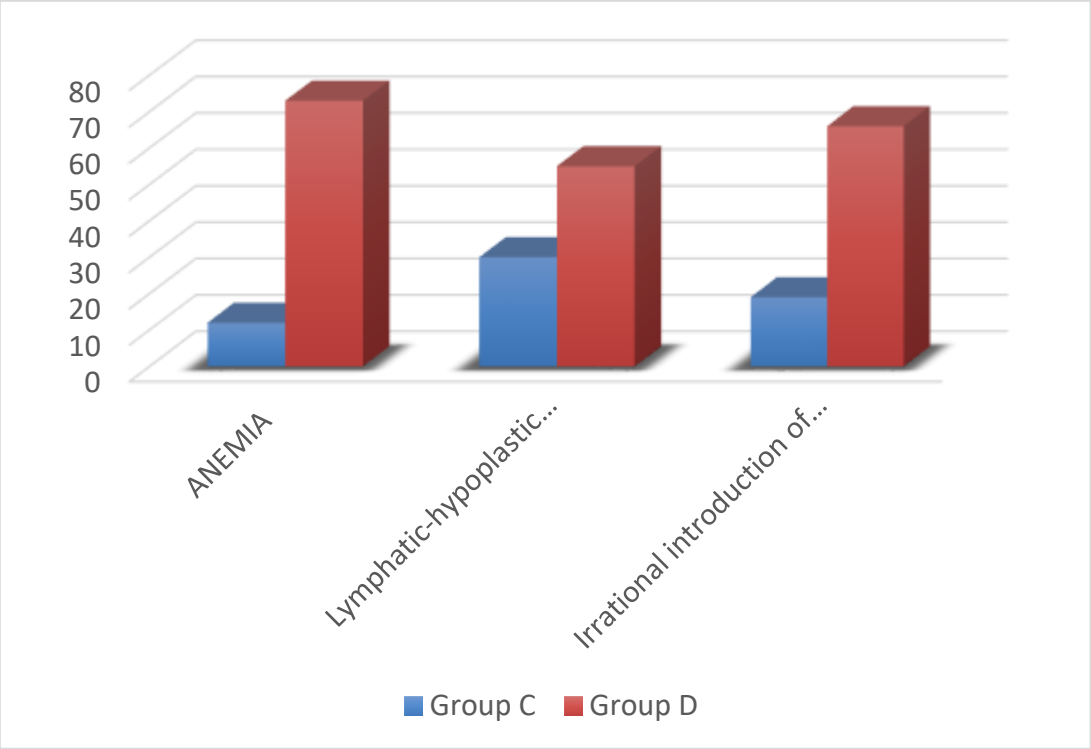


***Figure 3.1.2**. Common groups of risk factors*

Consequently, the obtained statistically significant data allow us to determine the tactics of managing children with functional diseases of the gastrointestinal tract. Why is it necessary to develop an effective program to prevent the transformation of gastrointestinal RF into organic pathology in young children?

3.2. Immune status in various clinical manifestations of functional disorders of the gastrointestinal tract in children

In order to study the immune parameters in gastrointestinal diseases in children, 63 children aged 1 to 3 years, who were undergoing inpatient examination and treatment at the Children's Medical Center, underwent a medical examination. The study population was divided into two clinical groups based on diagnosis: one

consisting of 32 children diagnosed with functional diarrhea, and the other including 31 children with functional constipation. Each participant underwent a comprehensive diagnostic evaluation, which included general clinical assessments, biochemical blood analysis, enzyme-linked immunosorbent assay (ELISA), and a range of immunological investigations.

The gender distribution among the 63 patients revealed a higher proportion of females: 39 girls (61.9%) and 24 boys (38.1%). All participants were within the early childhood age range of 1 to 3 years. An analysis of morbidity and hospitalization patterns based on residential location indicated a higher rate of hospital admissions among urban residents, with 39 children (61.9%) coming from urban areas, compared to their rural counterparts. Immunological blood tests were performed on children with gastrointestinal infarction to study immune status.

The concentration of CD 3+ and CD 4+ lymphocytes in both observation groups showed significant changes compared to the cut-off values of the control group. Regardless of the form of the disease, the relative concentration of CD 3+ and CD 4+ lymphocytes in the gastrointestinal FD is significantly reduced ($P < 0.05$) (Table 3.2.1).

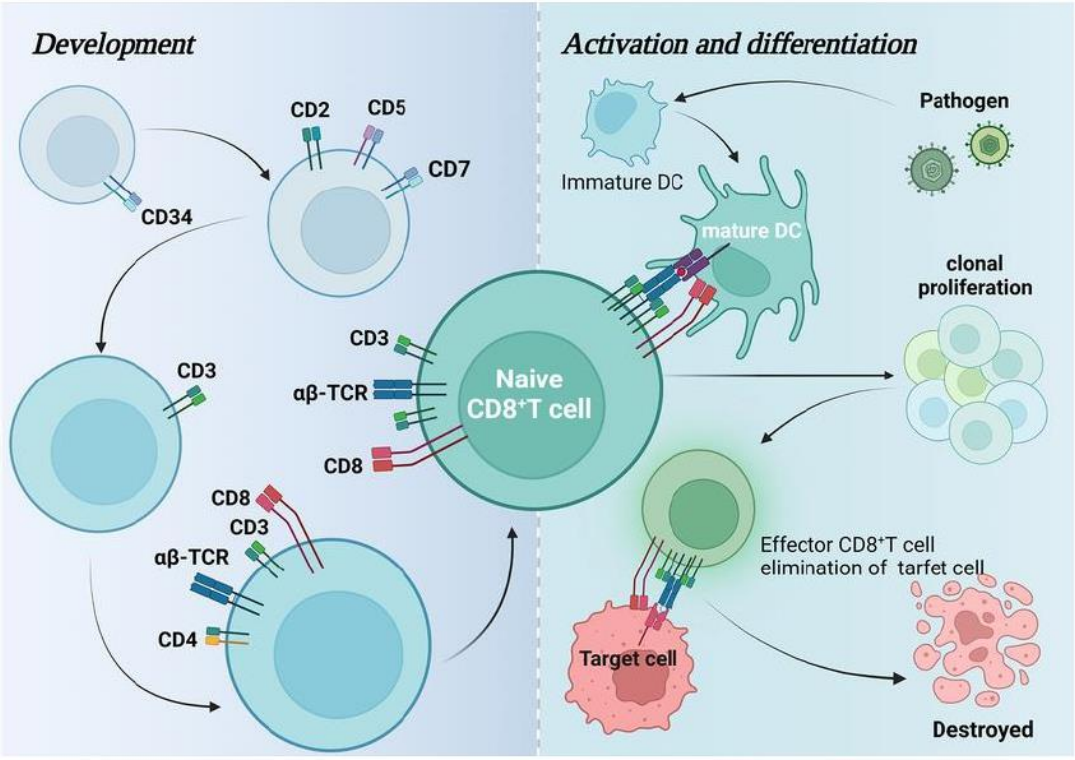
Table 3.2.1

Indicators of T-cell immunity in sick children with gastrointestinal infarction

Blood count	Control group (n=30)	Functional diarrhea (n=32)	Functional constipation (n=31)
CD3,%	52.0 ±1.0	38.3± 2.3*	44.27±0.41**
CD3+, abs	780 ±27	675 ± 23*	1325.6± 90.03**
CD4, %	32.4 ±0.5	29.4 ±0.9 *	22.3±0.61**
CD4+, abs	521 ± 21	435 ± 32*	658.63± 44.78**
CD8, %	21.0 ±0.8	17.8 ±1.5	19.4±0.99
CD8+, abs	372 ± 13	238± 12*	567.17± 45.46**
CD16+, %	16.4 ±1.0	18.4 ±0.8	15.2±0.95
CD16+, abs	182 ± 9.0	198 ± 7.0	178±3.0

As for the absolute concentration, a significant reverse change is observed: a decrease in functional diarrhea to 675.0 ± 23.0 μl and 435 ± 32 μl, compared to the control - 780.0 ± ±27.0 ($P < 0.05$) and an increase in CD. With functional constipation, CD 3+ lymphocytes increased 1.7 times (up to 1325.6 ± 90.03 μl ±) and CD 4+ lymphocytes 1.3 times (up to 658.63 ± 44.78 μl) ($P < 0.05$).

T-cell immunity in children with is characterized by a decrease in the relative and absolute number of CD 3+ and CD 4+ lymphocytes, as well as a decrease in the relative number of CD 8+ lymphocytes against the background of an unreliable increase in the activity of killer cells (CD 16+) (Picture – 9).



Pic.9 *The function of T-cells in association with CD3 and CD4 cells*

CD3 + lymphocytes are known to be involved in delayed-type allergic reactions [18] . Decreased concentrations of CD3 + and CD4 + lymphocytes observed in studies indicate the presence of infections and secondary immunodeficiency states.

Immunological blood tests in children with functional constipation revealed a significant increase in the absolute values of CD 3+ CD 4+ CD 8+ lymphocytes , with a tendency to decrease in CD 16+ lymphocytes (Figure 3.2.1).

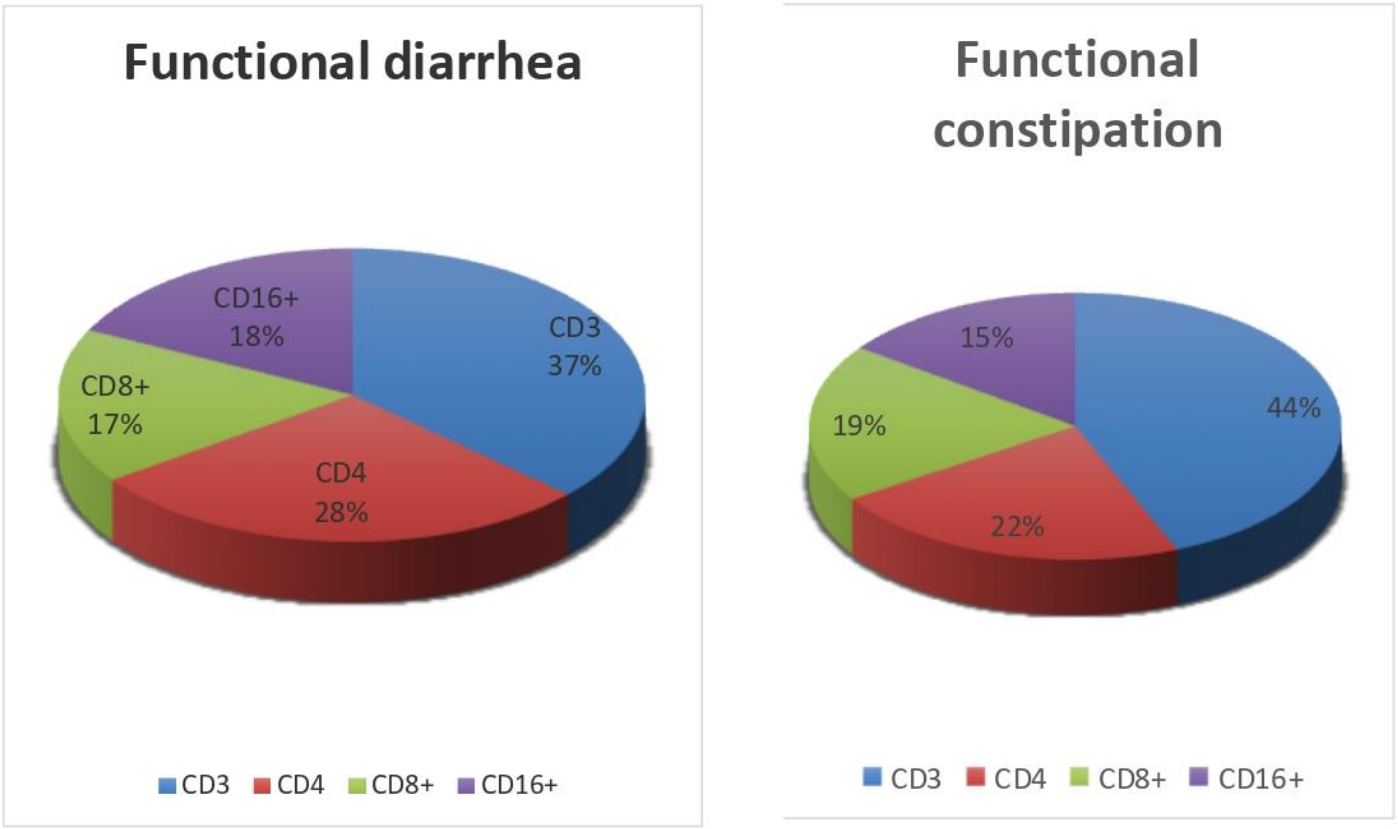


Figure 3.2.1. Absolute values of lymphocytes in percentages

An increase in the absolute concentration of CD3+ CD4+ CD8+ lymphocytes indicates the acute phase of allergy and stimulation of the immune system in response to an allergen (antigen) or infection, which confirms the formation of hyperreactive syndromes.

CD8+ lymphocytes , a decrease in their relative number was found regardless of the form of the disease .

T-cell deficiency is characteristic of many chronic autoimmune diseases of the gastrointestinal tract, including primary biliary cirrhosis, primary sclerosing cholangitis, ulcerative colitis, Crohn's disease, pernicious anemia, and others.

In our studies, the detected deficiency of CD8+ T cells in functional diarrhea is significant in terms of their absolute concentration - 238 ± 12.0 µl compared to the control - 372 ± 13.0 µl (P <0.05), which confirms the presence and/or the formation of chronic gastrointestinal diseases through impaired control of CD8+ T-cell infections, as a result of which there is a high risk of developing an autoimmune mechanism.

During an immune response, B-lymphocytes differentiate into plasma cells that secrete antibodies.

IgG, IgA, IgM and IgE antibodies (Table 3.2.2).

B lymphocytes can develop an adequate immune response only with the help of T helper cells. In the group of patients with functional diarrhea , the level of B lymphocytes was found to be significantly higher than the control values of 28.8 ± 1.2 mg% ±- 25.4 ± ±0.8 mg% (P < 0.05). There was also a significant increase in the relative and absolute levels of CD 23+ cells - 12.2 ±± 0.8 mg% and ±165 ± 5.0 µl compared to the control - 9.4 ± 0.3 mg% and 145 ±± 3.0 µl, respectively .±

Table 3.2.2.

B-cell immunity in gastrointestinal RF in children

Blood indicators	Control group (n=30)	Functional diarrhea (n=32)	Functional constipation (n=31)
CD20+, B-lymphocytes, %	25.4 ±0.8	28.8 ±1.2*	18.17±0.99**
CD20+, B-lymphocytes (ml)	438 ±12	441± 3 2	539.97±53.15
CD23+ %	9.4 ±0.3	12.2 ±0.8*	19.47±0.77***
CD23+ml	145 ±3.0	165 ±5.0 *	334± 6.0***
IgA (g/l)	3, 1± 0.5	8 , 8± 12 *	1.36±0.17*

IgM (g/l)	2, 2± 0.5	3.5± 0.8	1.91±0.19
Ig G (g/l)	1 4.8 1.0±	21.5 1.0 ±*	9.54±0.43*
IgE (IU/ml)	22.0 ±1.2	25 .0 1.1±	88.67±4.84***

There is a significant decrease in the relative level of CD 20+ lymphocytes - 18.17±0.99 mg% compared to control - 25.4 ±0.8 mg% (P <0.05) and an increase in CD 23+ lymphocytes - 19 .47 ±0.77 mg% compared to control - 9.4 ±0.3 mg% (P <0.001).

There is evidence that B cells are a component of the humoral response in adaptive immunity, secreting antibodies and acting as antigen-presenting cells. They have an anti-inflammatory phenotype and have a high proliferative capacity .

Taking into account the above, the increase in CD 23+ lymphocytes confirms the acute phase of the inflammatory process. In a study conducted in patients with functional constipation, a significant increase in Ig G was noted - 88.67±4.84 μl - 22.0 ±1.2 μl compared to control values (P <0.001). An essential indicator of the functional activity of B-lymphocytes is the serum concentration of immunoglobulins, particularly of the main classes: IgG, IgA, and IgM. The analysis of immunoglobulin levels in children with functional diarrhea revealed a statistically significant elevation in both IgA and IgG compared to age-matched healthy controls. Specifically, the concentration of IgA in patients with functional diarrhea was markedly increased, averaging 8.8 ± 1.2 g/L, in contrast to 3.1 ± 0.5 g/L in the control group ($P < 0.05$). Similarly, serum IgG levels were elevated to 21.5 ± 1.0 g/L versus 14.8 ± 1.0 g/L in controls ($P < 0.05$). These findings suggest enhanced mucosal and systemic immune activation in patients with functional diarrhea.

In contrast, the concentration of IgM exhibited a non-significant trend toward elevation in the functional diarrhea group. However, in patients with functional constipation, IgM levels tended to decline, while IgG showed a significant increase, averaging 88.67 ± 4.84 IU/mL compared to 22.0 ± 1.2 IU/mL in the control group, indicating a differential pattern of immune response associated with distinct functional gastrointestinal disorders.

The study of blood humoral immunity factors in patients with gastrointestinal diseases showed a characteristic imbalance in the composition of immunoglobulins (Table 3.2.3).

Table 3.2.3.

Concentration of immunoglobulins in gastrointestinal FD (M ± m)

Blood count	Control group (n=30)	Functional diarrhea (n=32)	Functional constipation (n=31)
IgA (g/l)	3, 1± 0.5	8 , 8± 12 *	1.36±0.17*
IgM (g/l)	2, 2± 0.5	3.5± 0.8	1.91±0.19
Ig G (g/l)	1 4.8 1.0±	21.5 1.0 ±*	88.67±0.43*
IgE (IU/ml)	22.0 ±1.2	25 .0 1.1±	43.07±4.84***

A study in patients with functional constipation reported a significant increase in Ig E - 43.07±4.84 μl - 22.0 ±1.2 μl compared to control values (P <0.001).

Thus, the data obtained indicate that functional diarrhea occurs through the mechanism of a delayed-type allergic reaction. It is characterized by a state of secondary immunodeficiency and the formation of infection against the background of a hyporeactive syndrome with an increase in the process of antibody formation . The lack of CD 8+ lymphocytes contributes to the formation of chronic gastrointestinal diseases with an autoimmune mechanism . A significant increase in the level of CD 23+ lymphocytes indicates allergic sensitivity of the body in chronic gastrointestinal diseases. In this case, depending on the form of FD of the gastrointestinal tract, an imbalance in the content of immunoglobulins is characteristic.

CD20+ lymphocytes are directly involved in specific immune defence reactions of the organism. Comparative characterisation of the content of circulating CD20+ cells showed that in IBS the level of these cells is significantly increased in all groups of observation (P<0.01) compared to the control group. The analysis of absolute values showed that a significantly increased level was observed in the group of patients with IBS +CG-678 ±28.0 in 1 μl of blood (P<0.01). The obtained results allow us to consider that IBS is characterised by activation of the B-cellular

link of the immune system against the background of imbalance in the population of T-lymphocytes.

The soluble form of CD23 molecule on the surface of B-lymphocytes acts as a low-affinity receptor. Under the influence of IL-4 CD23 starts to be produced by B-cells and monocytes in soluble form. The soluble CD23 molecule interacts with the receptor complex of B-cells. In this case through tyrosine kinase lyn into the cell a signal to increase proliferation of IgE+ B-cells and IgE secretion by them is triggered.

The data of our studies showed that in all examined groups of patients the level of relative and absolute values of CD23+-cells was significantly increased (P<0,001). The study of the concentration of the main classes of immunoglobulins G, A and M, as well as immunoglobulin E showed that in IBS there is a multidirectional change in the levels of IgM and IgG.

IgG is the primary antibody of the secondary immune response. The main biological function of immunoglobulins of this class is to protect the organism from infectious agents and products of their vital activity [52]. Being thymus-dependent, IgG are produced only with the obligatory participation of T-lymphocytes.

As can be seen from the above data, the increase of IgA level is not unambiguous in the groups of patients with IBS: the most increased synthesis of IgA occurs in the group of patients with IBS + CHG -128 □ 2.6mg/% (P<0.001). IgM content was characterised by multidirectionality, i.e. decreased synthesis was observed in IBS with CH - 68,0□ 1,3mg/% (P<0,05), and the most increased synthesis was observed in the group of patients with IBS+ CH - 138 □ 4,8mg/% (P<0,001). As it is known, this type of antibodies is produced against infectious agents, activates complement and enhances phagocytosis [52]. Probably, the increased synthesis of IgM in the group of patients with IBS is associated with the accession of the infectious process. Very important properties of IgM are their attraction of phagocytic cells to the site of antigen or infection and activation of phagocytosis. In the immediate hypersensitivity reaction, specific antibodies

(reactants) are detected in the body, which have the ability to sensitise their own tissues - IgE. Its concentration in blood serum in the control group averaged 22.0 □ 1.2mg/ml. In the group of patients with IBS the level of - IgE was significantly increased: 8,2 times in the group of patients with IBS+CHD - 180□21,0mg/ml (P<0,001); 1,59 times in the group of IBS with CHD and JD - 35□ 1,1mg/ml (P<0,001). The concentration of immunoglobulins shows that in food sensitisation of IBS with CG there is a significant increase in the concentration of Ig A and E. For IBS with CGD and JB on the background of microbial sensitisation is characterized by a significant increase in the concentrations of immunoglobulins of class G (P<0.05), and the level of Ig E- tends to increase. In IBS with CX on the background of microbial and parasitic sensitisation there is an increase in the concentration of all classes of immunoglobulins than in the control.

Special attention of researchers is attracted by the class of immunocompetent cells, which performs killer function. It is about natural killer cells - NK-cells (CD16+).

The control group contained natural killer cells (CD16+ cells) in average 16.4±1.0%. The absolute value of this index averaged 182±9.0 in 1 μl (Table 3.2.4).

Table 3.2.4.

Parameters of non-specific defence factors (M+m)

Indicators	Control group n =20	ARD with HG n =18	IBS with XX n =24	IBS with HGD and YAB n =20
CD16+, %	16.4 ±1.0	9.5 ±1.4*	21.4 ±1.8*	18.4 ±0.8
CD16+, abs	182 ± 9.0	187±13.0	221± 7.0*	198 ± 7.0
Fag	48.0 ±1.3	44.5 ±1.6	38.4 ±1.8*	42.7 ±1.3*
CEC	40.0 ±1.5	54.0 ±1.8*	48 ±1.5*	46.0 ±1.4*

The relative content of NK-cells in the bloodstream of patients with IBS with CH was 1.7 times lower than the control group data and averaged 9.5±1.4% (P<0.01). The absolute content of CD16+ B-lymphocytes was almost at the level of control values(P<0,001). In the group of patients with IBS+ XX, the level of relative number of CD16+ B-lymphocytes was elevated 1.3 times and averaged 21.4±1.8% (P<0.01), and the absolute value was elevated 1.2 times -221.0±7.0 in 1 μl. (P<0,001).

The concentration of CD8+-lymphocytes (in %) in the group of IBS patients with CH (P<0.05) has a lower concentration than in the control, and the absolute value of CD16+ B-lymphocytes was higher than in the control.

When studying the nonspecific defence factor, it was revealed that functional phagocyte deficiency was widespread in patients. In the patients with IBS examined by us the percentage of phagocytosis in the group with IBS+CHD and IBS+CHD group was on the average 38,4±1,8% and 42,7±1,3%, which is significantly lower than the values of the control group (P<0,001).

The phagocytic reaction initiates the immune response. Reduced activity of phagocytic defence naturally provides low level of immune response, including humoral, delay of assimilation products, balance disorders and tolerance to autoantigens.

The presence of deficiency of immunocompetent cells reserve, the presence of deficiency of humoral defence determines the risk of accumulation of abnormally high concentrations of CIC.

The study of CIC level showed that in practically healthy people living in Bukhara city the concentration of CIC is 40.0 ± 1.5 u.u. on average. In patients with IBS the level of CIC is significantly higher than the control values in all groups (P<0.01).

It is known that CIC is formed by the interaction of specific antibodies - immunoglobulins formed in the organism with antigens that induced immune response and production of these antibodies. The interaction of specific antibodies

with antigens is the most important mechanism of anti-infectious defence: antibodies neutralise bacterial exotoxins, neutralise extracellular viruses, opsonise bacteria, promoting their phagocytosis and intracellular death. When CICs are formed, the structure and biological activity of the antigen are altered.

At least two sequential processes are required for T-lymphocyte activation. The first signal is provided by binding of MHC-associated peptides to the T-cell receptor. The second activation signal induces IL-2 receptor (CD25) expression on T-lymphocytes, which promotes cell entry into the S-phase of the cell cycle followed by cell replication.

The analysis of the obtained results showed that in IBS there is a significant increase in the expression of activation markers of both early activation - CD25+ cells, and late activation HLA-DR+ cells. Moreover, the level of lymphocytes with receptor to IL-2 was increased 1.43-fold (23±1.3%) ($P<0.05$) in IBS+CHD and JD, 1.37-fold (22.0±1.7%) ($P<0.05$) in IBS+CHD and 1.31-fold (21.1±1.7% (control 16.0 ± 1.4%), (Table 3.2.5.).

Table 3.2.5.

Lymphocyte content with activation marker in examined children (M ±m)

Indicators	Control group n =20	IRC with HG n =18	IBS with XX n =24	IBS with HGD and YAB n =20
CD25, %	16.0 ±1.4	21.1 ±1.7*	22.0 ±1.7*	23 ±1.3*
CD25abs	260 ± 16	345 ± 16*	3 5 5 ± 22*	340 ± 22*
CD95, %	22.0 ±1.0	38.5 ±1.5*	34.5 ±1.2*	30.3 ±0.5*
CD95, abs	380 ± 11	482 ± 21*	400 ± 22	450 ± 25*
HLA-DR $^{+}$,	22.0 ±0.8	32.2 ±1.1*	32.0 ±1.0*	27.6 ±0.5*

%				
HLA - DR , abs	440 ± 11	457± 19	487 ± 13*	461 ± 18

HLA-DR on T-lymphocytes was maximally elevated in CRP+CX -32,0±1,0 % and CRP+CG- 32,2±1,1 % (control 22,0±0,8 %, P < 0,05). Thus, the expression of HLA-DR and CD25 activation markers on lymphocytes of patients was increased compared to that of controls. The increased number of lymphocytes expressing CD25 and HLA-DR antigens indicate the stability of the activation process and the transition to proliferation.

Apoptosis is one of the forms of programmed cell death, which is characterised by DNA damage under the influence of endonuclease. The resulting apoptotic cells undergo phagocytosis. Apaptosis is as important a component of immunological processes as proliferation and differentiation.

The level of lymphocytes with receptor to apoptosis in our studies in all examined groups of patients with IBS is significantly increased. So the maximum rise in their relative number is observed in IBS+CG, where the level is increased 1.75 times and averages 38.5±1.5% (P<0.01), and the level of absolute number is increased 1.26 times - 482 ± 21 in 1 μl (P<0.001).

Cytokines are low molecular weight protein substances produced by activated cells that endogenously regulate intercellular interactions of all parts of the immune system, haematopoiesis, inflammation and intersystem interactions.

Cytokines influence cell survival, growth stimulation, differentiation, functional activity and apoptosis of cells. All cytokines are interconnected and form a complete system with its own regularities: locality, short-distance and rapidity of action, cascade and pleiotropic influences with duplication and overlapping of effects, ability to autocrine and paracrine regulation, multilevel interrelations.

The action of cytokines is closely related to physiological and pathophysiological reactions of the organism. Both local and systemic defence mechanisms are modulated. One of the most important functions of the cytokine system is to ensure the coordinated action of the immune, endocrine, and nervous systems in response to stress.

It is obvious that in case of multidirectional effects of IFNγ and IL-4 in the regulation of the pathological process, the formation of the immune response phenotype will depend on the balance of their production. There is evidence that the ratio of these cytokines can serve as an additional criterion in the differential diagnosis of IBS. In our study, the indicators of cytokine status were characterised by significant diversity (Table 3.2.6.).

Table 3.2.6.

Cytokine status indicators in patients with IBS

Indicators	Control group n =20	IRC with HG n =18	IBS with XX n =24	IBS with HGD and YAB n =20
INFγ	110 ±1. 3	64.5± 2.2 *	7 8.5± 3 , 2*	8 4. 6 ± 2. 8 *
IL-4	2.6 ± 0.6	3.2 ± 0.8	3.7 ± 1.1	3.6± 1.6

In conditions of comorbidity in all groups of observation, haematological parameters of immunogram of patients with IBS showed tendencies to decrease the number of CD3+, CD4+-lymphocytes, absolute values of CD8+-lymphocytes, phagocytosis and INFγ, against the background of increase of B-lymphocytes, proliferation cells, circulating immune complexes (CIC) and IL-4.

Thus, the conducted studies in patients with IBS have shown that one of the functional-metabolic systems of the organism, able to respond quickly and

universally to different endogenous influences, is the immune system. It was found that the majority of patients with IBS have no T-cell reserves, or at least their reserve is significantly reduced. The low content of CD3+-cells indicates a reduction in the reserves of the pool of circulating T-lymphocytes and, therefore, a possible risk of their insufficiency when an intensive immune response is required. The reduction in the content of functionally active T cells naturally affects the content of specialised phenotypes performing helper function. Due to the fact that immunoregulatory T- and B-cells play an important role in the integration of immunity, the balance of all immunological functions, disturbance in this link of immunogenesis in IBS, expressed in either direction - enhancement or suppression - apparently, are an essential component of the mechanism of immunological insufficiency development.

Analysis of the results of the obtained data of patients with IBS revealed multidirectional changes in the number of NK-cells. Undoubtedly, the decrease or increase in their number can have a negative effect and, in all probability, is one of the pathogenetic factors in hypersensitivity. As is known, NK cells play an important role in the defence of the organism and their changes in one side or the other, apparently, are explained by several reasons: partial immunodeficiency, insufficient production of non-toxic antibodies that block the activity of immunocompetent cells.

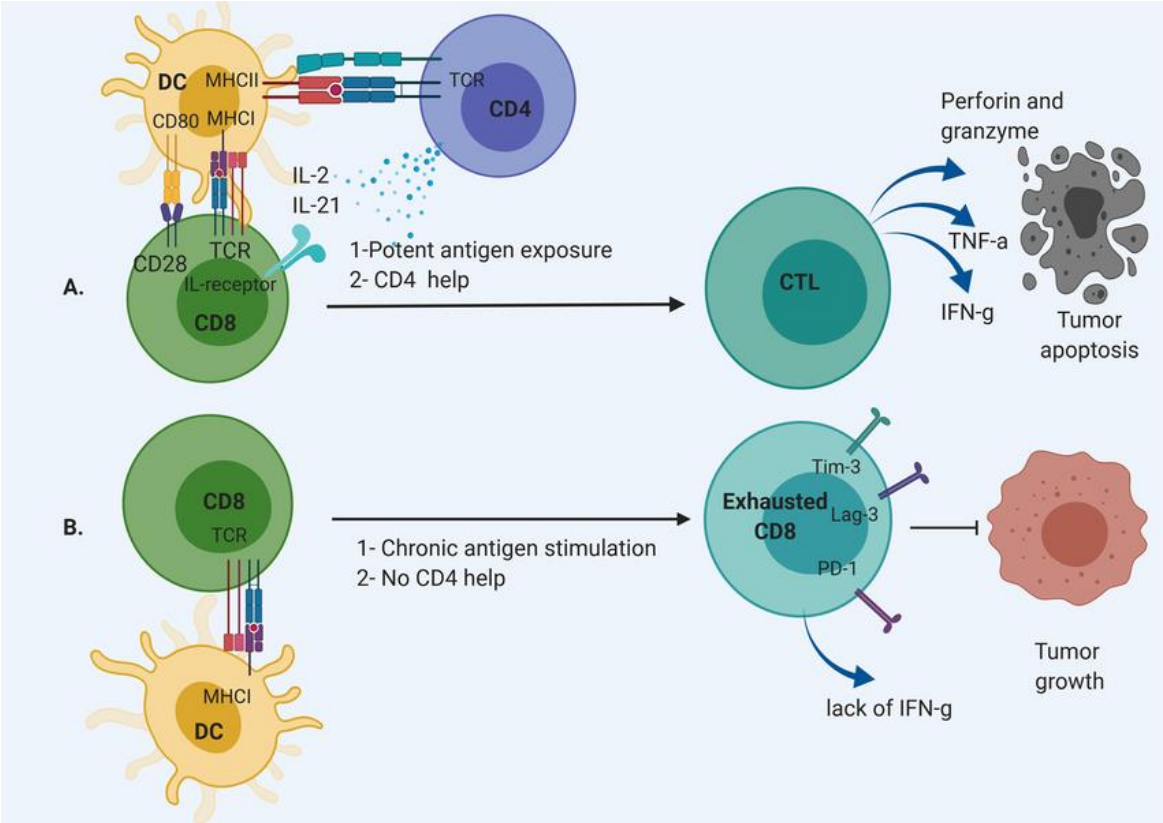
In the development of the immune response immunoglobulins have an important function of mediators that determine the effector reactions of cellular immunity to inactivate and eliminate bacterial, viral and fungal antigens. Immunoglobulins activate immunocompetent cells involved in the implementation of inflammation processes, thereby increasing the efficiency of immune phagocytosis. Immunoglobulins trigger the classical pathway of activation of the complement system, thus contributing to the elimination and dissociation of pathological immune complexes.

A pronounced increase in circulating immune complexes (CIC) is a reflection of the tension of immune processes in patients with IBS. Antigen-antibody complexes are the result of a dynamic process, constantly occurring in the body (Picture – 10).

All allergens that induce antibody synthesis actually serve as inducers of CIC formation, which is a component of the normal immune response of the organism.

In the phagocytic immune system, the patients examined showed quantitative changes, which consisted of a decrease in the number of major phagocytic cells: neutrophils and monocytes. In addition to phagocytosis, macrophages perform an important function: they present foreign antigenic determinants in complex with their HLA-DR antigens to T- and B-lymphocytes. This initiates the development of both cellular and humoral immune responses. Allergic reactions disrupt this function of monocytes/macrophages, leading to a significant change in the expression of HLA-DR and HLA-DQ antigens on these cells, resulting in a reduced ability of the body to develop a specific immune response.

Recognition of antigenic epitopes by lymphocytes and signal exchange with other immune system cells are conditions for the activation of lymphocytes — a process upon which almost all immunological reactions and immune responses are based. The essence of activation is the transition of the cell to a state that is associated with performing functions and displaying specific cell activity. An increase in the number of CD25+ lymphocytes indicates greater sensitivity of lymphocytes to the action of the corresponding cytokine, which acts as a growth factor for T-cells and promotes the proliferation of NK cells. It should be noted that IL-2 expression occurs in parallel with cell activation and protects it from apoptosis. If lymphocytes do not receive the full “set” of activating signals in pathology, they undergo so-called “activation” apoptosis, which develops as a result of the imbalance of activation signals.



Pic.10 *The effect of dendritic cells on CD8 cells and its type A(CD4 cells are involved) and B (CD4 cells are not involved in the process).*

Currently, some of the main causes of immune deficiency states are becoming clearer. One such cause is a disruption in immunoregulatory processes in the body under the influence of various agents, mediated by Th1- and Th2-helper cells. As known, Th1 cells synthesize cytokines that stimulate cellular immunity (IL-1, 2, 6, 8, 12, IFN, TNF, etc.), while Th2 cells synthesize cytokines that stimulate humoral immunity (IL-4, 5, 10, transforming growth factor-beta, etc.). In a normally functioning body, there is a certain balance of interaction between Th1 and Th2 helpers. However, significant changes in their activity under the influence of any factors can lead to serious adverse consequences for the functioning of the immune system as a whole.

It has been established that allergic diseases cause activation of Th2-helper cells and the synthesis of cytokines that have a suppressive effect on cellular immunity. The cytotoxic mechanism of injury is triggered, which is related to T-

killers. The IgE response is induced by the interaction of T-cells and antigen-presenting cells, leading to the stimulation of IL-4 production and simultaneously suppressing the secretion of interferon-gamma (IFNγ), which shifts activated IgM-bearing B-cells to the synthesis of IgE. At the same time, IL-4 increases the expression of the CD23 molecule, which is a low-affinity receptor for IgE. The elevated level of IL-4 in patients with IBS correlates with the level of hyperreactivity. IFNγ, on the other hand, stimulates the proliferation of Th1-type helpers, and it is believed that an increase in IFNγ levels can reduce the activity of the inflammatory process. The systemic levels of IL-4 and IFNγ in the serum of patients with IBS reflect the course of the disease, and during exacerbations, an imbalance in the levels of these cytokines is observed.

It is widely accepted that the determination of the total IgE level in serum has diagnostic and prognostic value in allergic diseases. IgE is primarily synthesized by plasma cells located in mucous membranes. Therefore, a normal level of IgE in peripheral blood serum does not exclude the involvement of IgE-dependent mechanisms in the disease, as local IgE synthesis and mast cell sensitization can occur even in the absence of IgE in the bloodstream. In some patients with classical IgE-associated pathology, there may be no systemic elevation of IgE levels. However, an increase in the total IgE concentration in these patients can be observed in bronchoalveolar lavage fluid, nasal secretions, and induced sputum.

Therefore, our results indicate disruptions in metabolic processes and pronounced immunological shifts that contribute to the development of complications in immediate hypersensitivity reactions.

RESEARCH RESULTS

Numerous studies conducted in different regions of the world and covering different age groups of the population have shown that in recent decades the problem of functional disorders of the gastrointestinal system in children has acquired the scale of a global medical and social problem. However, despite significant progress in the field of gastroenterology and pediatrics, the pathogenesis of functional disorders is only partially explained [21].

From 30 to 90% of the world's population is intolerant to one or more foods. However, the allergy they cause is true only in 4-5% of children and 2-3% of adults. 80% of people have hidden food intolerance to some foods, chemicals, environmental pollutants, etc. Gastrointestinal FD is often found in patients with atopic diseases, as well as pathologies of the digestive tract and hepatobiliary system [19] .

A number of studies have shown that the inflammatory process in the gastrointestinal tract associated with risk factors can be the cause of organic pathology of the gastrointestinal tract, which, according to various sources, is combined with metabolic disorders in 47% of cases, in 50. % with immunological disorders, in 12-20% with endocrine diseases

Work was carried out at the clinical base of the Bukhara State Medical Institute - the regional children's multidisciplinary medical center.

To study the frequency of gastrointestinal FD in children, the medical history of children admitted to the Bukhara Regional Children's Multidisciplinary Medical Center in 2021-2023 was used .

The results of a retrospective study showed that 3,150 children were hospitalized with gastrointestinal diseases between 2021 and 2023. At the same time, the average prevalence of gastrointestinal diseases is 2.17 per 1,000 children under the age of 18.

Among all patients hospitalized with gastrointestinal diseases, 439 patients had gastrointestinal FD, which is an average of -13.9%. The incidence of gastrointestinal FD for 2023 is 48.8%, which indicates an increase in dynamics and serves as the basis for studying the mechanisms of its development.

The overall frequency (prevalence) of gastrointestinal diseases was found to be 35.5% of all gastrointestinal pathologies in children under 18 years of age.

The distribution of sick children hospitalized with gastrointestinal infarction revealed a higher number of boys - 233 (53%) than girls - 206 (47%). Analysis by age showed that young children aged 1 to 3 years were more often hospitalized - 221 (50.4%).

The study of the anamnesis made it possible to identify the causes of gastrointestinal reflux in children. It is of interest to identify the causes of FD of the gastrointestinal tract, including comorbid forms in children. Given the presence of contraindications to invasive diagnostic procedures during an exacerbation of the disease and limited possibilities, in order to identify possible causative factors of functional disorders, we limited ourselves to collecting a complete anamnesis and identifying the relationship between the development of the disease and previous diseases. The study of the anamnesis made it possible to identify the causes of gastrointestinal allergies in children with digestive disorders in the gastrointestinal tract.

The identified provoking food products, for example, cow's milk - 12.2%, chicken and quail eggs - 10.3%, citrus fruits - 9.0%, allow us to characterize the regional characteristics of the causative structures of allergies in children aged 1 to 3 years. It should be noted that in the study there was a combined sensitization to several food products, and patients with polysensitization to food products amounted to 44 (28.0%).

The clinical form of FD manifestations of the gastrointestinal tract was diverse. Functional diarrhea dominated its structure. 166 (60.6%) of all hospitalized patients had concomitant gastrointestinal disease (Table 2.1.6), which affected the

course of the underlying disease. Clinically, functional gastrointestinal diseases are most often manifested in the form of functional constipation - 43.3% and functional diarrhea - 56.7%, anemia (46.6%) and gastrointestinal allergies (35.5%).

Among all identified concomitant pathologies, anemia prevails - 41 (15.4%), helminthiasis - 36 (13.5%), and gastrointestinal allergies - 156 (58.6%).

Consequently, the established data confirm the need for an individual approach to the diagnosis and management of this category of patients.

A prospective study was conducted at the Children's Medical Center in 2023. We selected a total of 63 pediatric patients with gastrointestinal reflux who were hospitalized at the BRMMC. The study cohort included 63 children aged 1 to 3 years, of whom 38 (60.3%) were boys and 25 (39.7%) were girls. The control group consisted of 30 age-matched healthy children, including 11 children (6 girls and 5 boys) and 19 children (7 girls and 12 boys), also within the 1 to 3-year age range.

Data collection was conducted using a structured questionnaire developed by the research team. The instrument comprised five sections: (1) passport and demographic data; (2) the child’s condition during the interview, as reported by the mother (including 33 questions); (3) parental background information (10 questions); (4) maternal responses to 27 targeted questions; and (5) survey findings and additional relevant information.

Diagnosis of the underlying condition was established based on a comprehensive review of the patient’s medical history and consultations with appropriate specialists. Information for the questionnaire was obtained from maternal reports, clinical examination, and laboratory investigations. The assessment included evaluation of the patient’s medical and perinatal history, breastfeeding practices, potential etiological and exacerbating factors, living conditions, and associated diagnoses.

Diagnostic criteria were aligned with the Rome IV Criteria (2016 revision) and classifications outlined in the International Classification of Diseases, 10th Revision (ICD-10). In each case, special attention was given to identifying

precipitating factors contributing to symptom manifestation, including genetic predisposition, previous intestinal infections, allergic conditions, parental habits, dietary patterns, psychosocial stressors, environmental exposures, and comorbid conditions.

Depending on the form of gastrointestinal FD, sick children are divided into 2 groups:

Group 1: 32 children with functional diarrhea;

Group 2: 31 pediatric patients with functional constipation.

It is noteworthy that in all age groups studied, the number of boys prevails over the total number of children by gender. As you can see, this pattern is very difficult to explain, the reason for which lies in the biological sexual characteristics of the child's body, which are still incomprehensible to us.

Interpretation In our study, for the first time in the literature, we identified several risk factors for the development of FGIDs in infants and toddlers using two different methodological approaches: conventional statistics and ML converged in identifying some potential risk factors, while diverged for other variables. Additionally, we developed a ML predictive model (FRIP) for the early diagnosis of FGIDs in children. Healthcare practitioners can input patient data into designated fields, and the interface processes this information through logistic regression models. The output is a set of risk coefficients, each corresponding to one of the three conditions, representing the likelihood of a patient developing a particular condition. This assists healthcare providers in making informed decisions about diagnosis, prevention, and treatment strategies.

The prediction score results indicate the probability (as a percentage) of the occurrence of one of the three disorders. Notably, instead of providing exact values for each risk factor, the result is generated by an equation that integrates all the factors. Traditional statistics evaluate the significance of each observed variable in relation to a disease. In this study, we utilized AI tools for feature selection to identify the minimum number of variables required for accurate prediction,

evaluating their combined influence on overall disease occurrence (e.g., colic). Specifically, we found that only three variables are needed to reliably predict the risk score, and these variables can thus be considered risk factors. According to our dataset, birth weight emerged as the main risk factor based on statistical analysis, while the trained AI model identified cord blood pH and maternal age as important variables for risk prediction.

Accurate identification of early life events is crucial for identifying children at risk of developing FGIDs, enabling timely intervention and improving the quality of life for both children and their families. However, the absence of a universally accepted gold standard often leads to overestimation or underestimation of potential early-life risk factors.

In our study population, the incidence of colic was 27.3 %, regurgitation 18.7 %, and constipation 10.2 %. In the preterm infant subgroup, the incidence was significantly higher at 38.1 %, 35.8 %, and 21.6 %, respectively, compared to term infants. The incidence of FGIDs has been reported with wide variability across different studies. This variability can be attributed to differences in diagnostic criteria and poor population stratification.

For instance, a cross-sectional Brazilian study evaluating FGIDs in the first two years of life found no significant difference between preterm and term infants.

However, a separate study from Türkiye reported a higher prevalence of regurgitation, infantile colic, and dyschezia in preterm infants during the first 12 months compared to term infant.

The perinatal period, during which the brain-gut-microbiota axis matures, is critical as various determinants during this time can have significant long-term consequences. Preterm infants are at high risk of both gastrointestinal and brain maturation impairments due to intrinsic immaturity and their unique developmental environment, including impaired gut microbiota assembly. These factors likely contribute to the development of FGIDs.

Our results indicate that low venous cord blood pH is a risk factor for FGIDs, confirming previous findings. Umbilical cord pH serves as a marker of neonatal metabolic and oxygenation status at birth, with low pH levels (acidosis) indicating potential fetal distress. While the link between neonatal acidemia and neurological problems is well established, there is limited information on the impact of low venous cord blood pH on gastrointestinal diseases. We speculate that this condition may disrupt gastrointestinal development, alter gut microbiota, and affect the enteric nervous system, increasing the risk of FGIDs. Hypoxia–ischemia and reperfusion in the brain are known to trigger harmful events leading to neuronal death, while in the gastrointestinal tract, hypoxia increases TLR4 expression in the intestinal mucosa, causing an imbalance between pro-inflammatory and anti-inflammatory signals, thereby increasing mucosal susceptibility to harmful stimuli. These findings suggest that increased monitoring of infants with low venous cord blood pH at birth could be beneficial, potentially allowing for early detection of an increased risk of FGIDs during the first year of life.

Finally, maternal age further contributes to this risk, as younger mothers may face higher rates of pregnancy complications or stress, while older mothers are more likely to experience conditions such as gestational diabetes or hypertension, which can impact fetal development. Additionally, maternal microbiota changes associated with age may influence neonatal gut health during delivery, highlighting the multifactorial nature of FGID risk.

It should be noted that the frequency of gastrointestinal diseases in this age group can be explained both by the anatomical, physiological and pathomorphological local and general characteristics of the body, and by the expansion of the nutritional spectrum.

62% of children with gastroesophageal reflux disease live in urban areas. Analysis of the frequency by place of residence and gender showed a predominance in boys permanently residing in the city.

In our study, we surveyed parents using a questionnaire we developed and general clinical research to develop a predictive scale for the formation of gastrointestinal risk factors in young children.

85 patients with functional constipation , 85 patients with functional diarrhea , and 170 children with no gastrointestinal symptoms were selected. All selected patients underwent general clinical, laboratory, functional, and biochemical examinations.

In order to develop an optimal method for assessing risk factors for the development of complications of functional constipation in children with the subsequent decision on the tactics of treating the patient, we carefully analyzed the results of research that should be used in the diagnosis of gastrointestinal diseases.

The groups of patients selected for the study were divided according to the main clinical, laboratory and functional indicators . A four-field prognostic table was constructed to determine the risk of developing gastrointestinal FD and determine patient management tactics.

A total of 15 features were studied and calculated using Excel . Relative risk (RR) with 95% confidence interval was studied to comparatively assess the reliability, sensitivity and specificity of the effect of the risk factor on the formation of gastrointestinal risk factors in children .

As a result of the calculation, the following was determined:

- The risk of functional diarrhea increases by 3.2-3.7 times in children with lymphatic-hypoplastic constitutional anomalies and irrational introduction of complementary foods ;
- The RR for the development of functional constipation in children with intrauterine growth retardation, hereditary predisposition to gastrointestinal risk factors and perinatal damage to the central nervous system is 1.9-2.9 times higher than in others ;
- The risk of developing functional diarrhea in children born prematurely, with exudative-catarrhal constitutional anomalies, food allergies,

nutritional risk factors, and behavioral disorders of various etiologies is 1.4 -1.6 times higher than in others;

- The risk of developing functional diarrhea is also 1.2-1.3 times higher in children with acute intestinal infections, who are on artificial and mixed feeding, and who often suffer from acute respiratory infections.

Consequently, the obtained statistically significant data allow us to determine the tactics of managing children with functional diseases of the gastrointestinal tract. Why is it necessary to develop an effective program to prevent the transformation of gastrointestinal RF into organic pathology in young children?

In order to study the immune parameters in gastrointestinal diseases in children, 63 children aged 1 to 3 years, who were undergoing inpatient examination and treatment at the Children's Medical Center, underwent a medical examination. The patients were divided into 2 groups: 32 with functional diarrhea and 31 with functional constipation. All patients were examined for general, biochemical and ELISA blood tests, and immunological research methods were performed.

Among the examined boys - 24 (38.1%), girls - 39 (61.9%), aged 1 to 3 years. Analysis of morbidity and hospitalization by place of residence showed that children living in the city were hospitalized more often - 39 (61.9%).

Immunological blood tests were performed on children with gastrointestinal infarction to study immune status.

The concentration of CD 3+ and CD 4+ lymphocytes in both observation groups showed significant changes compared to the cut-off values of the control group.

As for the absolute concentration, a significant reverse change is observed: a decrease in functional diarrhea to 675.0 ± 23.0 μl and 435 ± 32 μl, compared to the control - 780.0 ± ±27.0 ($P < 0.05$) and an increase in CD. With functional constipation, CD 3+ lymphocytes increased 1.7 times (up to 1325.6 ± 90.03 μl ±) and CD 4+ lymphocytes 1.3 times (up to 658.63 ± 44.78 μl) ($P < 0.05$).

It is characterized by a decrease in the relative and absolute number of CD 3+ and CD 4+ lymphocytes, as well as a decrease in the relative number of CD 8+ lymphocytes against the background of an unreliable increase in the activity of killer cells (CD 16+) .

CD3 + lymphocytes are known to be involved in delayed-type allergic reactions [18] . Decreased concentrations of CD3 + and CD4 + lymphocytes observed in studies indicate the presence of infections and secondary immunodeficiency states.

Immunological blood tests in children with functional constipation revealed a significant increase in the absolute values of CD 3+ CD 4+ CD 8+ lymphocytes , with a tendency to decrease in CD 16+ lymphocytes.

An increase in the absolute concentration of CD 3+ CD 4+ CD 8+ lymphocytes indicates the acute phase of allergy and stimulation of the immune system in response to an allergen (antigen) or infection, which confirms the formation of hyperreactive syndromes.

CD8 + lymphocytes , a decrease in their relative number was found regardless of the form of the disease .

In our studies, the detected deficiency of CD8 + T cells in functional diarrhea is significant in terms of their absolute concentration - 238 ± 12.0 μl compared to the control - 372 ± 13.0 μl ($P < 0.05$), which confirms the presence and/or the formation of chronic gastrointestinal diseases through impaired control of CD8 + T-cell infections, as a result of which there is a high risk of developing an autoimmune mechanism.

Differential Diagnoses and Comorbid Considerations. Obtaining a comprehensive history and physical is paramount in the diagnosis of GNDs and helps guide the evaluation, which usually includes endoscopy and imaging. Age- and gender-appropriate investigations must also be undertaken. For example, providers may recommend pelvic ultrasound for a woman of any age with early satiety, bloating, and abdominal pain to exclude an ovarian lesion in the appropriate clinical setting.

After the exclusion of structural and organic causes of symptoms, additional disorders of gut–brain interaction can be considered. Chronic nausea vomiting syndrome (CNVS) is defined by Rome IV Criteria as bothersome nausea and/or vomiting occurring at least once per week for the last 3 months with initial symptoms occurring at least 6 months prior to diagnosis, in the absence of organic causes. The shared symptomatology with gastroparesis suggests that underlying mechanisms may be at play. Cyclic vomiting syndrome (CVS) is characterized by acute episodes of intractable vomiting with intervening periods of normalcy and is associated with a personal or family history of migraine. It is notable that 36% of patients with gastroparesis have overlapping diagnoses of CVS. Cannabis hyperemesis syndrome (CHS) is similar in presentation but preceded by prolonged (often daily, heavy) cannabis use and resolves with sustained cannabis cessation. CHS is well known for alleviation of symptoms with a hot shower, but this can be seen in CVS as well and does not reliably distinguish the two entities. Rumination syndrome involves persistent regurgitation of recently ingested food to the mouth followed by spitting or remastication and swallowing, in the absence of retching. The diagnosis is primarily made by history, but the diagnosis can be confirmed through characteristic esophageal manometry findings. Lastly, patients with gastroparesis-like symptoms frequently have symptoms of food intake disorders such as avoidant restricted food intake disorder (ARFID). It is important to evaluate for these conditions and refer patients for treatment if such symptoms are present.

B lymphocytes can develop an adequate immune response only with the help of T helper cells. In the group of patients with functional diarrhea , the level of B lymphocytes was found to be significantly higher than the control values of 28.8 ± 1.2 mg% ±- 25.4 ± ±0.8 mg% ($P < 0.05$). There was also a significant increase in the relative and absolute levels of CD 23+ cells - 12.2 ±± 0.8 mg% and ±165 ± 5.0 μl compared to the control - 9.4 ± 0.3 mg% and 145 ±± 3.0 μl, respectively .±

There is a significant decrease in the relative level of CD 20+ lymphocytes - 18.17±0.99 mg% compared to control - 25.4 ±0.8 mg% ($P <0.05$) and an increase

in CD 23+ lymphocytes - 19 .47 ±0.77 mg% compared to control - 9.4 ±0.3 mg% (P <0.001).

There is evidence that B cells are a component of the humoral response in adaptive immunity, secreting antibodies and acting as antigen-presenting cells. They have an anti-inflammatory phenotype and have a high proliferative capacity .

Taking into account the above, the increase in CD 23+ lymphocytes confirms the acute phase of the inflammatory process. In a study conducted in patients with functional constipation, a significant increase in Ig G was noted - 88.67±4.84 µl - 22.0 ±1.2 µl compared to control values (P <0.001).

An indispensable indicator of the functional activity of B-lymphocytes is the content of immunoglobulins of the main classes (G, A, M).

Analysis of blood test results in patients with functional diarrhea showed a significant increase in Ig A- 8.8 ±1.2 g/l compared to 3.1 ±0.5 g/l in controls and Ig G- 21.5 ±1.0 g/l compared to 14.8 1.0 ±g/l in controls (P < 0.05).

As for IgM , its concentration had a tendency to increase insignificantly compared to the control with functional diarrhea, and, conversely, with constipation, a tendency to decrease was observed against the background of a significant increase in the level of IgG. -88.67±4.84 IU/ml compared to -22.0 ±±1.2 IU /ml in the control .

Thus, the data obtained indicate that functional diarrhea occurs through the mechanism of a delayed allergic reaction. It is characterized by a state of secondary immunodeficiency and the formation of infection against the background of a hyporeactive syndrome with an increase in the process of antibody formation . The lack of CD 8+ lymphocytes contributes to the formation of chronic gastrointestinal diseases with an autoimmune mechanism . A significant increase in the level of CD 23+ lymphocytes indicates allergic sensitivity of the body in chronic gastrointestinal diseases. In this case, an imbalance in the composition of immunoglobulins is characteristic, depending on the form of FD of the gastrointestinal tract. The results

of immunological studies of children with gastrointestinal infarction have shown the need to introduce new concepts in the management of patients in this population.

CONCLUSIONS

Generally, according to the results of a retrospective analysis for 2021-2024, the overall incidence of functional disorders of the gastrointestinal tract in children under 18 years of age is 35.5% of all gastrointestinal pathologies. Most often, young children aged 1 to 3 years are affected (40.6%). Clinically, functional diseases of the gastrointestinal tract are most often manifested in the form of functional constipation - 43.3% and functional diarrhea - 56.7%, anemia (46.6%) and gastrointestinal allergies (35.5%). As a result of the calculation, it was found that anemia of various etiologies, lymphatic-hypoplastic anomalies of the constitution and the unjustified introduction of complementary therapies . foods, the risk of functional diarrhea increases by 3.2 -3.7 times. CD 3+ lymphocytes was detected by 1.7 times ($P < 0.01$), CD 4+ lymphocytes decreased by 1.3 times ($P < 0.01$), a significant decrease in the concentration of IgA and IgG ($P < 0.05$), a 4-fold increase in Ig E ($P < 0.001$) for functional diarrhea . A deficiency of CD8+ T cells was detected in functional constipation ($P<0.05$), which confirms the presence and/or formation of chronic diseases of the gastrointestinal tract, with a high risk of developing an autoimmune mechanism.

For early identification of children at risk and diagnosis of functional gastrointestinal diseases, it is necessary to introduce into practice a scale and questionnaire of predictors of the formation of gastrointestinal risk factors. Children at risk are advised to have their immune status examined to prevent the disease from progressing to organic pathology. For children with established immunological imbalances, comprehensive treatment with analysis of the immune status over time by an immunologist and gastroenterologist is recommended.

Case-based questions related to the topic:

1. **An 8-year-old boy fell ill acutely: he presents with fever, weakness, headache, abdominal pain, recurrent vomiting, then diarrhea and tenesmus. Stools occur 12 times daily, are scanty, contain a lot of mucus, pus, streaks of blood. His sigmoid gut is tender and hardened. What is your diagnosis?**

   A. Dysentery

   B. Cholera

   C. Escherichiosis

   D. Staphylococcal gastroenteritis

   E. Salmonellosis

2. **A mother consulted a pediatrician about her son. Her son was born with body mass of 3 kg and length of 48 cm. He is 1 year old now. What is the required normal mass?**

   A. 10,5 kg

   B. 9,0 kg

   C. 12,0 kg

   D. 15,0 kg

   E. 11,0 kg

3. **6 m.o. infant was born with bodys mass 3 kg and length 50 cm. He is given natural feeding. How many times per day the infant should be fed?**

   A. 5

   B. 4

   C. 6

   D. 7

   E. 8

4. **Infant is 6,5 months now and is given natural feeding since birth. Body mass was 3,5 kg, with length 52 cm at birth. How many times per day the**

supplement (up feeding) should be given?

A. 2

B. 1

C. 4

D. 0

E. 3

5. **A 2 month old healthy infant with good appetite is given artificial feeding since he turned 1 month old. When is it recommended to start the corrective**
feeding (fruit juice)?

A. 4,0 months

B. 2,0 months

C. 1,5 months

D. 3,0 months

E. 1,0 months

6. **A 12 year old child has the ulcer disease of stomach. What is the etiology of this disease?**

A. Intestinal bacillus

B. Influenza

C. Salmonella

D. Helicobacter pylory

E. Lambliosis

7. **A 10 month old boy has been ill for 5 days after consumption of unboiled milk. Body temperature is 38-39°C, there is vomiting, liquid stool. The child is pale and inert. His tongue is covered with white deposition. Heart sounds are muffled. Abdomen is swollen, there is borborygmus in the region of ubbilicus, liver is enlarged by 3 cm. Stool is liquid, dark-green, with admixtures of mucus, 5 times a day. What is the most probable diagnosis?**

A. Salmonellosis

B. Acute shigellosis

C. Rotaviral infection

D. Staphylococcal enteric infection

E. Escherichiosis

8. **A child is 7 months old. Birth weight was 3450, the child is breastfed. Supplemental feeding was introduced on time. Determine the daily protein requirements for the child:**

A. 3,0 g/kg

B. 2,0 g/kg

C. 3,5 g/kg

D. 4,0 g/kg

E. 2,5 g/kg

9. **A full-term baby was born with body weight of 3200 g, body length of 50 cm, Apgar score - 8-10 points. What is the optimum time for the first breast-feeding?**

A. First 30 minutes

B. First 6 hours

C. First 48 hours

D. After 48 hours

E. First 24 hours

10. **A 6-year-old child has duodenal ulcer. What antibacterial drug should be co-administered together with metronidazole and De-Nol in order to eradicate Helicobacter pylori infection?**

A. Amoxicillin

B. Oleandomycin

C. Sulfadimethoxinum

D. Biseptol

E. Tetracycline

11. **Which of the following is the most common functional gastrointestinal disorder in children?**

    A. Peptic ulcer disease

    B. Functional abdominal pain

    C. Celiac disease

    D. Gastroesophageal reflux disease

12. **Which Rome IV criteria is essential for diagnosing functional constipation in children?**

    A. Presence of blood in stool

    B. Defecation frequency <2 per week

    C. Abdominal pain relieved by defecation

    D. Growth retardation

13. **Infant colic is typically characterized by crying episodes that occur for more than:**

    A. 1 hour/day for 3 days/week

    B. 2 hours/day for 2 days/week

    C. 3 hours/day for 3 days/week

    D. 4 hours/day for 1 week

14. **Functional abdominal pain in children is usually associated with:**

    A. Organic gastrointestinal disease

    B. Night-time awakening due to pain

    C. Normal physical examination and lab findings

    D. Bloody diarrhea

15. **Which of the following is NOT typically considered a functional gastrointestinal disorder in children?**

    A. Irritable bowel syndrome

    B. Functional dyspepsia

C. Appendicitis

D. Cyclic vomiting syndrome

Case-based questions related to the topic:

1. **An 11-year-old girl, sick for 1 year. Complaints of 'hungry' pain in the epigastrium, appearing in the morning on an empty stomach, 1.5-2 hours after eating, at night, relieved by food intake. Concerns 'sour' belching, stools are regular and regular. First visit to the doctor a week ago, after an outpatient EFGDS, she was hospitalised.**

Family history: the child's mother has duodenal ulcer, father has gastritis, maternal grandmother has duodenal ulcer.

She studies in a special school 6 days a week, does choreography 3 times a week. By character intravert.

On examination: skin is pale pink, clean. Abdomen: Mendel's syndrome positive, painfulness in the point of Desjardins and Meyo-Robson, in epigastrium at superficial and deep palpation - small muscle defans, at deep palpation - painfulness in epigastrium and pyloroduodenal area. The liver is not enlarged. No pathology in other organs.

General blood analysis: HGB - 120 g/l, RBC - 4,3*1012/l, MCV - 75 fl, MCH - 26 pg, MCHC - 27 g/l, RDW - 3,5%, PLT – 217*109/l, WBC - 7,4*109/l, E - 2%, P - 1%, C -52%, L - 40%, M - 5%, COE - 11 mm/h.

General urinalysis: KPO - NEG, BNL - NEG, YRO - NORM, KET - NEG, BEL - NEG, NIT - NEG, GLU - NEG, pH. - 5.0, U.V = 1017, LEI - 2-1-2 in p/zr, ASC - 2 mg/dl, COL LT - Yellow, CLA Clear.

Biochemical blood tests: total protein - 72 g/l, AlAT - 19 U/l, AsAT - 24 U/l, ALP - 138 U/l (norm 107-213 U/l), amylase - 100 U/l (norm 28-100 U/l), thymol test - 4 units, bilirubin - 15 μmol/l, of which lig. - 3 μmol/l.

Esophagogastroduodenoscopy: oesophageal mucosa is pink, cardia is closed. In the stomach turbid mucus, mucosa with focal hyperaemia, in the antrum there are multiple multiscale bulges on the walls. Duodenum bulb mucosa - focally hyperaemic, edematous, on the posterior wall ulcerous defect 0,8x0,6 cm, round in shape with hyperaemic roll, the bottom is covered with fibrin. A biopsy was taken.

Ultrasound of abdominal cavity organs: liver was not enlarged, parenchyma was homogeneous, echogenicity was not changed, vascular network was not dilated. Gallbladder is pear-shaped 55x21 mm with a bend in the bottom area, its content is homogeneous, wall thickness is 1 mm. The stomach has a large amount of heterogeneous content, its walls are thickened. Pancreas: head 21 mm (normal 18), body 15 mm (normal 15), tail 22 mm (normal 18), echogenicity of the head and tail is reduced.

Gastric acidometry: on empty stomach - pH in the body 2.4; in the antrum 4.2; 30 minutes after stimulation with 0.1% histamine solution at a dose of 0.008 mg/kg - pH in the body 0.9; in the antrum 2.8.

Respiratory urease test: positive.

Biopsy test for HP infection: positive (++).

1. Formulate the clinical diagnosis and its justification.
2. Etiopathogenesis of the disease.
3. Epidemiology of Helicobacter infection and ways of its transmission.
4. List the main methods and ways of diagnostics of HP-infection.
5. What is the essence of the breath test?
6. Assess the acid-forming function of the stomach.
7. Evaluate the ultrasound picture, what is the informativeness of ultrasound for diagnosis?
8. Prescribe treatment for this patient.

2. **A 12-year-old girl complains of dull, aching abdominal pain, occurring 30-45 minutes after eating, as well as weakness, rapid fatigue, frequent headaches. The above complaints first appeared 6 months ago, but no examination or treatment was carried out.**

Life history: since the age of 10 she has been on the dispensary registration with a neurologist for vegeto-vascular dystonia.

Family history: mother suffers from duodenal ulcer. Father - chronic gastroduodenitis.

On examination: the skin is pale, moderately moist. On the part of the lungs and heart without pathology. The abdomen is enlarged. At superficial and deep palpation in the right subcostal area and in the epigastrium there is painfulness. The liver protrudes from under the edge of the rib arch by 1.5 cm. The edge of the liver is soft, elastic, painless. Ortner-Grekov's symptom (+). Stools are regular and regular. Urination is not disturbed.

General blood analysis: HGB - 125 g/l, RBC - 4,2*1012/l, MCV - 75 fl, MCH - 26 pg, MCHC - 27 g/l, RDW - 3,5%, PLT – 217*109/l, WBC - 7,8*109/l, E - 3%, P - 1%, C -54%, L - 33%, M - 4%, COE - 9 mm/h.

General urinalysis: KPO - NEG, BNL - NEG, YRO - NORM, KET - NEG, BEL - NEG, NIT - NEG, GLU - NEG, pH. - 5.7, U.V = 1017, LEI - 2-3 in p/zr, ASC - 2 mg/dl, COL LT - Yellow, CLA Clear.

Biochemical blood tests: total protein - 79 g/l, AlAT - 30 U/l, AsAT - 40 U/l, alkaline phosphate - 150 U/l (norm 70-140), amylase - 78 U/l (norm 12-110 U/l), thymol test - 4 units, bilirubin - 17 μmol; of which lig. - 3 μmol/l.

Urine diastase: 32 units.

Ultrasound of abdominal cavity organs: liver - contours smooth, parenchyma homogeneous, echogenicity increased, vasculature not dilated, portal vein not changed. Gall bladder 85x37 mm (norm 75x30), the walls are not

thickened. Choledochus up to 3.5 mm (norm 4), the walls are not thickened. After choleretic breakfast - gallbladder shrank by 10%.

1. Formulate the clinical diagnosis.
2. Name the etiopathogenetic causes of this disease.
3. Make a differential diagnosis of different types of biliary dyskinesia.
4. How to evaluate the function of the gallbladder after giving a choleretic breakfast?
5. Prescribe treatment for this child.
6. Prognosis of the disease

3. **A 12-year-old girl complains of abdominal pain for 2 years, stabbing, localised in the left subcostal region and epigastrium, occurring 20-25 minutes after meals. She does not follow diet and nutrition regime**.

Family history. Mother has chronic gastritis, father - duodenal ulcer, grandmother (maternal) - gastritis.

On examination: the skin is clean, pale pink. The abdomen is not enlarged, at superficial and deep palpation in epigastrium and pyloroduodenal region there is muscle tension and painfulness, positive Mendel's and Meyo-Robson's symptoms. Liver at the edge of the rib arch, other organs without pathology.

General blood analysis: HGB - 130 g/l, RBC - 4,5□1012/l, MCV - 75 fl, MCH - 26 pg, MCHC - 27 g/l, RDW - 3,5%, PLT - 215□109/l, WBC - 6,0□109/l, E - 0%, P - 2%, C -62%, L - 29%, M - 7%, COE - 7 mm/h.

General urinalysis: KPO - NEG, BNL - NEG, YRO - NORM, KET - NEG, BEL - NEG, NIT - NEG, GLU - NEG, pH. - 6.2, U.V = 1019, LEI -1- 2-3 in p/zr, ASC - 2 mg/dl, COL LT - Yellow, CLA Clear.

Biochemical blood tests: total protein - 79g/l, albumin - 61, globulins: α-1 - 4%, α-2 - 8%, β - 12%, γ - 15%; alkaline phosphate - 160 units/l (norm 70-140), AlAT - 26 units/l, AsAT - 28 units/l, amylase - 60 units/l (norm10-120),

thymol test - 4 units, total bilirubin - 12mcg/l, bilirubin - 12mcg/l (norm 10-120), bilirubin - 12mcg/l. Bilirubin - 12 μmol/l, of which the ligand - 2 μmol/l. 2μmol/l.

Esophagogastroduodenoscopy: oesophageal mucosa is pink, a little mucus in the stomach, gastric mucosa in the antral region is mottled, with thickened folds, on the wall of the stomach there are multiple multi-calibre bulges, dot haemorrhages of different age. The mucosa of the bulb of the 12th p.c. is focally hyperaemic, edematous.

Ultrasound of abdominal cavity organs: liver - not enlarged, parenchyma homogeneous, echogenicity normal. Gall bladder is oval in shape 50* 19mm. Pancreas: head-18mm (normal 18), body-16mm (normal 14), tail-20mm (normal 14), parenchyma homogeneous.

Respiratory urease test: positive.

Biopsy test for HP-infection: positive (+++).

1. Formulate the clinical diagnosis.
2. Name the route of transmission of Helicobacter infection.
3. List the main methods of diagnosis of Helicobacteriosis in children.
4. What is eradication of HP infection?
5. What does painfulness in Meyo-Robson's t. indicate?
6. What aggravating factors can be identified in the course of this disease?
7. Prescribe treatment for this patient.

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