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Inflammatory Bowel Diseases in Children: Modern Achievements in Diagnostics and Therapy

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Aim: to highlight current trends in the diagnosis and treatment of inflammatory bowel diseases in children.
Key points. The incidence of inflammatory bowel disease among children has increased significantly over the past three decades. Moreover, these diseases are often characterized by a severe course. At the same time, strategies for diagnosing and treating these patients are being improved: doctors began using high-definition endoscopy and video capsule endoscopy, the determination of fecal calprotectin, biological therapy (infliximab, adalimumab, vedolizumab, and ustekinumab) and drug monitoring. Particular attention is paid to the role of dietary recommendations.
Conclusion. Currently, there has been significant progress in the diagnosis and treatment of inflammatory bowel diseases in children.
Keywords: inflammatory bowel diseases, ulcerative colitis, Crohn's disease, fecal calprotectin, infliximab, adalimumab, vedolizumab, ustekinumab.
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Воспалительные заболевания кишечника у детей: современные достижения в диагностике и терапии

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Цель обзора литературы: осветить современные тенденции в диагностике и лечении воспалительных заболеваний кишечника у детей.
Основные положения. Заболеваемость воспалительными заболеваниями кишечника среди детей значительно выросла за последние три десятилетия, причем эти болезни часто характеризуются тяжелым течением. В то же время совершенствуются стратегии диагностики и лечения пациентов с этими заболеваниями желудочно-кишечного тракта: в качестве методов диагностики применяют эндоскопию высокого разрешения и видеокапсульную эндоскопию, определение фекального кальпротектина, внедряется биологическая терапия (инфликсимаб, адалимумаб, ведолизумаб и устекинумаб) и лекарственный мониторинг. Особое внимание уделяется роли диетических рекомендаций.
Заключение. В настоящее время наблюдается значительный прогресс в диагностике и лечение воспалительных заболеваний кишечника у детей.
Ключевые слова: воспалительные заболевания кишечника, язвенный колит, болезнь Крона, фекальный кальпротектин, инфликсимаб, адалимумаб, ведолизумаб, устекинумаб.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Introduction

There has been a significant increase in the incidence and prevalence of Inflammatory Bowel Diseases (IBD) in children over the past 25 years. This group of diseases is a severe pathology with a complex interaction of etiological pathogenetic mechanisms, including genetic and epigenetic, environmental, and microbial factors. Their treatment in most cases remains largely empirical though there is a significant progress made in the instrumental diagnosis of IBD over the past decades [1].

Nevertheless, the ever-growing range of diagnostic laboratory and instrumental studies, the expansion of therapeutic possibilities allow to improve long-term treatment results.

In this review paper, we have tried to focus the attention of specialists on recent clinical developments in IBD in children and current studies, the results of which will be used in practical medicine in the nearest future.

Epidemiology of IBD in children

It is important to note that over the past 25 years, the incidence and prevalence of IBD in children in Europe and North America have increased dramatically. In addition, the results of studies conducted in Asia and South America indicate similar trends in these regions [2].

The highest incidence rates of IBD in the world were observed in Northern Europe (Scandinavia — up to 23.1 cases per 100,000 population per year), Western Europe (Scotland — up to 17.4 cases per 100,000 population per year) and Canada (up to 15.4 cases per 100,000 population per year) [2–5]. As a rule, Crohn's disease (CD) continues to prevail in these populations with a frequency approximately twice as high relative to ulcerative colitis (UC). IBD is more common among boys, and the majority of cases occur in patients with CD aged 11–17 years [3]. There are conflicting data on trends in the incidence of IBD with very early and early onset (< 6 years at the time of diagnosis). For example, studies conducted in Canada indicate an increase in the number of these patients. However, most studies conducted in Europe report the incidence of IBD with a very early onset over the past 15 years, about 1–2 cases of 100,000 people per year. The reason for this phenomenon remains unclear to the end, and among the theories explaining this phenomenon the following are considered: a decrease and/or violation of the effects of microbiota within the framework of the dyad "microorganism/macroorganism" in early childhood; a change in nutrition ("Western diet"); the hygiene hypothesis. The influence of exclusively genetic factors does not fully explain the decrease in the age threshold for the onset of the disease, since the increase in the number of patients occurs too quickly to be associated with any deep genomic changes. It should also be recognized that increased awareness of the disease and improved diagnostic methods play an important role in improving the quality and timeliness of diagnosis of IBD.

Phenotypic variants of IBD

IBD are traditionally divided into Crohn's disease and ulcerative colitis. The existence of unclassifiable IBD is also certain. This group of diseases is more characterized by differences in the localization of the pathological process, to a lesser extent — by histological changes. Quite often in childhood, the differential diagnosis of IBD remains rather conditional. In this regard, the use of the term "inflammatory bowel diseases" is more appropriate, and personalized molecular diagnostics in the future will help to establish a more accurate diagnosis for individuals with the possibility of obtaining an individual prognosis and treatment [6, 7].

Diagnostic and treatment strategies

Establishing a diagnosis in a short time is the key to better treatment of IBD and ensuring an early therapeutic effect. Unfortunately, most patients often do not seek specialized help for months or even years, thereby complicating and lengthening the diagnostic process with endoscopic and histological examinations [7, 8]. The reasons for this are diverse, including the absence of a pronounced or specific clinical picture, the prevalence of erased symptoms, along with not always elevated markers of inflammation [9].

One of the most important achievements in screening patients for the potential presence of IBD is rapid testing to determine the level of fecal calprotectin (FC). This dimer, formed by two protein subunits (S100A8 and S100A9), is released into the intestinal lumen mainly by neutrophils and can be detected in feces. FC is a relatively stable biomarker, however, if the biomaterial is not stored at low temperatures, this can lead to the decay of FC, which is the reason for obtaining falsely underestimated values. The standard values of FC are described at the level of < 50 μg/g, although the normal values depend on the age of the patient, the diets they follow and the time of the collection of biological material. The particular attention should be paid to the interpretation of the results in young children (< 6 years), whose FC values are initially higher (up to 500 μg/g in some cases) due to active

maturation processes of the intestinal immune system [9, 10].

As a rule, children with IBD have FC values in the range of 100–1000 μg/g. In rare cases, patients may have normal or slightly elevated FC values, which may probably occur with isolated inflammation of the upper gastrointestinal tract, limited damage to the small intestine, or with improper collection and storage of biomaterial [10]. Many diseases (for example, intestinal infections) or taking medications can also cause an increase of FC levels. FC determination should not be carried out in acute diarrhea. This analysis should always be accompanied by stool tests for bacterial and viral screening. Taking medications (such as nonsteroidal anti-inflammatory drugs), other inflammatory pathology of the gastrointestinal tract, including celiac disease, benign polyps can also lead to an increase in the level of FC [9–11].

Repeated determination of FC with a slight increase in primary values will help to suspect IBD in the patient and refer them to a specialist for further examination. However, if the patient has symptoms of anxiety, the referral to a specialist should not be postponed. FC is also commonly used as a screening response to therapy and for monitoring exacerbations in patients with established IBD [11–13].

All patients with IBD require consistent histological diagnosis using modified Porto criteria [14]. Standard practice includes endoscopy of the upper and lower gastrointestinal tract with multiple biopsies. Endoscopy is also used to monitor the course of the disease, the response to ongoing therapy (in particular, biological), screening for colorectal cancer before moving from the supervision of a pediatrician to a therapist. Visualization of the small intestine is a mandatory part of the study for the diagnosis of IBD and during monitoring of the effectiveness of therapy [15–17]. As a rule, magnetic resonance enterography is used to assess the condition of the small intestine. A new method is ultrasound of the small intestine, during which the thickness of the intestinal wall is measured, which can help both in diagnosis and in monitoring patients [15].

The desire for better visualization and assessment of the prevalence of the pathological process in patients with IBD has increased the frequency of using videocapsular endoscopy, the use of which is possible in children older than 2 years. Practice shows that before the introduction of a video capsule, it is possible to introduce a “blank” one to make sure that its passage will not be delayed in strictures. Important aspects in increasing the diagnostic significance of the method are the correct interpretation of the images obtained, high-quality preparation of the intestine or careful adherence to a special diet before the introduction of the capsule by ingestion or endoscopic administration. Over time, with the expansion of the use of this method, it will become a part of the initial diagnostic program, especially in patients with small intestine lesions [16].

Genetic testing

A new area of research in children with IBD is genetic testing [17]. As a rule, a combination of factors such as primary immunodeficiency, autoinflammatory processes, dysfunction of the intestinal epithelial barrier, microbiotic intestinal imbalance against the background of genetic disorders play a role in the development of IBD. In very rare cases (< 0.5 %) at the onset of IBD in childhood, the disease is caused only by gene disorders [17]. To date, more than 100 genes have been identified to be responsible for the development of IBD [18]. Genetic testing is advisable for all patients with IBD who are younger than 2 years and for some other patients who are older than this age (Table) [19].

Genetic counseling on future pregnancy and genetic screening of concomitant risks (including lymphoproliferative diseases) are important aspects in the prevention of IBD. Depending on the detection of a specific genetic defect, additional treatment options may appear — for example, hematopoietic stem cell transplantation.

Strategies for monitoring and curation of children with IBD

Optimizing treatment outcomes requires optimal management strategies. This can be done through patient clinical care networks with careful monitoring of outcomes so that treatment processes and methods can be reviewed, updated and improved to optimize clinical care. Figure 1 summarizes current aspects of the treatment of IBD in children, along with recent and future developments.

ECCO-ESPGHAN (European Crohn’s and Colitis Organization — European Society of Paediatric Gastroenterology, Hepatology and Nutrition) presented Recommendations for the treatment of CD and UC with an emphasis on the rapid transfer of a patient with resistance to treatment to biologics with immunomodulators or “top-down” therapy in patients with a disease with a high risk of complications [20]. It is necessary to develop the tools for predicting the course of the disease and the response to the therapy.

Over the past 20 years, there has been a centralization of medical care for patients with IBD. A similar trend is observed with many acute and

Table. Criteria for the appropriateness of genomic testing for patients with inflammatory bowel diseases

Таблица. Критерии целесообразности геномного тестирования для пациентов с воспалительными заболеваниями кишечника

When to test ***Когда следует проводить***	**Additional criteria** ***Дополнительные критерии***
A. Onset of IBD before the age of 2 years. B. Onset of IBD before 6 years of age and the presence of one or more additional criteria (1–6). C. Children over 6 years of age only if a monogenic variant of IBD is suspected and additional criteria 1–6 are present *A. Дебют ВЗК в возрасте до 2 лет.* *B. Дебют ВЗК до 6 лет и наличие одного и более дополнительных критериев (1–6).* *C. Дети старше 6 лет только при подозрении на моногенный вариант ВЗК при наличии дополнительных критериев 1–6*	1. Susceptibility to infections when laboratory parameters deviate from the norm — immunodeficiency. 2. Congenital immune disorders (IPEX syndrome or hemophagocytic lymphohistiocytosis). 3. Congenital multiple intestinal atresia or congenital diarrhea. 4. Malignant neoplasm with early onset (before 25 years). 5. Family history of suspected monogenic IBD. 6. Before performing surgical interventions and/or starting therapy *1. Восприимчивость к инфекциям при отклонении лабораторных показателей от нормы — иммунодефицит.* *2. Врожденные нарушения иммунитета (IPEX-синдром или гемофагоцитарный лимфогистиоцитоз).* *3. Врожденные множественные атрезии кишечника или врожденная диарея.* *4. Злокачественное новообразование с ранним началом (до 25 лет).* *5. Семейный анамнез с подозрением на моногенное ВЗК.* *6. Перед проведением оперативного вмешательствами и/или началом проведения терапии*

Note: IBD — inflammatory bowel diseases.

Примечание: ВЗК — воспалительные заболевания кишечника.

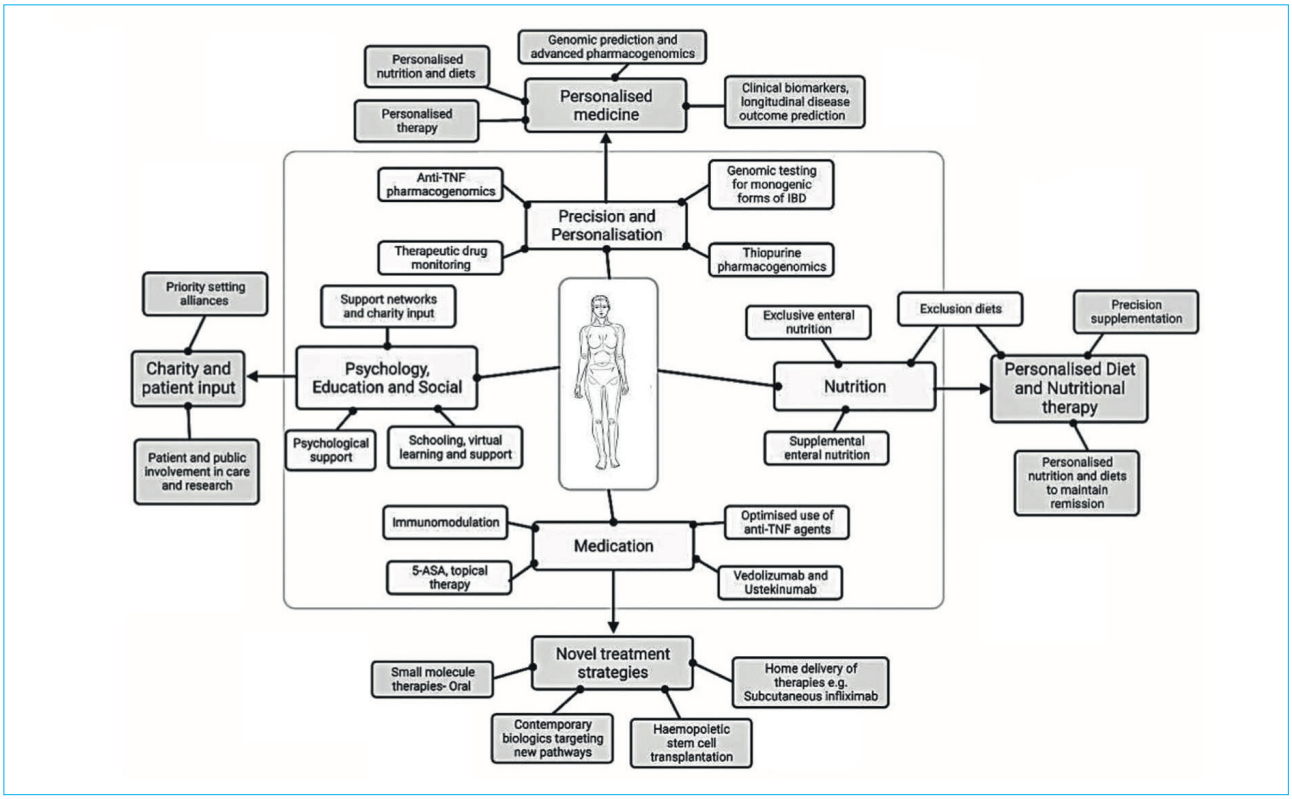

Figure 1. Current and future aspects of the treatment of inflammatory bowel diseases in children

Рисунок 1. Текущие и будущие аспекты лечения воспалительных заболеваний кишечника у детей

chronic diseases in children when specialized centers for the treatment of a certain pathology provide a leading role in their management [21]. Help is provided closer to home — after an initial visit to a general pediatrician or gastroenterologist in an outpatient healthcare unit, the patient is sent to a specialized center for the treatment of IBD or to local hospitals where doctors with the necessary competencies work.

It should be emphasized that the rapid increase in the incidence of IBD in children has a great impact on the healthcare system. Doubling the number of patients in a short time causes a heavy burden on diagnostic services (including endoscopists), requires rapid training of relevant specialists, related medical professionals and the expansion of hospital staff. Psychological assistance to the child is also an important aspect. In the future, the possibility of delivering monoclonal therapy at home (subcutaneous infliximab) should also be considered in the treatment of patients with IBD [22].

Stratification of patients with IBD

The concept of the early use of biological therapy of CD, which leads to a longer remission of the disease, remains today mainly theoretical and is rarely used in practical medicine. Optimization of the therapy and prevention of complications still require rapid diagnosis of the disease and early treatment of the patients for medical help. Not all patients will require biological, immunomodulator or small molecule therapy to achieve long-term remission. Other individuals will require tailored therapy due to underlying genetic variation. Achieving a personalized approach will have a profound impact on patient quality of life outcomes.

New developments in diet therapy

Exclusive enteral nutrition has a long-standing and significant evidence base of efficacy at inducing and maintaining remission in CD. The works established the achievement of induction of remission in more than 80 % of children with CD using exclusive enteral nutrition. To date, more and more attention is being paid to the study of the effectiveness of the use of exclusive enteral nutrition in patients with UC.

Despite the interest in the use of various diets and dietary correction in IBD, none of them has significant evidence of effectiveness in maintaining remission, including low-FODMAP (fermentable oligo-, di-, monosaccharides and polyols), Mediterranean, vegetarian, and other restrictive diets (gluten-free or dairy-free) [23, 24]. The role and effectiveness of partial enteral nutrition remain not fully established today [25]. At the moment, the evidence to recommend a certain diet, volume or percentage of calories as a partial enteral nutrition or to adhere to exceptions from the diet of certain food groups as a treatment direction for induction or maintenance of remission is contradictory or absent altogether. However, this does not mean that diet therapy is not a viable treatment option in the future. Today, data are accumulating on the effectiveness of new diets with the exclusion of certain food groups in CD. In addition, the prevention of obesity in children with IBD is currently as important as the prevention of prolonged malnutrition [26, 27].

Pharmacotherapy

The pharmacological landscape of IBD is a rapidly developing area. At the same time, new drugs used in adult patients are gradually beginning to be used in pediatric practice. Despite a significant shift that was seen with anti-tumour necrosis factor (TNF) agents in the 2000s, additional therapeutic options have been slow to emerge but are now much more available. Understanding of the best ways to use current drugs, including therapeutic drug monitoring (TDM), is also having patient impact. Selecting the best drug for a patient, based on clinical and anamnestic data, will further improve efficacy and outcome. A summary of the various current treatments targeting the pathogenesis of the underlying disease is presented in Figure 2.

Information about the formation of antibodies against infliximab has been accumulating for decades. The ability to use this knowledge and adapt therapy to the patient through TDM increases, which increases the effectiveness of therapy [28].

"Top-down" therapy, especially in patients with CD, is quite widespread. At the same time, the data obtained in children with IBD indicate comparable results after one year and potentially fewer treatment failures compared to "step-up" therapy [29]. There is still insufficient evidence of the long-term effect of this strategy in CD, including in the pediatric population; although early remission rates are often higher with first-line biological therapy, the effect seems to weaken over time [30]. Despite this, differentiating "top-down" from aggressive therapy in moderate to severe disease is very important. "Top-down" therapy has its focus on treating all patients with biologics at disease onset to prevent complications and aims at "turning off" the inflammatory process [31]. Aggressive therapy for refractory disease or severe disease may also require the introduction of biological therapy at diagnosis.

Ways to use monoclonal antibodies more effectively

Infliximab and adalimumab have been approved for use in pediatric practice for many years.

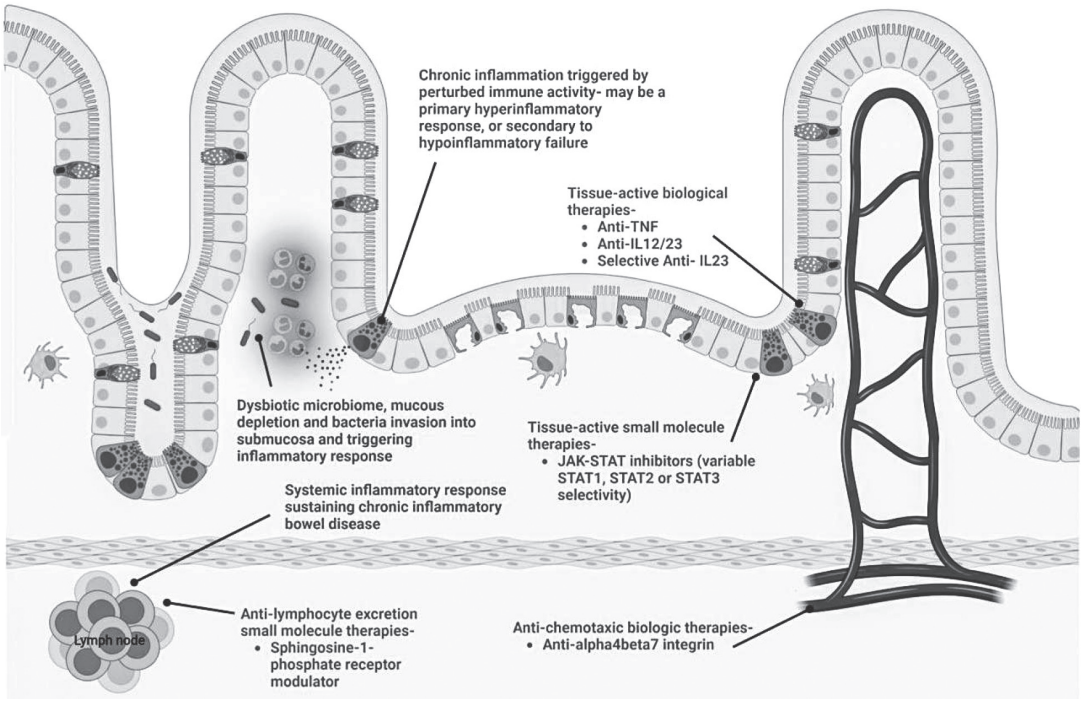

Figure 2. Mechanism of action of biologics and small molecule drugs (the etiopathogenesis of inflammatory bowel diseases is characterized by heterogeneity due to genetic and epigenetic factors, epithelial dysfunction, intestinal dysbiosis, and immunological disorders; multiple mechanisms operate within each individual, often leading to similar pathogenic phenotypes)

Рисунок 2. Механизм действия биологических препаратов и низкомолекулярных препаратов (этиопатогенез воспалительных заболеваний кишечника характеризуется гетерогенностью, обусловленной генетическими и эпигенетическими факторами, эпителиальной дисфункцией, кишечным дисбиозом и иммунологическими нарушениями; у каждого индивидуума действуют многочисленные механизмы, часто приводящие к сходным патогенным фенотипам)

However, we are only now beginning to optimize their use, to make personalized treatment regimens and to understand the pharmacodynamics in young children. Perhaps the best example of this is the dosing of infliximab, since anti-TNF therapy were the basis for the treatment of IBD first in CD, and then in UC.

The traditional infliximab therapy regimen consisted of administering the drug at a dosage of 5 mg/kg once intravenously at weeks 0, 2 and 6, and to maintain remission, infusions were repeated every 8 weeks. Today, this scheme is outdated. Often, the terms of induction of remission are shortened by shortening the interval between injections, and the initial dose may be 10 mg/kg [32]. In accordance with the TDM, the maintenance dose is selected individually for patients to ensure an adequate level of the drug, reduce inflammation markers (C-reactive protein, erythrocyte sedimentation rate) and minimize the risk of anti-drug antibodies [33]. Simultaneous immunomodulation with thiopurines or methotrexate was the basis of therapy aimed at reducing the immunogenicity of monoclonal therapy [20]. Although the routine use of these drugs is widely discussed due to the potential toxicity and risk of lymphoma.

Adalimumab is apparently less immunogenic than infliximab. However, it is unclear whether the subcutaneous route of its administration affects this. Modern genetic data have identified human leukocyte antigen (HLA) of the HLA DQA1*05 genotype as the main risk factor for the development of anti-drug antibodies [23]. Since subcutaneous administration of the drug appears to be less immunogenic, subcutaneous infliximab is also planned to be used in pediatric practice in addition to adalimumab [22, 34].

Increasingly, the possibilities of the more effective usage of available drugs and, thus, better stratification of patients by the risk of loss of response to treatment are being studied. At the same time, there is also evidence of the possibility of

canceling simultaneous immunomodulation after 12 months of dual anti-TNF therapy [35].

New monoclonal drugs and small molecules

In pediatric practice, ustekinumab (anti-IL-12/23) and vedolizumab (anti-α4β7) are beginning to be used and are proving their effectiveness and safety. The drugs are an alternative to anti-TNF therapy with special advantages for the treatment of concomitant pathologies, including psoriasis (ustekinumab) [36, 37]. New drugs are emerging, including the biological risankizumab (selective anti-IL-23), which is likely to be available within the next year for patients aged 16 and older. Additional p19 inhibitors (such as mirikizumab) may also be transferred to pediatric practice from adult medicine. Similarly, the small molecule class joins the pediatric therapeutic arsenal, while in certain cases, such as acute severe colitis, JAK-STAT inhibitors (filgotinib, tofacitinib, upadacitinib) and sphingosine-1-phosphate inhibitors (ozanimod) appear as potent oral variants [38]. Widespread use of these drugs in everyday clinical practice is likely to take some time. The results of evaluating of the effectiveness of drugs vary depending on the indications [39].

Linking with adult therapy

Studying the experience of treating adult patients has a great positive value. In pediatric practice, there is considerable experience in the field of genetics, and more attention is paid to the nutrition of patients with IBD. The expansion of therapeutic opportunities, complex surgical interventions, problems of transitional age (first sexual experience, smoking, alcohol consumption) and genetic diagnosis require joint work of pediatric and therapeutic doctors, which goes beyond the traditional model of the transition period. Although this period remains a very important stage, the available data suggest that the lack of knowledge and involvement of patients and clinicians have a decisive impact on long-term treatment outcomes [39, 40].

Conclusion

Diagnosis and treatment of IBD in children is a developing field of pediatrics, which is greatly clinically influenced by the achievements of fundamental and translational science. This review examines some significant practical achievements of recent years, and also presents promising future vectors in the diagnosis and treatment of IBD in children.

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