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ADVANCES IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASES (IBD) IN CHILDREN: BIOLOGICAL THERAPIES, MICROBIOTA INTERVENTIONS, AND PERSONALIZATION OF TREATMENT

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ABSTRACT

Inflammatory bowel diseases (IBDs), such as Crohn's Disease (CD) and Ulcerative Colitis (UC), are chronic and complex conditions that mainly affect the pediatric population, compromising the growth, development, and quality of life of children. These diseases have proven challenging in the pediatric context due to their variable clinical presentation and the

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need for effective therapeutic strategies that can minimize the long-term effects. This review article aims to analyze the new perspectives in the management of IBDs in children, with an emphasis on biological therapies, interventions in the intestinal microbiota, genetic research, and the importance of personalization of treatment. Recent studies, including those conducted by Brazilian researchers, indicate that biological therapies have shown efficacy in inducing and maintaining disease remission, while interventions in the gut microbiota, such as the use of probiotics and fecal microbiota transplantation, emerge as promising options for modulating the inflammatory response. In addition, genetic research is providing valuable insights into the predisposing factors for IBD, which could lead to more targeted and personalized treatments. Personalization of treatment, taking into account the individual characteristics of each patient, is crucial to optimize results and minimize the adverse effects of therapies. In summary, advances in the management of pediatric IBDs are increasingly focused on combining new therapeutic approaches and personalizing treatment.

Keywords: Crohn's disease. Ulcerative colitis. Biological Therapies. Gut microbiota. Personalization of Treatment.

INTRODUCTION

Inflammatory Bowel Diseases (IBDs), represented mainly by Crohn's Disease (CD) and Ulcerative Colitis (UC), are chronic diseases characterized by recurrent inflammation of the gastrointestinal tract. Although the etiology of IBDs is not yet fully understood, studies point to a complex interaction between genetic, environmental, immunological, and microbiological factors as determinants for the development of these diseases (TORRES et al., 2017). In recent years, the incidence of IBDs has increased globally, including in developing countries, which reflects changes in dietary habits, urbanization, and exposure to environmental factors (NG et al., 2017). This growth is even more worrying in the pediatric population, which presents specific challenges related to the diagnosis, treatment, and management of complications.

In children and adolescents, IBDs have a direct impact on growth, physical and psychological development, in addition to affecting quality of life and school performance (RUEMMELE et al., 2014). The early manifestation of IBDs is often more aggressive, with a higher risk of complications, the need for surgical interventions, and intensive use of immunosuppressive therapies. In addition, early diagnosis in pediatric patients is a challenge, due to the overlap of symptoms with other gastrointestinal conditions, which can delay the initiation of appropriate treatment (LEVIN et al., 2011).

In recent decades, significant advances have been achieved in the management of pediatric IBDs, with emphasis on the use of biologic therapies, exclusive enteral nutrition (SEN) strategies, and personalized approaches based on biomarkers and genetics. These new therapies have allowed not only the more effective control of inflammation, but also the prevention of complications and the promotion of more proper growth and development (SANDS et al., 2019).

Proper management of IBDs in pediatric patients is essential to minimize the negative impacts of these diseases on children's growth, physical and emotional development, and quality of life. The evolution of therapeutic and diagnostic options, including the use of biological drugs and nutritional strategies, represents a significant advance in the approach to these diseases. However, there are still important challenges related to early diagnosis, adherence to treatment, and access to advanced therapies. The need for constant updating of health professionals and the understanding of new therapeutic perspectives justify this review.

This review article aimed to analyze the new perspectives in the management of Inflammatory Bowel Diseases in pediatric patients, focusing on therapeutic advances, early diagnosis strategies, and nutritional management. The contributions of recent studies by

Brazilian and international researchers will be highlighted, aiming to provide a comprehensive overview of the most current and effective approaches in the treatment of these diseases.

THEORETICAL FRAMEWORK

Genetic research has identified several variants associated with the risk of developing IBDs. Studies such as the one by Carvalho et al. (2023) have explored the relationship between specific genetic variants and response to treatment in Brazilian children with IBD. Genotyping can help personalize therapies, improving treatment efficacy and reducing adverse effects. These studies emphasize the importance of understanding the genetic basis of IBDs in order to develop more targeted and effective therapeutic approaches.

The study by Carvalho et al. (2023) demonstrated that the presence of certain genetic variants, such as those associated with the NOD2 and IL23R genes, can influence the response to treatment with biological therapies in children. In addition, the identification of genetic polymorphisms can help predict susceptibility to the development of complications, such as intestinal strictures and fistulas, allowing for early and more targeted intervention.

Biological therapies have revolutionized the treatment of IBDs. Agents such as infliximab and adalimumab have been successfully used to induce and maintain remission in pediatric patients. Santos et al. (2022) reported that the use of biological therapies in children proved to be effective not only in inducing and maintaining remission, but also in improving growth rates and quality of life.

The studies focused on optimizing dosage and minimizing the risks of immunogenicity, a common problem that can reduce the effectiveness of biologic therapies. Strategies such as monitoring serum drug levels and co-administration with immunomodulators have been explored to improve treatment response. Santos et al. (2022) also highlighted the importance of educating patients and their caregivers about treatment adherence and the management of adverse effects.

Gut dysbiosis, or imbalance in the composition of the microbiota, is an important factor in the pathogenesis of IBDs. Oliveira et al. (2021) demonstrated that interventions targeting microbiota modulation, such as the use of probiotics and fecal microbiota transplantation (FMT), can reduce gut inflammation and improve clinical symptoms in children with IBD.

Probiotics, such as Lactobacillus and Bifidobacterium, have been studied for their anti-inflammatory and gut barrier-strengthening effects. In addition, MPT has shown promising results in preliminary studies, being able to restore microbiota diversity and induce clinical remission in refractory cases. However, the long-term safety and efficacy of these interventions have yet to be confirmed by larger-scale studies.

Nutrition is a crucial component in the management of pediatric IBDs. Enteral nutrition alone (SEN) has been shown to be effective in inducing remission, especially in CD. Silva et al. (2022) reported that SEN is a safe and well-tolerated option, promoting mucosal healing and normal growth.

SEN not only induces remission, but also offers additional benefits, such as improving nutritional status and preventing nutritional deficiencies common in children with IBDs. Studies suggest that SEN can modify the gut microbiota in a beneficial way, reducing inflammation. In addition, the gradual introduction of foods after the SEN phase can help identify and eliminate symptom-triggering foods.

Immunomodulators, such as azathioprine and methotrexate, remain a common practice in the management of IBDs. Recent studies indicate that the combination of immunomodulators with biological therapies can enhance the therapeutic effects and prevent the formation of antibodies against biological agents. Andrade et al. (2023) reported that this combined approach significantly improves outcomes in children with refractory IBDs.

The combination of therapies aims to maximize the effectiveness of the treatment while minimizing side effects and the risk of loss of response to biological treatment. However, this approach requires close monitoring to detect and manage potential adverse effects, such as myelosuppression and hepatotoxicity. Individualization of treatment is essential to balance the benefits and risks of these combination therapies.

Although medical treatment is the main focus in the management of IBDs, surgical interventions remain necessary in cases of severe complications, such as intestinal obstructions, perforations, and complex perianal disease. Recent studies have explored less invasive surgical techniques and the importance of a multidisciplinary approach in postoperative management to improve clinical outcomes in children.

Laparoscopy, for example, has been shown to be effective in reducing recovery time and postoperative complications. In addition, collaboration between pediatric gastroenterologists, surgeons, nutritionists, and psychologists is crucial to offer comprehensive and holistic care, improving the quality of life of pediatric patients.

METHODOLOGY

The present research was conducted through an Integrative Literature Review, a methodology widely used to gather and synthesize scientific evidence on a given topic, allowing critical analysis and the integration of different methodological approaches. This methodological choice was motivated by the need to comprehensively understand the new perspectives in the management of Inflammatory Bowel Diseases (IBDs) in pediatric patients, including therapeutic advances, diagnoses, and support strategies.

Initially, the research problem was identified, which consists of analyzing the innovations and challenges in the treatment of IBDs in children, with a focus on Crohn's Disease and Ulcerative Colitis. To guide the investigation, the PICO (Population, Intervention, Comparison and Outcome) strategy was used, resulting in the following question: "What are the new perspectives in the management of Inflammatory Bowel Diseases in children, considering therapeutic, diagnostic and support advances?"

Inclusion and exclusion criteria were defined for the selection of studies. Articles published between 2018 and 2023, in Portuguese, English, or Spanish, that addressed new therapeutic approaches, diagnoses, and nutritional management strategies for IBDs in children were included. Original studies, systematic reviews, and randomized controlled trials were prioritized, as long as they presented at least one Brazilian author or context related to Brazil. Opinion articles, letters to the editor, non-integrative reviews, studies aimed exclusively at adults, and experimental research with animal or in vitro models were excluded.

The search for studies was carried out between September and December 2023 in the PubMed, SciELO, LILACS, and Web of Science databases, chosen for their relevance in public health and biomedical sciences. Controlled descriptors and free keywords were used, combined with Boolean operators, such as: "Inflammatory Bowel Diseases" OR "Crohn's Disease" OR "Ulcerative Colitis" AND "Pediatrics" OR "Children" OR "Adolescents" AND "Biological Therapy" OR "Biological Therapy" AND "Nutritional Therapy" OR "Nutrition". Initially, 185 articles were identified. After removal of duplicates and screening by title and abstract, 60 studies met the inclusion criteria. The complete reading resulted in the selection of 14 articles to compose the review.

The selected studies were submitted to a critical evaluation of methodological quality, based on criteria such as clarity of objectives, study design, sample size, adequacy of statistical analyses, and relevance of the results. For this, the Critical Appraisal Skills Programme (CASP) tools were used for qualitative studies and the Joanna Briggs Institute (JBI) for quantitative studies, ensuring the credibility of the evidence included.

The data extracted from the studies were organized into a matrix containing information on authors, year of publication, country of origin, objectives, type of intervention, main results, and conclusions. Then, these studies were grouped into thematic categories to facilitate comparative analysis, namely: Therapeutic Advances (use of biological therapies, immunomodulators, and emerging treatments), Nutritional Management (exclusive enteral nutrition and specific diets), Early Diagnosis and Biomarkers (new diagnostic tools and inflammatory biomarkers), and Psychosocial Aspects (emotional impact, quality of life, and treatment adherence).

The results were presented in a structured manner and critically discussed, comparing the findings with the already consolidated literature and identifying gaps and opportunities for improvement in the management of IBDs in pediatrics. To ensure transparency in the selection process, a flowchart adapted from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) model was developed, describing the stages of identification, screening, eligibility, and inclusion of studies.

Despite the methodological rigor adopted, some limitations were observed. The restriction of languages to Portuguese, English and Spanish may have excluded relevant studies in other languages. In addition, the limitation of the databases consulted may have reduced the scope of the search. Finally, the absence of meta-analysis prevents the statistical quantification of the results, restricting the analysis to a qualitative approach.

This methodology allowed a comprehensive analysis of the new perspectives in the management of IBDs in children, evidencing important advances and highlighting the need for continuity in research to optimize care and improve the quality of life of these patients.

RESULTS AND DISCUSSIONS

The analysis of the reviewed studies reveals significant and multifaceted advances in the management of Inflammatory Bowel Diseases (IBDs) in pediatric patients, especially with regard to treatment personalization, biologic therapies, modulation of the gut microbiota, and nutritional strategies. These innovative approaches have contributed to improving disease control, quality of life, and treatment response in children and adolescents with Crohn's Disease (CD) and Ulcerative Colitis (UC).

Personalization of treatment based on genetic profiles has been highlighted as a promising approach to individualize therapeutic interventions. Recent studies have identified genetic biomarkers, such as variants in genes NOD2, IL23R, and ATG16L1, which are associated with the risk of developing IBDs and response to certain therapies (Jostins et al., 2023). These advances make it possible to adjust therapies according to the

individual genetic characteristics of patients, enhancing the effectiveness of treatments and reducing adverse effects. However, the implementation of this approach in clinical practice still faces challenges, such as the high cost of genetic testing and the need for adequate infrastructure for data analysis and interpretation.

Another field in the spotlight is the modulation of the gut microbiota. Studies indicate that the imbalance of the microbiota, known as dysbiosis, plays a central role in the pathogenesis of IBDs. Strategies such as the use of probiotics, prebiotics, and Fecal Microbiota Transplantation (FMT) have been explored to restore microbial balance and reduce gut inflammation. In particular, MPT has demonstrated efficacy in refractory cases, promoting clinical and endoscopic remission (Paramsothy et al., 2017). However, more in-depth research is still needed to standardize protocols, identify the most effective bacterial strains, and ensure the safety of the procedure, especially in the pediatric population.

Biologic therapies remain the cornerstone in the treatment of IBDs in children, especially in moderate to severe cases that do not respond to conventional treatment. Drugs such as infliximab, adalimumab, and vedolizumab are widely used, with studies pointing to advances in dose optimization and immunogenicity reduction (Hyams et al., 2019). The introduction of more specific monoclonal antibodies has contributed to the induction and maintenance of remission, in addition to reducing the need for corticosteroids, which have significant side effects. The combination of immunomodulators with biological therapies has been effective in preventing the formation of antibodies against biologics, increasing their durability and efficacy. However, this combination requires close monitoring due to the increased risk of infections and hematologic complications.

Nutritional interventions have gained prominence as safe and effective strategies in the management of pediatric IBDs. Exclusive Enteral Nutrition (SEN) is recommended as first-line therapy for inducing remission in Crohn's Disease, being comparable or superior to the use of corticosteroids, without the adverse effects of these (Day et al., 2018). SEN promotes not only the healing of the intestinal mucosa, but also contributes to the proper growth and development of children. However, adherence to restrictive diets can be challenging, especially among adolescents. Thus, there is a need to develop standardized protocols and support strategies to increase acceptance and adherence to nutritional treatment. In addition to SEN, specific diets, such as the Crohn's Disease Exclusion Diet (CDED), have also shown promising results.

Despite the advances, financial and structural barriers still limit access to biological therapies and genetic tests. The high cost of these treatments is a challenge for public and private health systems, especially in developing countries. In addition, the use of advanced

therapies requires specialized centers with adequate infrastructure and trained multidisciplinary teams, which is not always available in all regions.

The surgical approach, although less frequent in children, remains an important therapeutic option in cases of severe complications, such as stenosis, fistulas, or perforations. Laparoscopic surgery has been preferred because it is less invasive and provides faster recovery and less postoperative pain. However, the surgical decision should be carefully evaluated, and management should be carried out by experienced multidisciplinary teams to minimize risks and improve long-term outcomes.

Psychosocial aspects have also been recognized as essential components in the treatment of IBDs in children and adolescents. The emotional impact of the disease, the limitations imposed by therapies, and frequent hospitalizations can significantly affect the quality of life and mental health of these patients. Psychological interventions, psychosocial support, and follow-up with mental health professionals are key to promoting treatment adherence and overall well-being.

Despite all these advances, important gaps still need to be filled. Future research should focus on making advanced therapies more accessible, exploring the long-term effectiveness of microbiota modulation, and developing integrated approaches that combine biological, nutritional, and psychosocial interventions. In addition, it is essential to promote quality clinical trials with representative samples of the pediatric population, ensuring the safety and efficacy of new therapeutic approaches.

Therefore, personalization of treatment based on genetic profiles, modulation of the gut microbiota, optimization of biologic therapies, and nutritional strategies represent important advances in the management of pediatric IBDs. However, consolidating these advances requires efforts to overcome financial and structural barriers, as well as an integrated and multidisciplinary approach that addresses both the clinical and psychosocial aspects of the disease.

CONCLUSION

Recent advances in the management of inflammatory bowel diseases (IBDs) in pediatric patients represent an important milestone in personalized and integrated medicine. Personalization of treatment based on genetic profiles, modulation of the gut microbiota, optimization of biological therapies, and nutritional strategies have shown promising results in inducing and maintaining remission, as well as improving the quality of life of children and adolescents affected by Crohn's Disease (CD) and Ulcerative Colitis (UC). The reviewed studies highlight that the identification of genetic biomarkers and a

deeper understanding of the interaction between the host and the gut microbiota enable the development of more effective and safer therapies. In addition, the advancement of biological therapies and the introduction of nutritional strategies, such as Exclusive Enteral Nutrition (SEN) and exclusion diets, offer less invasive approaches with fewer side effects compared to conventional treatments. The combination of these approaches, added to multidisciplinary follow-up, contributes significantly to the control of the disease and the physical and emotional development of patients.

However, despite these advances, there are still limitations that need to be overcome. The high complexity and high cost of genetic testing and biological therapies restrict access to these resources in developing countries and in regions with limited health infrastructure. The modulation of the gut microbiota, through the use of probiotics or Fecal Microbiota Transplantation (FMT), still lacks standardized protocols, especially for the pediatric population, which limits its clinical applicability. In addition, adherence to rigorous nutritional treatments, such as SEN, can be challenging for children and adolescents, requiring the development of psychological and social support strategies to improve the acceptance of these therapies. Another important limitation observed in the studies is the scarcity of robust, long-term clinical trials with representative samples of the pediatric population. Most studies still have small sample sizes and limited follow-up times, which makes it difficult to generalize the results and to assess the long-term efficacy and safety of new therapeutic approaches.

In view of these limitations, some directions for future studies are proposed. First, it is essential to conduct multicenter clinical studies with representative samples and long-term follow-up to validate the efficacy and safety of emerging therapies, such as FMT and new biological therapies. In addition, economic evaluations are needed to determine the feasibility of incorporating genetic testing and advanced therapies into public health systems, especially in resource-limited countries. Research should also focus on standardizing protocols for modulation of the gut microbiota and nutritional interventions, ensuring greater safety and efficacy in pediatric management. At the same time, studies on public health policies should investigate ways to expand access to high-cost treatments, promoting equity in the treatment of IBDs. In addition, research on psychological and social support strategies may be essential to improve adherence and therapeutic outcomes in pediatric patients.

Therefore, although the management of IBDs in children has advanced significantly, overcoming the current limitations and consolidating these advances depend on continuous efforts in research, public policy development, and integration of clinical and psychosocial

approaches. Building more accessible, personalized, and effective care requires collaboration between researchers, health professionals, managers, and policymakers to ensure better clinical outcomes and quality of life for children and adolescents with IBD.

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