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Literature Review

Inflammatory Bowel Disease in Children

Nabila Annisa Harum[1], Primadita Syahbani[1], Idznika Nurannisa Wibowo[1]
[1]Faculty of Medicine Universitas Airlangga – Dr. Soetomo General Hospital, Surabaya, Indonesia

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Corresponding author:
Nabila Annisa Harum
ila.harumm@gmail.com

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Abstract:

Background: Pediatric inflammatory bowel disease (IBD) is an idiopathic inflammatory disease in the digestive system with chronic onset, which often presents with unique and atypical phenotypes. This study aimed to dissect the important features of inflammatory bowel disease in children

Discussion: The two types of inflammatory bowel disease (IBD) are ulcerative colitis (UC) and Crohn's disease (CD). In children, IBD may exhibit classic symptoms such as weight loss, abdominal pain, and bloody diarrhea. However, many patient present with atypical symptoms such as isolated poor growth, anemia, or other extraintestinal manifestations. Early diagnosis of IBD in children is crucial as delayed diagnosis may lead to serious complications like bowel narrowing or abnormal connections, and stunted growth. The recommended initial evaluations in a pediatric patient with suspected IBD are complete blood test, stool examination, endoscopy and imaging. Furthermore, the aims of IBD treatment in children are to improve quality of life, relieve symptoms, promote normal growth, and prevent complications, all while minimizing medication side effects.

Conclusion: Early diagnosis and treatment are essential in managing pediatric IBD. Additionally, addressing the disease's impact on bone health, growth, development, and psychosocial well-being is also crucial to achieve comprehensive management.

Keywords: children, crohn's disease, inflammatory bowel disease, ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) which includes Ulcerative colitis and Crohn's disease are long-term inflammatory conditions affecting the digestive system. These conditions commonly start in adolescence or early adulthood, with a growing number of cases occurring in children.[1] A pediatric onset of disease occurs in about 10% of all cases. Pediatric inflammatory bowel disease often presents with unique and atypical phenotypes compared to adult-onset IBD due to distinct genetic factors and age-related differences in inflammatory regulation. In ulcerative colitis (UC), unusual presentations may include rectal sparing in untreated cases, a short disease duration, involvement of the upper gastrointestinal (GI) tract, the presence of a cecal patch, and acute transmural disease. In Crohn's disease (CD), children tend to have more extensive and aggressive lesions in the left colon, while in adults, inflammation typically occurs in the terminal ileum.[2,3]

Children and adolescents with IBD face unique challenges including delayed growth, puberty, and body image issues. Even when the disease is in remission, many continue to experience ongoing problems like stomach pain and tiredness. Transitioning to adult care is often linked to disease flare-ups, highlighting the need for specialized support during this process.[3] In up to 10% of children with IBD, it's difficult to determine if they have Crohn's disease or ulcerative colitis. Over time, some of these unclear cases develop into one of these conditions.[4] Early diagnosis of IBD in children is crucial. Promptly identifying and examining patients with suspected IBD is important because delayed diagnosis can lead to serious complications like bowel narrowing or abnormal connections, and stunted growth.[5]

Epidemiology

The global incidence and prevalence of IBD show an increasing trend in the last decade. In Asia, the incidence and prevalence per 100,000 people ranged from 0.5 to 21.6 and 5.0 to 52.2, respectively. Worldwide, the incidence and prevalence of IBD in children and adolescents remained steady from 1990 to 2019. Gender-wise the prevalence of IBD is similar in 2019 with 3.16 and 3.41 per 100,000 for boys and girls, respectively.[6] However, certain countries and regions, particularly in East Asia, have experienced a notable increase in the incidence of IBD among this age group. Around 25% of IBD patients are diagnosed before the age of 20. Among children with IBD, 4% are diagnosed before the age of 5, and 18% before the age of 10, with the highest incidence occurring during adolescence.[7]

Pathogenesis

IBD is an idiopathic disorder caused by chronic and excessive inflammation of the gastrointestinal tract, leading to rectal bleeding, and weight loss.[8] The gastrointestinal

tract (GI) is chronically exposed to various antigens found in bacteria and food. GI tract also involves in a central role in maintaining homeostasis of our immune system such as, tolerance to non-pathogenic commensal bacteria, self-antigens, and food antigens. The GI tract defends the host by initiating an inflammatory response when it is attacked by pathogenic organisms.[9]

In the absence of intestinal inflammation, gut homeostasis is maintained by suppressing excessive immune responses to foreign antigens. When the homeostasis state is interrupted by some triggering factors, intestine barriers may be disrupted and chronic inflammation will occur resulting in disease such as IBD. IBD is classified into 2 archetypal phenotypes, ulcerative colitis (UC) and Crohn's disease (CD). Even though IBD is known as idiopathic and the mechanism of chronic gut inflammation is not fully understood, some triggering factors may make complex interactions related to pathogenesis of IBD. Genetic factors, changes in the gut microbiome, environmental changes, and immune response dysregulation including cytokines and immune cells are some factors that are frequently discussed along with IBD.[10]

a. Genetic factors

   Predisposition of some genetics may play a role occurring IBD in some people and progressing to abnormalities of the immune system. More than 240 different genetic risk loci have been identified by genome-wide association studies (GWAS), next generation sequencing investigations, and other analyses. Out of these genetic locations, around 30 of them are shared by both CD and UC. Predisposition on those genes will interfere with the permeability of epithelial barrier and launch some immune responses that lead to chronic inflammatory responses[11].

   The NOD2 gene, identified in 2001 as linked to Crohn's disease (CD), functions as an intracellular bacterial sensor that regulates immune responses against pathogens by recognizing muramyl dipeptide, a component of bacterial cell walls. Mutations in the NOD2 gene can impair the activation of the NF-kB pathway and reduce cytokine production, disrupting normal immune responses and contributing to inflammation in CD. Additionally, NOD2 plays a role in autophagy, a process that helps eliminate pathogens by degrading cellular components. Mutations in ATG16L1, another gene associated with CD, disrupt autophagy in intestinal cells, leading to increased bacterial invasion.Other genetic factors associated with CD and ulcerative colitis (UC) include mutations in the CARD9 and CLEC7A genes, as well as single-nucleotide polymorphisms (SNPs) in the IL-23R gene. Although many people carry these genetic markers, only a small percentage develop inflammatory bowel disease (IBD), indicating that environmental factors and changes in gut microbiota interactions with the mucosal immune system also play crucial roles in the disease's development.[12,13]

b. Gut microbiome

Gut microbiota play a vital role in maintaining intestinal homeostasis, health, and disease by acting as a key interface between the environment and the host. They contribute to immune system development, protect against enteric pathogens, and support overall gut function through mechanisms like colonization resistance and promoting mutualism. However, factors such as nutrition, probiotics, antibiotics, and environmental influences can alter gut microbiota composition. In genetically susceptible individuals, these changes can lead to dysbiosis, disrupting mucosal immune function and potentially contributing to the development of inflammatory bowel disease (IBD).[14]

Dysbiosis refers to an imbalance in gut bacteria, leading to a disruption in the balance between beneficial and harmful microbes, and a reduction in beneficial metabolites. This imbalance, combined with ongoing inflammation, creates a chronic inflammatory cycle that impairs immune function and delays healing of the gut lining. Although dysbiosis is linked to inflammatory bowel disease (IBD), the exact mechanisms remain unclear. Research has shown that individuals with IBD have a different gut microbiota composition compared to healthy individuals.[15,16]

c. Environmental changes

Environmental factors such as lifestyle, diet, psychological stress, medications, and exposure to pathogens are linked to the risk of developing inflammatory bowel disease (IBD). Specifically, factors like vaginal delivery, age above 10, low physical activity, deficient fruit intake, and exposure to antibiotics are associated with an increased risk of pediatric IBD. Prenatal exposures, including antibiotics, tobacco smoke, and early life otitis media, also contribute to IBD risk. Research has established a clear link between antibiotic use, particularly metronidazole and quinolones, and a higher likelihood of developing new-onset IBD in both adults and children, with risks heightened by antibiotic exposure during pregnancy.[17,18,19]

Diet and lifestyle factors, such as the adoption of Western diets high in saturated fats and simple carbohydrates, are contributing to the rising incidence of IBD, especially in newly industrialized countries. In pediatric cases, extended breastfeeding and safe water consumption may reduce the odds of developing IBD and ulcerative colitis. Stressful events have also been identified as novel risk factors for IBD, particularly in children. Stress can lead to the release of corticotrophin-releasing factor (CRF), which increases intestinal permeability and promotes inflammation, exacerbating existing IBD or triggering its onset.[20,21]

Childhood vaccines generally do not increase IBD risk, although studies on the rotavirus vaccine have shown mixed results, with some indicating a reduced risk of IBD in Asian children. Other factors, such as smoking, body mass index (BMI), and body fat percentage, have been associated with an increased risk of Crohn's disease. However, passive smoking has not been found to significantly increase IBD risk in pediatric cases in Saudi Arabia.[22]

d. Immune response

Inflammatory bowel disease (IBD) develops in genetically predisposed individuals due to an impaired immune response against intestinal pathogens. Both innate and adaptive immune systems are involved, with the innate system being activated by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) from damaged cells. In IBD, innate immune functions are altered, leading to further inflammation. Neutrophils, a key component of the innate response, eliminate pathogens through processes like phagocytosis and degranulation, but also contribute to tissue damage and disruption of crypt architecture in IBD. Cytokines play a crucial role in the immunological development of IBD, with pro-inflammatory cytokines (IL-6, IL-12/IL-23, IL-17, IL-1β/IL-18, and TNF) promoting inflammation, while IL-10 acts as an anti-inflammatory cytokine, and IL-22 has a complex role in IBD's etiology.[23,24]

Classifications

IBD is categorized into ulcerative colitis (UC) and Crohn's disease (CD). UC affects the colon continuously, while CD can occur anywhere in the digestive system. A key difference is the pattern of inflammation: UC involves continuous inflammation, while CD often has patchy inflammation. CD is more likely to cause complications around the anus. While both diseases show signs of inflammation and damage, UC is confined to the surface layer of the colon, while CD can affect the entire thickness of the bowel. Granulomas, small clumps of tissue, are often found in CD but rarely in UC.[25]

The Montreal Classification is the most common way to categorize IBD. This system divides CD based on Age (A), Location (L), behaviour (B), and if it affects the area of perianal (p). Based on the age it is classified into A1 category for individuals diagnosed at 16 years of age or younger, while A2 and A3 account for diagnoses made at 17–40 years of age and >40 years of age, respectively .The main types of locations are the small intestine, colon, or both. Based on the location of the disease and the 3 main phenotypes, location of IBD is classified into: involvement of the terminal ileum (L1), colon (L2), or both (L3), with an additional modifier if located in the upper

gastrointestinal location for denoting the presence proximal to the terminal ileum (+L4) (**Table 1**).[26]

Table 1. Montreal classification of Crohn's disease[26]

Age at diagnosis	Location	Behaviour
A1 below 16 y	L1 ileal	B1 non-stricturing, non-penetrating
A2 between 17 and 40 y	L2 colonic	B2 stricturing
A3 above 40 y	L3 ileocolonic	B3 penetrating
	L4 isolated upper disease*	P perianal disease**

*L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present.
**is added to B1–B3 when concomitant perianal disease is present.

In contrast with Crohn's disease, The Montreal classification of disease extent of ulcerative colitis allows extent to be defined into three subgroups (**Table 2**).[26]

Table 2. Montreal classification of extent of ulcerative colitis (UC)[26]

Extent		Anatomy
E1	Ulcerative proctitis	Involvement limited to the rectum (proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

Diagnosis Criteria

IBD is diagnosed based on history and clinical findings, laboratory works, endoscopy, radiology and histopathology. In up to 10% of pediatric cases, it can be challenging to distinguish between CD and UC. As the disease advances, some of these IBD-unclassified cases eventually develop into either CD or UC. Additionally, a small

percentage of children, particularly those with UC, may also have primary sclerosing cholangitis.[27] Suspicions toward IBD are raised when patients present with persistent (-4 weeks) or recurrent (-2 if there are episodes in 6 weeks) symptoms such as abdominal pain, diarrhea, rectal bleeding and weight loss. It may also manifest as anemia, fever, growth retardation, and extraintestinal manifestations (such as episcleritis and erythema nodosum).[28] Patients who experience obvious rectal bleeding or perianal disease (such as abscesses, ulcers, or fistulae, but not skin tags or fissures) should undergo a colonoscopy, regardless of biomarker results. The likelihood of IBD is elevated in children with rectal bleeding or perianal disease. For those with nonspecific symptoms, using blood and stool markers is the best approach to determine which children should undergo endoscopy. However, in children with milder symptoms, distinguishing IBD from other organic or functional disorders can be more challenging. Laboratory results, such as reduced hemoglobin, increased ESR and CRP, thrombocytosis, hypoalbuminemia, suggest IBD. Infectious etiologies should be excluded by stool cultures. Colonoscopy and histology are conducted to confirm the diagnosis. In UC, there is continuous mucosal inflammation of the colon (without small bowel involvement) and granulomas are absent on biopsy. In CD, key features such as skip lesions, well-formed noncaseating granulomas, macroscopic lesions of the upper intestinal tract, stenosis or cobblestoning, and ulcers are usually identified. In addition, various Imaging modalities can be used to diagnose IBD, such as barium small bowel follow-through, computed tomography, magnetic resonance enterography, and bowel ultrasonography. [29]

Clinical Manifestation

IBD is a multifactorial immune disorder characterised by chronic relapsing inflammation of the intestine. Two types of IBD, whether UC and DC, have similar clinical manifestations such as diarrhea, hematochezia, and abdominal pain. However, some differences between UC and DC are found in some aspects like the location and depth of inflammation, complications, and prevalence.[30] Case of IBD in pediatric are found to be more severe than adults and childhood-onset IBD exhibits a higher level of aggressiveness and more rapid progression when compared to IBD that develops in adulthood.[31] Based on a cross sectional study, most common symptoms of CD in pediatric are weight loss (81.81%), diarrhea (72.72%) and abdominal pain (69.69%). Meanwhile in UC, most common symptoms in pediatric are bloody diarrhea (80%), abdominal pain (77.5%) and weight loss (57.5%).[32] Another study in IBD case of pediatric also stated that rectal bleeding is more prevalent in UC.[33] IBD may also affect other organs outside the intestine, called extraintestinal manifestations (EIMs). EIMs may be involved in many systems, such as musculoskeletal, dermatology, oral, and ophthalmological.The most common organs that are involved in EIMs in IBD are joints, skin, and eyes. Based on cross-sectional study, EIMs that commonly manifest in pediatrics IBD are arthritis, oral plaque, and erythema nodosum.[32]

Additional Examination

In any case of suspected IBD, a full blood count including ESR, liver function tests (including albumin), iron status, and CRP should be performed. In IBD patients, anemia, thrombocytosis, hypoalbuminemia, and elevated ESR and CRP levels are typical. On the other hand, in moderate UC (54%) or mild CD (21%), the readings could be deceptively normal.[34]

Stool Examination

Stool tests should be analyzed for occult blood, bacterial pathogens (including Clostridium difficile), as well as ova and parasites. Fecal calprotectin, a protein produced by neutrophils that increases with intestinal inflammation, is becoming a valuable biomarker. It has shown 98% sensitivity and 68% specificity in children suspected of having IBD. In order to rule out infectious diarrhea, a stool culture is required. A recent stool sample should be examined for the presence of Clostridium difficile toxin, particularly if the children has taken many antibiotics. An established enteric infection does not rule out IBD.[35]

Endoscopy and histopathology

Endoscopy is crucial for diagnosing, managing, and treating inflammatory bowel disease (IBD). It is vital for ruling out other causes, confirming diagnoses, distinguishing between Crohn's disease (CD) and ulcerative colitis (UC), tracking disease activity and treatment effectiveness, and identifying and addressing complications. In ulcerative colitis (UC), endoscopic observations often reveal signs such as swelling, diminished vascularity, redness, granular and fragile mucosa, erosions, ulcers, and pseudopolyps. In patients who have not yet received treatment, these symptoms usually start at the rectum and progress continuously in an upstream direction, eventually transitioning gradually to areas of normal mucosa. Several classic features of UC can also be observed in CD. However, three key endoscopic characteristics that help differentiate CD from UC include the presence of aphthous ulcers, cobblestoning, and discontinuous or "skip" lesions. While isolated involvement of the terminal ileum strongly suggests CD, "backwash ileitis" can occur in UC, especially with pancolitis. To resolve diagnostic uncertainties, mucosal biopsies with histological examination, upper gastrointestinal and small bowel endoscopy, small bowel imaging, and serologic markers can provide additional clarity.[36]

Histologically, ulcerative colitis (UC) is characterized by a widespread, continuous pattern of inflammation affecting the mucosa. This inflammation is marked by an elevated density of neutrophils, lymphocytes, and plasma cells in the lamina propria. Additionally, UC presents with epithelial architectural changes, including irregular mucosal surfaces that can resemble a "pseudovillous" appearance and distortion of

the glandular structure. Histological characteristics of Crohn's disease encompass localized active inflammation, marked by neutrophil-induced damage to epithelial glands, as well as nonactive inflammation, which includes transmucosal inflammation with the presence of plasma cells and eosinophils. Additionally, the disease often features granulomas and localized architectural distortion of the glandular structures. The histopathological report for Crohn's disease should thoroughly detail the various morphological aspects of the diagnosis, including: (a) a localized pattern of active inflammation accompanied by architectural distortion of crypts; (b) basal plasmacytosis with the presence of interspersed eosinophils; and (c) the presence of granulomas.[37]

Imaging studies

Cross-sectional imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), are increasingly used for evaluating inflammatory bowel disease (IBD) because they can assess both mural and extramural manifestations of the disease simultaneously. CT findings in IBD can include thinning of the colonic wall, luminal distension, and pneumatosis. In severe cases, these issues can lead to perforation and free air. Common indicators of active Crohn's disease on CT enterography (CTE) include bowel wall thickening, increased mural enhancement with hyperenhancing mucosa, and haziness of the surrounding mesenteric fat.[38]

Magnetic resonance (MR) imaging findings indicative of the acute active inflammatory stage in Crohn's disease (CD) include bowel wall thickening (over 3 mm) with increased signal on T2-weighted fat-suppressed images, early and intense mucosal enhancement, and progressive transmural enhancement on post-gadolinium T1-weighted images. Ulcers and fistulas, best seen on fast imaging with steady-state precession, exhibit strong contrast enhancement. Enlarged adjacent mesenteric lymph nodes (>5 mm) often show contrast enhancement and high signal on diffusion-weighted imaging (DWI). DWI sequences, particularly with high b-values, are highly sensitive (95%) but less specific (82%) for detecting bowel wall inflammation.[39]

Management of Inflammatory Bowel Disease in Children

The management of IBD, which consists of pharmacotherapy, surgery, nutrition, and psychosocial therapy, is individualized to each patient and clinical case. Changing the treatment regimens can be considered if clinical response is inadequate- a decrease of at least 20 points in PUCAI (Paediatric Ulcerative Colitis Activity Index) or a decrease of at least 12.5 in PCDAI (Paediatric Crohn's Disease Activity Index).[40]

5-aminosalicylates

According to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recommended the use of oral 5-aminosalicylates (5-ASA) in first-line induction therapy for mild-to-moderate UC. 5-ASA inhibits multiple inflammatory pathways and possesses antioxidant properties. [41]

Immunomodulators

Immunomodulators, which possess immunosuppressive properties, are recommended in maintaining remission. The Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition (APPSPGHAN) recommended azathioprine (AZA) as a first-line maintenance therapy for CD and UC.[41]

Oral Steroids

According to the ESPGHAN and NASPGHAN guideline, oral steroids are effective in inducing but not maintaining remission. Oral steroids downregulate pro-inflammatory cytokines by the inhibition of protein synthesis and transcription.

In pediatric UC, remission is typically induced using corticosteroids, aminosalicylates, or a combination of both, with maintenance therapy primarily relying on aminosalicylate monotherapy.[42]

Antibiotics and Probiotics

Antibiotics can be used to induce remission in perianal fistulizing disease. Further investigations are required to evaluate the efficacy of these agents in IBD.[43]

Biological agents

Biologic therapy is recommended in induction and maintenance therapy (**Table 3**).[3]

Nutritional therapy

Exclusive enteral nutrition (EEN) can be used to induce remission in CD while partial enteral nutrition (PEN) is used in maintaining remission.[44] Other dietary approaches that can be used as adjuvant maintenance therapy include PEN, specific carbohydrate diet, anti-inflammatory diet, low FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols) diet, and paleolithic diet.[45]

Surgery

Surgery is indicated in emergency cases such as perforation and complete bowel obstruction. Aside from perforations, surgery is recommended in patients with medical treatment failure, bleeding, and toxic megacolon. Elective surgeries are indicated in patients with chronic disease, chronic steroid dependent and high level of dysplasia.[46]

Table 3. Pediatric IBD Biological Agents Treatments

Mechanism of Action	Generic Name	Route of administration	
Anti TNF	Infliximab	IV	CD : Start with intensive treatment in patients who have predictors of poor outcomes and/or significant growth delays. For others, escalate treatment if there is no response to conventional induction therapies (such as EEN or steroids) or maintenance therapies (like methotrexate or thiopurines). UC: Lack of response or loss of effectiveness to conventional induction or maintenance therapy (such as aminosalicylate monotherapy or combination therapy with a thiopurine), also indicated for steroid-dependent UC.
	Adalimumab	SC	CD : Begin with aggressive treatment for patients who have predictors of poor outcomes and/or severe growth delays. For others, escalate treatment if there is no response to conventional induction or maintenance therapies. UC : Loss of response to infliximab or intolerance to infliximab
	Golimumab	SC	UC : Loss of response to standard maintenance therapy
Anti-integrin (a4b7 integrin heterodimer)	Vedolizumab	IV	UC and CD: Anti-TNF failure (nonresponse or loss of response)
Anti-IL-12 and anti-IL-23	Ustekinumab	Single IV-loading dose, then SC maintenance doses	CD: Anti-TNF failure (nonresponse or loss of response)

Conclusion

Inflammatory bowel disease (IBD) presents unique challenges in pediatric patients, characterized by distinctive clinical manifestations and diagnostic complexities. Early and accurate diagnosis, combined with tailored management strategies, including pharmacotherapy and supportive care, is crucial for optimizing outcomes and improving quality of life

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Conflict of Interest

None declared.

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