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Review Article

The Growing Concern of Inflammatory Bowel Disease in Youth: A Review of Trends and Treatment Approaches

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Abstract

Inflammatory Bowel Disease (IBD) is a chronic condition that results in inflammation of the gastrointestinal tract, increasingly diagnosed in children and adolescents. The two main types of IBD, Ulcerative Colitis (UC) and Crohn's Disease (CD) have distinct characteristics. UC primarily affects the colon's mucosal layer, typically starting at the rectum and extending proximally, while CD can involve any part of the gastrointestinal tract, often leading to deeper, transmural inflammation with potential complications such as strictures and fistulas. The etiology of IBD is multifactorial, involving genetic predispositions, environmental influences, and changes in the gut microbiome. Recent epidemiological studies indicate a rising incidence of IBD among pediatric populations, particularly in urban areas of developing nations. Diagnosing IBD in children can be challenging due to nonspecific symptoms and the overlap with other conditions, necessitating a combination of clinical evaluation, endoscopy, imaging, and laboratory tests. Treatment strategies are aimed at inducing and maintaining remission through medications such as corticosteroids, immunomodulators, and biologic therapies, all tailored to the unique needs of young patients. Surgical options, particularly for UC, may involve restorative procedures to preserve bowel function. Long-term outcomes for children and adolescents with IBD include risks of growth delays, nutritional deficiencies, and psychosocial issues.

Keywords: Crohns Disease; Ulcerative Colitis; Remission; Children; Adolescent

Introduction

Inflammatory Bowel Disease (IBD) refers to chronic inflammation of the gastrointestinal (GI) tract, primarily due to an atypical immune response directed at gut microorganisms. IBD typically begins during adolescence or early adulthood and encompasses two main types: Ulcerative Colitis and Crohn's Disease. Each type has distinct patterns regarding the affected location within the GI tract and the severity of tissue involvement [1].

Ulcerative Colitis (UC) involves continuous inflammation restricted to the mucosal layer of the colon. It commonly starts in the rectum (proctitis) and can extend progressively into other regions: to the sigmoid colon (proctosigmoiditis), beyond the sigmoid (distal ulcerative colitis), or even involve the entire colon up to the cecum (pancolitis). In UC, the inflammation pattern is more superficial and limited to the mucosal layer, without affecting deeper layers of the bowel wall.

On the other hand, Crohn's Disease (CD) is characterized by a more aggressive, transmural inflammation that penetrates the entire thickness of the bowel wall, which can lead to complications such as strictures, fistulas, and abscesses. CD can affect any part of the GI tract, though it most commonly impacts the terminal ileum and portions of the colon. CD can be further classified based on its behavior: it may present as inflammatory (primarily involving inflammation), stricturing (narrowing of the GI tract due to scar tissue), or penetrating (development of fistulas or abscesses that invade other tissues or organs).

Both UC and CD are assessed based on disease severity classified as mild, moderate, or severe, and on their specific locations within the GI tract [2,3].

Epidemiology

- The global rates of IBD, including incidence and prevalence, have seen a significant rise, indicating that IBD is becoming a growing health concern worldwide [4].
- While Western countries have traditionally recorded higher rates of IBD, particularly in North America and Europe, countries in Asia have reported a lower prevalence. However, this gap is diminishing, with increasing numbers of cases in Asian regions, particularly among urban populations. This shift is attributed to changes in lifestyle, dietary patterns, and environmental factors that may influence immune response and gut health [5].
- In Western populations, the estimated mean prevalence of IBD is approximately 1 in 1,000 people. In Korea, the prevalence is lower, with rates for CD at about 29.6 per 100,000 and UC at 66.0 per 100,000. Despite being lower, these numbers are gradually increasing and approaching levels seen in the West [6,7].
- Approximately 25% of IBD patients experience their first symptoms before the age of 20 [8].
- Among pediatric cases, the age of onset varies, with around 4% of children developing IBD before the age of 5 and 18% before reaching 10 years. The incidence notably peaks during adolescence [9].
- In Europe, an annual pediatric incidence of 23 cases per 100,000 person-years has been reported, while Asia has seen lower but rising numbers, with 11.4 cases per 100,000 person-years [10].
- In Korea specifically, pediatric IBD incidence rose significantly, from 0.86 per 100,000 in 2011 to 3.33 per 100,000 in 2016 [11].

Pathophysiology

IBD is recognized as a complex, multifactorial condition resulting from an interplay of genetic, environmental, and microbial influences. Genetic predisposition significantly shapes susceptibility, with genome-wide association studies identifying over 200 loci tied to IBD [12]. These genes are largely responsible for encoding proteins that modulate immune responses, mucosal barrier integrity, autophagy, and overall immune homeostasis.

Certain genetic factors have been linked to an increased susceptibility to IBD, with specific genetic markers associated with each subtype. In UC, genes such as HLA-DRB1 and HLA-DQB play a significant role, predisposing individuals to the disease by affecting immune responses and interactions with gut microflora. In contrast, CD has been associated with mutations in the IBD1 gene on chromosome 16q12, specifically involving the NOD2 gene. This mutation contributes to compromised mucosal barrier integrity, which is a key factor in CD pathogenesis, allowing an abnormal immune response to bacteria in the gut [13].

Environmental factors play a critical role, especially as rates of IBD have escalated in developed countries over the past century. Rising incidence and prevalence cannot be solely attributed to genetic makeup, as changes in genetics over such a short period are unlikely. Instead, diet, lifestyle, sanitation, and antibiotic usage are seen as key contributors. The "hygiene hypothesis" suggests that individuals in highly sanitized environments, typical of developed nations, are exposed to fewer infections early in life, potentially leading to an immune system more prone to react against the body's own cells, contributing to immune-mediated diseases like IBD [14].

The gut microbiome's dysbiosis is a prominent area of research, as IBD patients generally show an imbalance in gut bacteria diversity compared to healthy individuals. This dysbiosis involves not just a loss of beneficial bacteria but often an overrepresentation of specific strains, such as entero-invasive Escherichia coli, which can disrupt the gut's mucosal barrier and exacerbate inflammation. In both pediatric and adult IBD, dysbiosis highlights the importance of microbial balance, spurring research into potential microbiomarkers to distinguish IBD subtypes like CD and UC [15,16].

Diagnosis

Clinical presentation

- Pediatric IBD presents with a diverse and complex symptom profile, often varying between UC and CD. In UC, children typically experience pronounced symptoms like persistent diarrhea (98%) and rectal bleeding (83%), which tend to prompt earlier medical attention [13].
- In contrast, CD often presents with a broader array of symp-

toms, including significant weight loss or growth failure (55%–90%), abdominal pain, and intermittent diarrhea (67%–80%), with growth delays sometimes preceding more obvious gastrointestinal issues [17]. This delayed onset of noticeable symptoms in CD can contribute to later diagnosis compared to UC, where bloody diarrhea and abdominal pain are primary indicators [14].

- Perianal disease is a notable complication in pediatric CD, occurring in 15% to 20% of children and progressively worsening over time particularly from 5 to 20 years of age. It manifests in forms like fistulae, abscesses, and skin tags, and the presence of multiple perianal features can signal underlying CD, particularly if accompanied by chronic weight loss [13].
- Extraintestinal manifestations (EIMs) are common in pediatric IBD, often appearing before gastrointestinal symptoms, especially in CD [8].
- About 28% of children may exhibit EIMs at diagnosis, affecting various systems: arthritis and osteopenia (musculoskeletal), erythema nodosum and pyoderma gangrenosum (dermatologic), primary sclerosing cholangitis and pancreatitis (hepatobiliary), uveitis and episcleritis (ocular), and anemia and venous thromboembolism (hematologic). While some EIMs, like episcleritis and erythema nodosum, align with intestinal disease flares, others, such as primary sclerosing cholangitis, remain independent of bowel inflammation [13].
- Children under five, comprising about 10% of pediatric CD cases, may present with rectal bleeding and other severe symptoms, sometimes leading to an initial misdiagnosis of UC [14].
- Additionally, short stature is observed in around 20% of pediatric CD cases at onset, underlining growth challenges as a significant concern in this population.

Histological features

- CD is characterized by transmural inflammation affecting the entire gastrointestinal (GI) tract, from the mouth to the anus, and is most commonly seen in the ileocolonic region. It presents with patchy disease activity, known as skipped lesions, and can feature complications such as strictures and fistulas. Granulomas, which are often present in CD, serve as a histological marker that helps differentiate it from UC.
- In contrast, UC is confined to the colon, marked by continuous inflammation that begins in the rectum and extends proximally, potentially resulting in backwash ileitis in cases of pancolitis, which is common in children [18].
- Both CD and UC show signs of active inflammation, indicated by neutrophil presence, as well as chronic changes such as crypt loss, branching, mucin depletion, and lymphocytosis in the lamina propria.
- However, while UC primarily affects the mucosa, CD can result in more profound, transmural damage [8].
- Noncaseating granulomas may be observed in up to 60% of pediatric CD cases, serving as a distinguishing feature when evaluated in the appropriate clinical context.
- Distinguishing between CD and UC can be challenging in children, especially when CD is limited to the colon. In such cases where a definitive classification is not possible, the term "IBD unspecified" (formerly known as indeterminate colitis) is used [8].

Endoscopy

- The gold standard for diagnosing IBD involves both esophagogastroduodenoscopy and colonoscopy with biopsies from the ileum and colon. In UC, continuous colonic mucosal inflammation that begins in the rectum and lacks small bowel involvement (except in cases of backwash ileitis) is a key endoscopic feature. CD presents endoscopically with patchy inflammation, mucosal aphthous ulcers, cobblestoning, skip lesions, and linear ulcerations [13].
- Colonoscopy with ileal intubation and multiple biopsies is essential to accurately distinguish CD from UC and assess the disease's extent.
- In children, isolated ileal inflammation can present with a normal colon in up to 9% of CD cases, underscoring the importance of ileal examination. Notably, 10-34% of children with new-onset UC may initially lack histological features of chronic colitis.
- Endoscopic evaluation of the upper GI tract via esophagogastroduodenoscopy is recommended in all suspected cases of IBD, regardless of specific upper GI symptoms [14].
- Guidelines from NASPGHAN and ESPGHAN recommend a comprehensive diagnostic approach, including total colonoscopy with ileal intubation, upper endoscopy, multiple biopsies, and thorough small bowel examination to ensure accurate diagnosis and effective management of pediatric IBD [8].

Serology

- Serological markers are valuable tools in diagnosing and assessing prognosis in pediatric inflammatory bowel disease (PIBD).
- Common markers include atypical perinuclear antineutro-

phil cytoplasmic antibody (pANCA), antisaccharomyces cerevisiae antibody (ASCA), antibodies to Escherichia coli outer membrane porin, Pseudomonas fluorescens sequence I2, and flagellin CBir1. However, serology alone has limited predictive accuracy [14].

- In CD, children with positive ASCA IgA/IgG markers have a high likelihood of terminal ileal or ileocecal disease, often necessitating surgical intervention.
- Conversely, CD patients with positive pANCA tend to exhibit pancolitis or left-sided colonic disease, typically sparing the terminal ileum and with less frequent surgical intervention like ileocecal resection [14].

Laboratory markers

- In PIBD, common laboratory abnormalities reflect a chronic inflammatory state, with anemia, thrombocytosis, hypoalbuminemia, and elevated inflammatory markers frequently observed at diagnosis.
- Anemia often results from chronic rectal bleeding, while hypoalbuminemia stems from protein losses due to colonic mucosal damage. Nevertheless, normal laboratory results do not exclude an IBD diagnosis, as up to 33% of cases may exhibit normal inflammatory markers [13].
- Fecal markers, particularly calprotectin, are emerging as useful indicators. Calprotectin, a neutrophil-derived cytosolic protein with bacteriostatic properties, rises in concentration as neutrophils increase within the intestinal lumen during inflammation [19].
- Fecal calprotectin levels below 50 µg/g reliably exclude IBD, while levels above 250 µg/g suggest a high probability of the disease, warranting endoscopic evaluation if infectious causes, such as Clostridium difficile, are ruled out [20].
- Lactoferrin, another fecal marker indicative of neutrophil-mediated inflammation, is sometimes used as an alternative to calprotectin, though its comparative utility is less well-studied [21].

Imaging

- Magnetic resonance enterography (MRE) with oral contrast is the imaging modality of choice due to its high diagnostic accuracy, minimal invasiveness, and lack of radiation exposure, which is crucial for children who may require repeated assessments.
- MRE provides excellent visualization of the intestinal wall and can detect subtle changes such as fibrofatty proliferation, mesenteric hypervascularity, and extraluminal complications like fistulas and abscesses.
- While computed tomography enterography (CTE) is also effective in visualizing active CD inflammation, its use in children is limited due to radiation risks, making it less suitable for routine monitoring [13].
- Ultrasound is valuable, especially in very early-onset IBD (VEO-IBD) cases, where small bowel ultrasonography can be a first-line tool since MRE may require anesthesia in younger patients. It can help detect features like bowel wall thickening, strictures, and mesenteric changes, though it is typically used as a supplementary tool alongside MRE [22].

Management

Goals of treatment

The management goals for CD and UC have shifted significantly, especially with the advent of biologics. The primary objectives now include not just reducing symptoms but also achieving remission, promoting mucosal healing, supporting growth, and altering the disease's natural progression, all while reducing treatment-related toxicity. Effective IBD management in children involves a combination of medical and, when necessary, surgical interventions. The overarching treatment goals focus on eliminating symptoms, improving quality of life, restoring normal growth, and preventing complications. Available therapies are tailored to either induce remission in active disease or maintain remission in stable cases, with some treatments suitable for both purposes [8,13].

Pharmacological treatment

Corticosteroids

- Corticosteroids play a critical role in the initial management of CD and UC, particularly during acute flare-ups or at the time of diagnosis to achieve clinical remission [8].
- Systemic corticosteroids, such as prednisone or prednisolone, are often prescribed at a dose of 1 mg/kg/day, with a maximum of 60 mg per day, and a gradual tapering process is recommended after 2-4 weeks to prevent adrenal insufficiency [23].
- For more severe cases requiring hospitalization, intravenous options like methylprednisolone (1-1.5 mg/kg, maximum dose of 60 mg/day) or hydrocortisone (2-4 mg/kg per dose, maximum 100 mg/dose, four times a day) are given at doses adjusted by weight and are effective at providing a rapid reduction in symptoms [24].
- Although oral corticosteroids show significant efficacy in con-

trolling active symptoms achieving remission in up to 80% of patients within one month, they are not recommended for maintenance therapy. This is due to the risk of steroid dependency, where patients require increasingly prolonged courses to maintain remission, [13] and their inability to induce sustained mucosal healing, which is essential for long-term disease control [8].

- Budesonide (maximum dose of 12 mg/day tapering over 2-4 weeks) is an alternative corticosteroid, formulated to release in specific areas of GI tract and designed with a high first-pass metabolism in the liver, reducing systemic side effects compared to conventional corticosteroids.
- Budesonide is effective in mild to moderate cases, particularly those with disease localized in the distal ileum or right colon.
- There are various budesonide formulations such as pH-dependent capsules target release in the ileum and right colon, while Budesonide-MMX® extends release across the entire colon, providing more targeted action and potentially better symptom control with fewer side effects [24].
- Despite their effectiveness, long-term use of corticosteroids, especially in adolescents, is associated with multiple adverse effects. Physical side effects include growth inhibition, bone density reduction, weight gain, acne, and Cushingoid features, while emotional side effects include mood swings and sleep disturbances [23].
- Consequently, guidelines recommend corticosteroids be reserved for remission induction only, with transition to other therapeutic options if remission is not achieved within 6-8 weeks.
- In cases of steroid dependency or inadequate response, clinicians are advised to consider alternative treatments, such as immunomodulators or biologics, or even surgical interventions if needed [14].

Antibiotics

- Antibiotics like metronidazole and ciprofloxacin are effective for inducing remission in cases of perianal fistulizing CD, particularly when initiating immunosuppressive therapy is delayed due to concurrent infection or the need for surgical intervention.
- These antibiotics help manage infection and inflammation, providing a bridge to further treatments.
- Another antibiotic, rifaximin, which is minimally absorbed systemically, has demonstrated efficacy in achieving remission, especially in colonic CD.
- This benefit was observed in a phase II multicenter, double-blind, placebo-controlled trial with 402 participants, highlighting its potential as an adjunctive therapy in specific CD presentations [25].

Aminosalicylates

- Oral 5-aminosalicylates (5-ASAs), such as mesalamine, are used to induce remission in mild to moderate UC but have limited efficacy in severe UC and are generally not recommended for CD due to inconsistent benefits.
- While 5-ASAs are sometimes used for very mild cases of pediatric CD, studies indicate that children on 5-ASA monotherapy experience more frequent exacerbations, shorter remissions, and prolonged steroid use compared to those on combination therapies (e.g., steroids, antibiotics, immunomodulators) [23].
- The effectiveness of 5-ASA formulations depends on their release sites in the GI tract.
- Oral preparations are designed to target specific sections, with pH-dependent and time-dependent coatings facilitating release in areas like the ileum and colon [24].
- Studies on 5-ASA for maintenance therapy in pediatric UC have shown mixed outcomes. A prospective observational study in 213 children found that 43% maintained steroid-free remission after one year on 5-ASA.
- However, a controlled trial on pediatric CD showed that mesalamine did not significantly reduce relapse rates compared to a placebo [26].
- Sulfasalazine, the oldest 5-ASA drug, is effective but poorly tolerated in many patients due to adverse effects from its sulfa component, such as GI distress, headaches, and fevers, which can lead to compliance issues, particularly in adolescents.
- Newer, sulfa-free formulations (e.g., balsalazide, olsalazine) minimize these side effects and provide an effective alternative for inducing and maintaining remission in mild to moderate UC [23].
- For adolescents, drug compliance can be challenging due to dosing frequency and pill burden, as traditional regimens require multiple daily doses.
- Newer, once-daily dosing options (1.6 g–4.8 g/day), as well as formulations with fewer pills, have improved adherence.
- When topical treatments are needed, discussing their benefits and establishing a clear timeline for tapering is essential to encourage compliance, especially in adolescents [23].

Exclusive and partial enteral nutrition

Exclusive enteral nutrition (EEN)

- EEN is increasingly recognized as a primary therapeutic strategy for children with newly diagnosed CD, aimed at inducing clinical remission and promoting mucosal healing.
- This treatment involves the exclusive use of elemental, semi-elemental, or polymeric formulas to provide 120% to 150% of the patient's daily caloric requirements over a period of 8 to 12 weeks.
- EEN has been shown to be effective in achieving clinical remission in up to 85% of newly diagnosed CD children and mucosal healing in approximately 74%, making it as effective as corticosteroids.
- Unlike corticosteroids, EEN supports growth in pediatric patients and minimizes the risk of serious systemic side effects, such as those associated with steroid use.
- The mechanisms contributing to EEN's effectiveness may include alterations in the gut microbiome, direct delivery of essential micronutrients, elimination of potential dietary allergens, enhancement of gastrointestinal permeability, and reduction of inflammatory cytokines in the gut.
- Despite its proven benefits, EEN is more widely adopted in Europe than in North America, where its use is limited by various barriers.
- These include the strict adherence to a liquid formula diet, which can be challenging for patients to maintain, particularly due to the poor palatability that often necessitates the use of a nasogastric tube for feeding.
- Additionally, the cost of specialized formulas can be prohibitive for some families, further complicating access to this treatment option.

Partial enteral nutrition (PEN)

- PEN involves using a liquid formula to cover 25% to 50% of a patient's total daily caloric intake, allowing for a regular diet during the day.
- While PEN has been shown to be beneficial for maintaining nutritional status and supporting remission alongside maintenance medications, it has not demonstrated efficacy in inducing remission during active disease.
- Rotating formulas in PEN can improve patient compliance by mitigating taste fatigue [27].

Immunomodulators

Thiopurines

- Thiopurines, such as azathioprine (AZA) and its metabolite 6-mercaptopurine (6-MP), are widely used for the maintenance of remission in children and adolescents with CD and UC.
- As immunomodulators, they help sustain remission achieved through corticosteroids but are not suitable for immediate symptom control due to their delayed onset of action, typically requiring 8–12 weeks to become effective.
- These drugs are often used in combination with anti-TNF agents to reduce the risk of antidrug antibodies, which can limit the efficacy of biologics.
- The effectiveness and safety of thiopurines are influenced by individual genetic variations in enzymes such as thiopurine methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15), which affect drug metabolism.
- Standard dosing guidelines suggest full doses (2.5 mg/kg/day or MP 1–1.5 mg/kg/day) for those with normal enzyme activity, while patients with intermediate activity should receive a reduced dose, and those with very low or absent enzyme activity should avoid thiopurines altogether.
- However, adverse effects like myelosuppression and hepatotoxicity occur in a significant portion of patients, especially within the first year of treatment, thereby requiring regular monitoring of blood counts and liver enzymes, particularly during dose adjustments and early stages of treatment.
- Thiopurines also carry risks of transaminitis, pancreatitis, and rare but severe complications, such as lymphomas, especially hepatosplenic T cell lymphoma (HSTCL) in young males on long-term therapy [23].

Methotrexate (MTX)

- MTX is a valuable immunomodulator for IBD, particularly as an alternative to thiopurines, which carry a slight risk of lymphoma. MTX is often prescribed for CD, either alone or with anti-TNF agents to minimize antibody formation that can reduce the efficacy of biologic treatments. Research shows that about 50% of pediatric patients achieve remission during the induction phase, with around 37% maintaining remission [28]. In children, MTX doses range from 10-17.5 mg/m^2 once weekly, administered either subcutaneously or orally, with a maximum dose of 25 mg. Once remission is sustained for 3-6 months, the maintenance dose may be reduced to 10 mg/m^2, with a maximum of 15 mg weekly.

- To reduce side effects like GI upset and leukopenia, patients are advised to take daily folic acid (1 mg); alternatively, 5 mg can be taken as a single dose 24-72 hours after MTX administration to support adherence in adolescents. Because MTX is teratogenic, adolescents should be counseled on safe sex practices and effective contraception. Regular monitoring of CBC and LFTs is essential initially weekly and later every 3-6 months due to risks of bone marrow suppression and hepatotoxicity [23].
- Although well tolerated, MTX can cause side effects, with nausea being most common, affecting up to 20% of patients. This can be managed with antiemetics such as ondansetron administered before MTX dosing. Other adverse effects may include flu-like symptoms, transaminitis, and, less frequently, myelosuppression, which may require dose adjustments or discontinuation. While severe liver damage is uncommon, transient or persistent liver enzyme elevations occur in some patients, underlining the importance of monitoring [24].

Biological agents

Anti-TNF agents

- Tumor necrosis factor (TNF) is a pro-inflammatory cytokine produced by macrophages, adipocytes, fibroblasts, and T cells, which triggers a cascade of events leading to tissue damage.
- Anti-TNF agents such as infliximab (IFX) and adalimumab (ADA) inhibit TNF-mediated pathways, which can lead to mucosal healing (MH), a significant therapeutic goal indicating potential for sustained clinical remission [24].
- Unlike previous strategies focused solely on clinical responses, the newer approach emphasizes "deep remission," which includes achieving MH.
- IFX was the first biologic approved for moderate to severe pediatric CD and has transformed management strategies for children [29].
- The latest consensus guidelines from ECCO/ESPGHAN explains the importance of IFX and ADA for treating moderate to severe pediatric IBD, particularly when conventional therapies are ineffective or contraindicated.
- IFX is now commonly used as primary induction therapy in children with active perianal fistulizing disease, especially when combined with surgery.
- In pediatric patients with luminal disease, response and remission rates for IFX can reach up to 90% and 55-60% at one year, respectively. However, repeated IFX administration may lead to immunogenicity, resulting in diminished efficacy or delayed hypersensitivity reactions [29].
- About 10-25% of children may be classified as primary anti-TNF non-responders post-induction (6 weeks).
- Secondary loss of response can occur when patients develop antibodies against the drug, but using thiopurines or methotrexate concurrently can help maintain efficacy.
- Therapeutic drug monitoring (TDM) is crucial for optimizing IFX therapy, with studies indicating that trough levels below 3 mg/mL during maintenance correlate with treatment failure.
- Children with lower serum albumin levels may require more than the standard maintenance dose to achieve optimal drug concentrations and prevent loss of response [24].
- ADA is a fully human IgG1κ monoclonal antibody targeting TNF-α, designed to minimize immunogenicity.
- ADA has been approved for pediatric CD in Europe and the United States, supported by the IMAgINE-1 phase-3 study involving 192 pediatric patients. This study examined how various factors influence ADA pharmacokinetics and found that higher serum concentrations correlate with better clinical outcomes, with a one-year remission rate of around 45% in anti-TNF naive children and nearly two-thirds of those who previously failed IFX showing efficacy with ADA [24].
- A systematic review highlighted ADA's reasonable safety profile, indicating it as an effective option for managing pediatric CD, especially for patients unresponsive to IFX therapy [29].

Vedolizumab

- Vedolizumab (VEDO), an anti-integrin monoclonal antibody approved in 2014 for treating moderate to severe CD and UC in adults who are biologic-naïve patients or those who have failed anti-TNF therapies, is an innovative biologic that specifically targets gut inflammation, minimizing the risk of systemic immunosuppression and associated complications.
- By blocking the α4β7 integrin on lymphocytes, VEDO prevents these cells from migrating into the intestinal tissue, thereby reducing local inflammation. Unlike its predecessor, natalizumab, which has a broader action affecting both the GI tract and CNS, VEDO's gut-specific mechanism significantly lowers concerns of progressive multifocal leukoencephalopathy (PML) [24].
- In pediatric studies, VEDO has shown promise, especially in UC, with clinical response rates around 50% during induction and a favorable safety profile, though pediatric data remain limited.

- Additional findings from a European multicenter study showed 37% of UC and 14% of CD pediatric patients achieved steroid-free remission at week 14. While its efficacy in CD is relatively slower and less potent compared to UC, VEDO's safety profile is advantageous, avoiding risks like tuberculosis or lymphoma.
- However, its limited action may require additional immunosuppressants to manage extraintestinal IBD manifestations, and its efficacy remains lower for CD [23].

Ustekimunab

- Ustekinumab (USTE) is a monoclonal antibody that inhibits interleukins 12 and 23 by targeting the shared p40 subunit.
- Approved in 2016 for CD and in 2019 for UC, it is used in patients who are anti-TNF-naive or have not responded to anti-TNF therapies.
- While pediatric data is limited, a study of 52 children and adolescents showed promising results with weight-based intravenous induction doses followed by 90 mg subcutaneous doses every eight weeks, with dose adjustments as needed [30].
- USTE offers a favorable safety profile, convenient dosing, and effectiveness for related conditions like psoriasis and arthritis.
- Comparing newer biologics, recent studies indicate that ustekinumab, targeting IL-23, may provide superior steroid-free and biochemical remission in refractory CD patients over VEDO [31].

Tacrolimus

- Tacrolimus, an immunosuppressive agent primarily used to prevent organ transplant rejection, works by inhibiting FK-binding protein to suppress T-cell activation, reducing proinflammatory cytokines like IL-2, TNF-α, and IFN-γ.
- Though data on its use in pediatric CD and UC is limited, tacrolimus is typically administered at 0.1 mg/kg/day in two doses, aiming for a trough level of 4–13 ng/ml.
- Regular blood monitoring is necessary to check electrolytes, creatinine, blood counts, and drug levels.
- Potential side effects include hypertension, seizures, neurotoxicity, and infections, making tacrolimus suitable as a bridging therapy or a temporary measure to postpone colectomy in adolescents with refractory IBD [23].

Surgical management

Ulcerative colitis

- Restorative proctocolectomy is a definitive procedure for UC, particularly beneficial for children with severe disease that does not respond to aggressive medical treatment. This surgery involves removing the diseased colon and creating a pouch from the end of the small intestine, which is then attached to the anus, preserving bowel continuity and avoiding a permanent ileostomy. While this procedure often results in improved quality of life comparable to the general population, a notable risk includes the development of chronic pouchitis, which may require ongoing management [8,14].
- In pediatric UC, about 8-26% of patients will need a colectomy within five years of diagnosis. Children undergoing elective colectomy typically have better outcomes and fewer complications than those needing emergency surgery. Post-surgery, children generally maintain a good health status and quality of life (QOL), comparable to peers without UC [24].
- For UC, elective surgeries are generally completed in a 2-stage procedure, especially for patients in stable condition. In this approach, a restorative proctocolectomy with ileoanal pouch anastomosis and an initial diversion (ileostomy) is performed in the first stage, followed by ileostomy closure in the second stage. This approach minimizes complications and is preferred for those with controlled disease and stable nutritional status.
- In urgent UC cases, a 3-stage surgical approach is more common. The first stage involves a subtotal colectomy with ileostomy, allowing for stabilization before the more complex pouch creation procedure.
- A modified 2-stage procedure is also emerging as a feasible option, particularly for patients with severe disease or poor nutritional status. In this variation, a subtotal colectomy with ileostomy is performed first to allow for recovery, followed by ileoanal pouch creation without requiring an additional ileostomy [13].

Crohn's disease

- For pediatric CD, surgery is a key option but is not curative due to the transmural nature of the disease. It's primarily reserved for inducing remission in localized disease or managing complications such as strictures, fistulas, and growth failure when medical therapy fails. This "surgically induced remission" is often temporary, necessitating subsequent maintenance therapy. Studies indicate a high recurrence rate

in CD post-surgery, with around 50% of patients experiencing recurrence within one year and 77% within a decade [32]. Younger age at resection, disease location, and surgical complications may increase the likelihood of recurrence and the need for additional surgeries [24].

- Surgical interventions in CD depend on the specific complication. For strictures, resection or stricturoplasty (bowel-preserving surgery) is often performed, especially for single or short segments. Fistulizing disease, where inflammation causes abnormal connections between organs, may involve resection with primary anastomosis. Medical therapy, often with biologics like infliximab, is typically attempted first for perianal or intestinal fistulas due to its efficacy in managing inflammation
- Emergent surgeries for CD, though rare, are necessary in life-threatening situations, such as perforation, severe bleeding, or complete bowel obstruction. In such cases, the primary aim is to manage sepsis, control bleeding, and, where feasible, preserve as much bowel as possible to minimize long-term complications.
- Managing perianal CD requires controlling infections and abscesses, supported by optimized medical treatment. For small abscesses (1–4 cm), incision and drainage are conducted with additional counterincisions to improve drainage, breaking loculations, and irrigating the area.
- A silicone vessel loop is then placed to maintain drainage. Larger abscesses (over 4 cm) may need more counterincisions and a Penrose drain for effective drainage.
- Fistulas, whether accompanied by an abscess or not, are managed with seton placement to allow continued drainage; these setons can remain indefinitely based on symptoms and inflammation observed on MRI.
- Fistulotomy is avoided in perianal CD to reduce the risk of wound healing issues and incontinence, as well as its known association with a lower quality of life in CD patients [13].

Long term outcomes

Nutritional deficiencies

Adolescents with IBD face an increased risk of vitamin and mineral deficiencies due to several factors, including active disease, chronic blood loss, malabsorption, lactose intolerance, poor dietary habits, and inadequate oral intake. It is essential to conduct annual assessments of vitamin and mineral levels and to periodically review patients' diets. This approach encourages the consumption of nutrient-dense foods rich in calcium, vitamin D, iron, folate, and vitamin B12 [23].

Children with IBD are particularly susceptible to macronutrient and micronutrient deficiencies, with weight loss reported in up to 70% of those with CD and 34% with UC. Nutritional support is vital for long-term survival and quality of life. Managing nutrition is as crucial as pharmacological treatment in pediatric IBD. The location of the disease and any history of surgical resection should guide proactive screening for specific micronutrient deficiencies, such as vitamin B12 following terminal ileum resection or zinc loss from diarrhea or high-output fistulas [24].

Vitamin D deficiency is common in IBD patients, with 35% of children exhibiting levels below 15 ng/mL and 60% having suboptimal levels (<30 ng/mL). Beyond supporting calcium absorption and bone health, vitamin D is believed to help maintain intestinal immune homeostasis and epithelial integrity. Children with low levels of vitamin D are more prone to disease recurrence, and maintaining serum levels above 30 ng/mL increases the likelihood of clinical remission [8]. Regular screening and treatment for vitamin D deficiency, including a dosage of 50,000 IU/week, are recommended to achieve adequate levels [24].

Anemia in IBD typically arises from a combination of chronic iron deficiency (microcytic) and anemia of chronic disease (normocytic). Mean corpuscular volume may not accurately indicate iron status due to various influencing factors, including megaloblastosis caused by thiopurines. Intravenous iron infusion is preferred in active disease, and vitamin B12 or folate deficiencies should be considered in patients with extensive small bowel resections [33].

Growth failure

Adolescence, a critical developmental stage between childhood and adulthood, usually spans from ages 9 to 19. This period is marked by significant physical, hormonal, and psychological changes, which can be profoundly affected by chronic inflammatory conditions like IBD. Among the challenges faced by children and adolescents with IBD, growth failure and delayed puberty are particularly common. Growth impairment in IBD patients often stems from malnutrition, malabsorption, increased gastrointestinal losses, higher caloric needs, inflammation-induced growth hormone resistance, and corticosteroid use. Growth failure is especially prevalent in CD, affecting about 40% of pediatric patients compared to 10% in those with UC. This condition can precede gastrointestinal symptoms, sometimes by several years, leading to short adult stature in nearly one in five children and often causing pubertal delays, especially in boys with CD.

Early intervention and multidisciplinary care, including disease management, limiting steroid use, and referrals to pediatric endocrinologists and dietitians, are essential. While corticosteroids can hinder growth, enteral feeding has been shown to improve short-term weight gain, and anti-TNF therapy, such as infliximab, can enhance growth velocity by controlling disease activity and maintaining remission. Growth monitoring through regular height, weight, and BMI measurements at each visit can help detect early signs of disease relapse and growth issues [34,35].

Bone deficiencies

Most individuals reach their peak bone mass by adolescence (around 16 years for boys and 18 years for girls) which is essential for lifelong bone health and minimizing fracture risks. However, adolescents with IBD, especially CD, face greater challenges in achieving optimal bone metabolism. Factors such as delayed puberty, poor nutrition, low intake of vitamin D-rich foods (like dairy), malabsorption, low body mass index (BMI), ongoing inflammation, and corticosteroid use all contribute to this risk. Additionally, active IBD often results in low energy, decreased muscle mass, and increased fatigue, which can lead to physical inactivity and further impede bone development [23].

To monitor bone health in pediatric IBD patients, the International Society of Clinical Densitometry recommends dual-energy X-ray absorptiometry (DXA) scans of the total body and lumbar spine, especially for those with low BMI, severe disease, or malnutrition. The DXA scan's z-score measures the patient's bone mineral density (BMD) relative to peers of the same age and sex, helping to identify low BMD. For adolescents with low BMD, a referral to a pediatric endocrinologist is advised. Follow-up DXA scans after six months can track bone mass changes due to IBD therapy. Interventions may include improving nutritional intake, increasing dietary or supplemental calcium and vitamin D, and promoting weight-bearing exercises within the patient's ability [36].

For optimal bone health, dietary guidelines for children and adolescents with IBD recommend daily intake of 1,000 to 1,600 mg of elemental calcium and 800 to 1,000 IU of vitamin D [8].

Colon cancer

While pediatric data on IBD-associated colorectal cancer is limited, research suggests that prolonged disease duration increases cancer risk. A study of 698 pediatric IBD patients identified two colon cancer cases during a median follow-up of 15 years [37]. Studies indicate that individuals diagnosed with IBD before age 15 face higher colorectal cancer risk over a 35-year period, with instances of colon cancer in patients as young as 15 after a decade of UC [38].

Following adult guidelines, such as those from the American Society for Gastrointestinal Endoscopy and ECCO, surveillance colonoscopies are recommended every 1–2 years starting 7–10 years after diagnosis, especially for patients with concurrent PSC, which further increases cancer risk [8,39,40].

PSC also increases the likelihood of other cancers, including hepatocellular carcinoma and gallbladder cancer, thereby requiring regular imaging and monitoring with liver specialists [23].

Cervical cancer

Adolescent girls and women with IBD face a heightened risk of cervical dysplasia, particularly when using thiopurines or other immunosuppressive treatments. Given that most cervical cancer cases are linked to HPV, it's highly recommended that both adolescent girls and boys receive the HPV vaccine. For sexually active adolescents, regular Pap smear screenings should also be considered to monitor for early signs of cervical changes [23].

Toxic megacolon

Toxic megacolon is a severe and potentially life-threatening complication of IBD, especially ulcerative colitis, marked by systemic toxicity symptoms (such as fever, rapid heart rate, elevated WBC count, and mental status changes) alongside colonic dilation, which may affect part or all of the colon. This condition has a high risk of morbidity and sometimes necessitates bowel resection. Infections, particularly Clostridium difficile, are common in IBD patients and can trigger toxic megacolon. In cases where medical treatment is ineffective, colectomy may be required in children [14].

Smoking hazards

Smoking is known to exacerbate symptoms in CD, leading to increased flare-ups, complications, and a higher likelihood of requiring surgery. Moreover, it can contribute to disease recurrence after surgical interventions. Therefore, adolescents with CD should be strongly advised to refrain from smoking, and those who already smoke should be encouraged to participate in smoking cessation programs.

Additionally, it is crucial for parents and caregivers of adolescents with CD who smoke to quit as well, since second hand smoke

can negatively affect the health of the child. The rising popularity of electronic cigarettes among teenagers is also a concern, as these devices contain harmful chemicals that can adversely impact health and should be discouraged [23].

Psychosocial health

During adolescence, a crucial phase characterized by self-exploration and the quest for independence, the presence of IBD can significantly disrupt psychosocial development. The chronicity of IBD, combined with the unpredictability of flare-ups and complications, leaves many teenagers grappling with feelings of fatigue that persist even when the disease appears controlled. This ongoing struggle can adversely affect their academic performance, athletic endeavors, social interactions, and emotional health.

Adolescents with IBD often experience feelings of isolation, perceiving themselves as "missing out" on life. They may find themselves unable to participate in eagerly awaited activities with peers, such as sports competitions, proms, or summer camps. This exclusion can foster a greater dependence on caregivers, amplifying feelings of helplessness and limiting their independence at a critical time in their lives. Furthermore, the pressures of regular clinical appointments and potential infusion therapies compound the challenge, as teenagers face societal expectations to excel in both academic and extracurricular activities, all while curating an image of a carefree and happy life on social media.

A significant portion of adolescents, nearly 25%, may encounter symptoms of depression and anxiety, which frequently remain unrecognized without proactive screening by healthcare professionals. The failure to address these mental health concerns can lead to poor adherence to treatment regimens and a subsequent exacerbation of IBD symptoms. Tools such as the Children's Depression Inventory serve as quick and effective screening methods, with a score of 10 or above indicating a need for early referral to a mental health specialist. This professional support can provide adolescents and their families with coping strategies and appropriate therapeutic interventions, such as cognitive behavioral therapy (CBT) [23].

Encouraging adolescents to engage with peers who also have IBD through platforms like summer camps or online support groups, can help cultivate a sense of community. This connection not only fosters resilience but also empowers young people to effect positive change in their own lives and in the lives of others, enhancing their overall QOL.

A meta-analysis involving 1,167 IBD patients found that depressive disorders were significantly more prevalent among young individuals with IBD, revealing an odds ratio of 5.80, suggesting a substantial psychological burden. The unpredictable nature of IBD symptoms, with the social embarrassment stemming from frequent bathroom use, complicates their psychosocial adjustment. Additional factors, such as concerns over potential growth delays and self-acceptance issues, further exacerbate the mental health challenges faced by these adolescents [41].

A multicenter observational study of 99 adolescents with Crohn's disease found a direct correlation between disease severity and increased parental stress, negatively impacting the adolescent's QOL [42].

The correlation between the severity of disease activity and psychological symptoms is evident, with factors such as the effects of pro-inflammatory cytokines on the brain, sleep disturbances, and the impact of corticosteroids contributing to mental health challenges. CBT has proven effective in managing these issues, with pharmacotherapy serving as a potential adjunct treatment when necessary.

Physical symptoms like abdominal pain, fatigue, and diarrhea not only affect quality of life but also hinder social functioning. Pediatricians and primary care providers should collaborate with families to develop formal plans at schools (such as a 504 plan in U.S. public schools) that ensure proper accommodations for students with IBD, including unrestricted restroom access and extended deadlines for assignments after periods of absence [41,43].

Conclusion

IBD poses significant challenges for children and adolescents, impacting their physical health, growth, and psychosocial well-being. The increasing prevalence of IBD in younger populations necessitates a proactive approach to diagnosis and management, as early intervention can significantly affect long-term outcomes. PIBD management must be tailored to address the unique needs of this age group, focusing on not only medical treatment but also nutritional support and mental health care. The interplay of genetic, environmental, and microbiological factors complicates the disease, underlining the importance of continued research to enhance our understanding and treatment of IBD. Healthcare providers must adopt a collaborative, multidisciplinary approach, ensuring comprehensive care that includes education, emotional support, and regular follow-ups.

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