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Viral Infection in Enhance the Inflammatory Bowel Disease in Children: A Review

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Abstract. Viral infections, which typically have a high rate of morbidity and mortality, are more challenging to identify. In particular, studies on rotavirus, hepatitis B virus, bacteriophages, enteric viruses, cytomegalovirus, and Epstein-Barr virus were evaluated for IBD. These results suggest that IBD patients are more likely to get viral infections. Therefore, medical practitioners should be more aware of the increased risk of viral infections in patients with inflammatory bowel disease. The incidence and prevalence of childhood-onset inflammatory bowel diseases (IBD), which include ulcerative colitis and Crohn's disease subtypes, have significantly increased in recent years, making them important pediatric chronic diseases on a global scale. Childhood-onset IBD is more widespread and dangerous than adult-onset IBD. The biological treatment for juvenile IBD is anti-tumor necrosis factor therapy, and more treatment options are urgently needed. Currently, this patient population is prescribed off-label other biologic medicines such as Steinman, and vedolizumab. Understanding the viral infection's causes, diagnosing and tracking the illness, treating patients, and managing the psychological and physical effects of having IBD are all crucial. Globally, the frequency of IBD varies greatly; estimates place the number of affected individuals at 2.2 million in Europe and 1.6 million in the United States.

Highlights:

1. Viral infections increase risk in IBD patients; awareness is crucial.
2. Childhood-onset IBD is rising; better treatments are urgently needed.
3. Global IBD cases exceed 3.8 million; management and diagnosis are vital.

Keywords: Viral Infection, Enhanced, Inflammatory Bowel Disease.

Introduction

Two clinical manifestations of inflammatory bowel disease (IBD), a collection of illnesses marked by chronic gastrointestinal inflammation, are Crohn's disease and ulcerative colitis which is not caused by a particular disease-producing organism. These two forms of IBD primarily differ in their pathological and clinical characteristics [1,2]. The colon is affected by ulcerative colitis, a distal-predominant, diffuse mucosal disease.

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Almost always, the rectum is affected, and other parts of the colon that reach proximally from the rectum in a continuous pattern may also be affected. CRD can affect any part of the gastrointestinal tract, however it most frequently affects the colon and distal small bowel. Deep fissuring ulcers are one of the many ways that inflammation, which is typically transmural, can appear, transmural scarring, tiny ulcers over lymphoid follicles, and persistent inflammation [3,4].

Males are more likely than females to be diagnosed with inflammatory bowel disease, which often affects those between the ages of 15 and 35. The worldwide increase in IBD may be due to dietary modifications, environmental contaminants, or genetic predisposition factors. To better comprehend IBD and strive toward improved treatment, it is imperative to acknowledge its global reach [5,6]. From little stomach pain to serious bleeding in the gastrointestinal tract, IBD can cause a wide range of symptoms. Anti-integrin monoclonal antibodies and anti-tumor necrosis factor are examples of biologics as well as immunomodulators like steroids and azathioprine, can be used to treat IBD. However, using anti-TNF medication with steroids increases the risk of developing opportunistic infections, which include bacterial, fungal, and viral infections [7,8].

IBD was previously mostly diagnosed in Western nations. However, the number of IBD diagnoses has increased over the last 20 years in some regions, including Asia, Africa, Eastern Europe, and South America [9,10]. Globally, the frequency of IBD varies greatly; estimates place the number of affected individuals at roughly 1.6 million in the US and 2.2 million in Europe [11,12]. One out of every 250 individuals worldwide are thought to have IBD. However, because of underdiagnosis and underreporting, it is challenging to pinpoint the precise number of individuals with IBD. The objective of this review was to determine the role of viral infection in the enhancement of inflammatory bowel disease in children [13,14]. A conducted study in AL-Mosul city 2019, showed the prevalence of Human Cytomegalovirus (HCMV) in patients with IBD was 13.85% [15,16].

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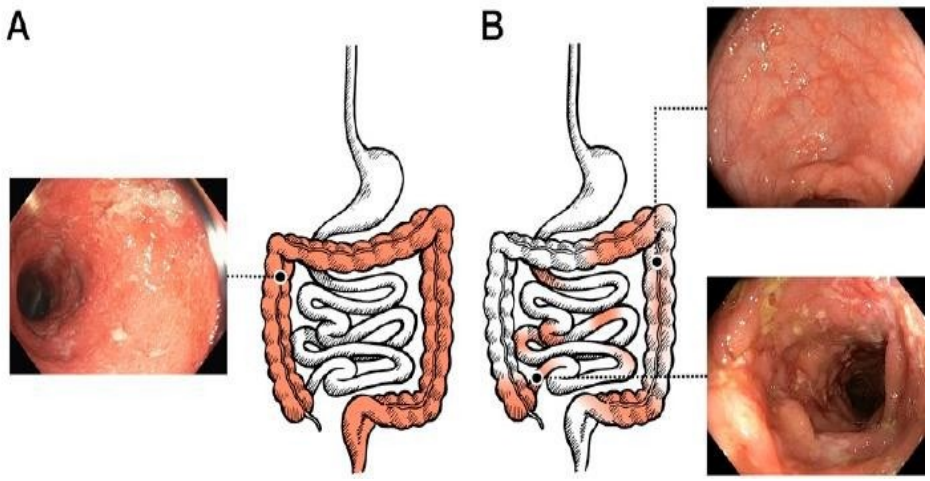

Figure-1: Common inflammatory patterns and endoscopic pictures in pediatric IBD. A: UC. Pancolitis. Erythema exudates, and a lack of vascular pattern are symptoms of diffuse inflammation. B: CD. Omitted the upper and lower gastrointestinal tract lesions. The terminal ileum has deep longitudinal ulcers. In the descending colon, there are several aphthous ulcers.

Epidemiology

IBD rates have increased globally, however precise estimates are still lacking. With a faster rise in incidence in younger children, one of the highest rates of IBD among children is found in Ontario. In the mid-1990s, the number of IBD diagnoses in Scotland increased by almost 76%, and the diagnosis was made at a younger age. People who move from low-prevalence to high-prevalence areas are more likely to acquire IBD, particularly first-generation children [8]. While PIBD is less prevalent in Indigenous populations, it is on the rise in children of European ancestry, according to data from Australasia. Over ten years, the prevalence of ulcerative colitis rose 2.7 times in a northern California community-based healthcare delivery system. Compared to Hispanic children and those with Crohn's disease, Asians were more likely to have ulcerative colitis. IBD was three times as common in South Asians in British Columbia than in non-South Asians [9].

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Pathophysiology

Inflammation and immunity illness are bowel diseases. In recent years, it has become clearer how innate and adaptive responses interact with the sickness process. Studies of genome-wide correlations have identified more than 200 genetic loci associated with IBD [10]. Because they encode proteins involved in autophagy, innate and adaptive immunity, and the integrity of the mucosal barrier, these genes are critical for immunological homeostasis. Therefore, an irregulated immune response to commensal gut bacteria is thought to be the origin of chronic inflammation, leading to an underlying genetic susceptibility. Environmental variables likely influence many pathophysiological processes, including how food and antibiotic use impact microbial diversity and the function of the epithelial barrier [17,18].

Certain bacterial families are more prevalent in the microbiome of people with Crohn's disease, while other bacterial families are less prevalent. It has been noted that entero-invasive Escherichia coli strains are more prevalent in IBD [19,20]. The involvement of environmental variables and the microbiome in the development of autoimmune and inflammatory diseases, such as IBD, has garnered more attention recently. According to the hygiene hypothesis, those who grow up in hygienic environments are more likely to contract immune-mediated illnesses like IBD. In line with the hygiene theory, a systematic study discovered a negative correlation between many environmental hygiene-related parameters and the risk of IBD [21,22].

The Role of Viral Infection in Inflammatory Bowel Diseases

1- Epstein-Barr Virus (EBV)

95% of individuals worldwide are infected with EBV, a herpes virus that is primarily spread through bodily fluids and blood. EBV is known to infect B cells, but it is also connected to several autoimmune disorders, malignancies, and inflammatory conditions like ulcerative colitis and Crohn's disease. EBV-positive cells have been found in IBD patients' colonic mucosa in earlier research. These cells are created by an increase in B cells and an increase in EBV replication following immunosuppressive therapy [23,24].

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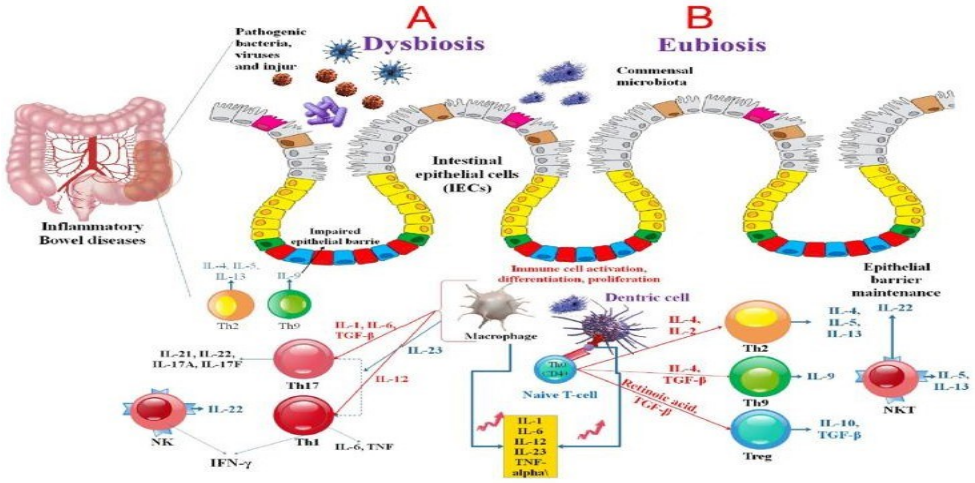
2- Cytomegalovirus (CMV)

With 236 kbp of genomic material and over 200 open reading frames (ORFs). The double-stranded DNA genome of herpesviruses is located in their icosahedral capsid. Previous studies have shown that can boost the synthesis of transcription molecules and chemokines in IBD patients, which can activate T cells and promote CMV reactivation [25,26].



3- Enteric viruses

Enteroviruses, rotaviruses, noroviruses, adenoviruses, and sapoviruses are examples of enteric viruses. RNA viruses belonging to the Picornaviridae family are known as enteroviruses. Hepatitis, polio, lung infections, encephalitis, and gastroenteritis can all be brought on by enteric viruses [27,28].

Enteroviruses have been discovered in CD patients' terminal ileum, and their detrimental effects on IBD are explained by their interactions with HBGA-like molecules [29,30]. The greatest recent study used a PCR panel of gastrointestinal pathogens to gather data from 9,403 individuals over two years, including 13,231 stool samples. In this study, Axelrad et al. contrasted 8826 controls with 577 IBD patients (277 CD and 300 UC) [31,32].

4- Rotavirus (RV)

RV is a non-enveloped triple-layered segmented double-stranded RNA (dsRNA) virus that infects adult intestinal epithelial cells (IECs). It is the most common cause of acute gastroenteritis, diarrhea, and dehydration accounting for about 200,000 deaths per year among young children and newborns worldwide [33,34].

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It was believed that the RV immunization, which was authorized for use in infants in 2006, was contributing to a rise in the incidence of IBD in American children. Inflammation of the gastrointestinal mucosa and immunological dysregulation may result from attenuated RV immunization. According to the results of this sizable pediatric cohort, the incidence of IBD in young children over 10 years has slightly increased [35,36].

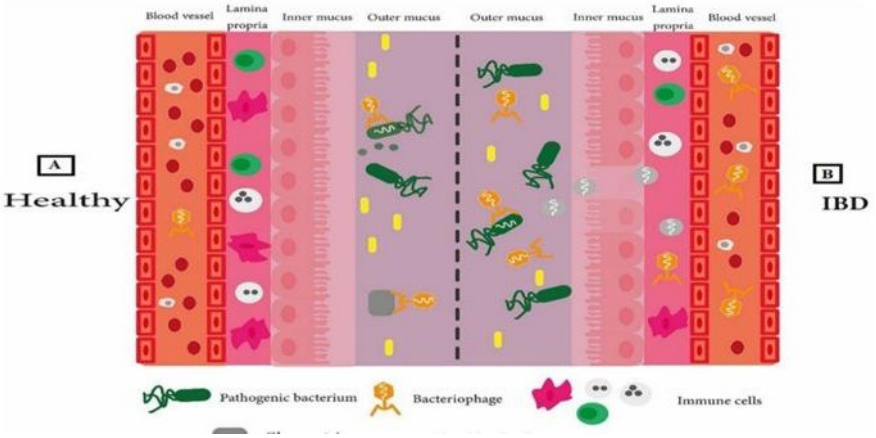
5- Hepatitis B Virus

The frequency of HBV in individuals with IBD has been the subject of numerous studies. Hepatitis reactivation is a problem with immunosuppressive treatments for people with IBD. A 1.5–2-fold rise in alanine aminotransferase (ALT) levels in comparison to baseline and the start of viral replication are its defining characteristics. HBV raises the likelihood of liver fibrosis in IBD patients [37,38].

6- Bacteriophages

Bacteriophages are essential to the evolution of microbial species because they are bacterial predators. It is anticipated that the gut microbiota, which is important for many illnesses, will have a major impact on IBD. Dysbiosis of the intestinal tract, which causes IBD, is influenced by the gut's predominant bacteriophages. Members of the Myoviridae, Podoviridae, Siphoviridae, and Microviridae families—all of which are prevalent in the human gastrointestinal tract—are caudovirales phages [39,40].

Phage presence frequently presents variably in UC and CD, two forms of IBD. Patients with IBD express phages differently than healthy people do; one phage may be smaller than another. The phage Caudovirales is negatively correlated with several gut microbes [41,42].



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Diagnosis

1- Clinical features

IBD is commonly diagnosed in children whose gastrointestinal symptoms are persistent (>1 month) or recurring (>2 in 6 months). Typical symptoms of IBD include stomachaches, recurrent diarrhea, weight loss, and rectal bleeding. While children with CD are more likely to lose weight (58% vs. 35%), children with UC are more likely to have abdominal pain, chronic diarrhea, and rectal bleeding. Merely one-fourth of pediatric CD cases are the traditional trifecta of abdominal pain, frequent diarrhea, and weight loss; 25% of children may merely exhibit vague symptoms including anorexia, lethargy, and abdominal discomfort [43,44].

CD patients are more likely to have perianal lesions such as skin tags, sentinel piles, and fistulae. Growth failure and impaired growth velocity are common in CD patients. Growth parameter impairment may occur months or years before the intestinal mucosal disease. Extraintestinal manifestations of certain features affect 6–17% of IBD patients. UC is more often linked to primary sclerosing cholangitis (PSC) [45,46].

2- Physical Examination

A wealth of physical examinations can advise on the main pathological properties. Evaluating growth curves is extremely important. Acute weight loss may occur in certain people, while a more subtle, long-term smoothing of the body weight and height curve may occur in others [47,48]. Abdominal examinations can reveal bloating associated with local sensitivity or distribution of their disease. Guarding and rebound soreness could be signs of an abscess or perforation that has to be quickly assessed with imaging. It is important to check for tags, fissures, fistulas, or abscesses in the perianal area. Information on anal restrictions, abscess variations, or occult blood can be obtained through digital rectal testing [49,50].

3- Laboratory Examinations

Children diagnosed with BCC may have aberrant laboratory results, such as anemia, thrombocytosis, hypoaltemia, and elevated inflammatory marker levels [28]. Since 10% to 20% of OZK children receive routine laboratory results, the diagnosis of BCC cannot be ruled out by normal laboratory assessment results. 26 It is necessary to check feces for parasites, eggs, bacterial infections (such as Clostridium difficile), and occult blood. With a sensitivity of 98% and 68% in children with suspected MII,

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Fakelecarprototin, a protein derived from neutrophils with elevated amounts in intestinal inflammatory conditions, is a helpful biomarker [51,52].

4-Visualization

Visualization with the small arm is required to map disease locations, assess gravity, and Find issues including intestinal limitation, abscesses, and f-foramen. Since imaging is less sensitive for colonic and mild illness of small buffoons, it must be performed following an endoscopic diagnosis. Specialized imaging methods are utilized to evaluate the MII [53,54]. Fluoroscopic monitoring of tiny currents has been supplanted by transversal enterography, which includes magnetic resonance enterography and computed tomographic enteroche. Two methods of neurosphere allow for the assessment of light, mucosal, intestinal walls, and intraperitoneal complications. Magnetic resonance tomography of pelvic and rectal endoscopic ultrasound is an experienced central and preferred method for assessing abscesses and fists around the peritoneum [55,56].

5- Endoscopy Imaging

Clinical and laboratory results show that if a leading medical clinician suspects MII in a child, it is appropriate to refer the patient right away for an endoscopic assessment to a pediatric gastroenterologist. The standard procedure for diagnosing and classifying OKK in children is still esophageal prolapse gastrodoodotocopies and ileoscopic examinations with biopsies [57,58]. Both gross and histopathologic data are necessary to distinguish UC from CD and to evaluate the severity and scope of the disease. The proximal small intestine may be evaluated with video capsule endoscopy when there is a high suspicion of CD and the findings of conventional endoscopy and imaging cannot validate the diagnosis [59,60].

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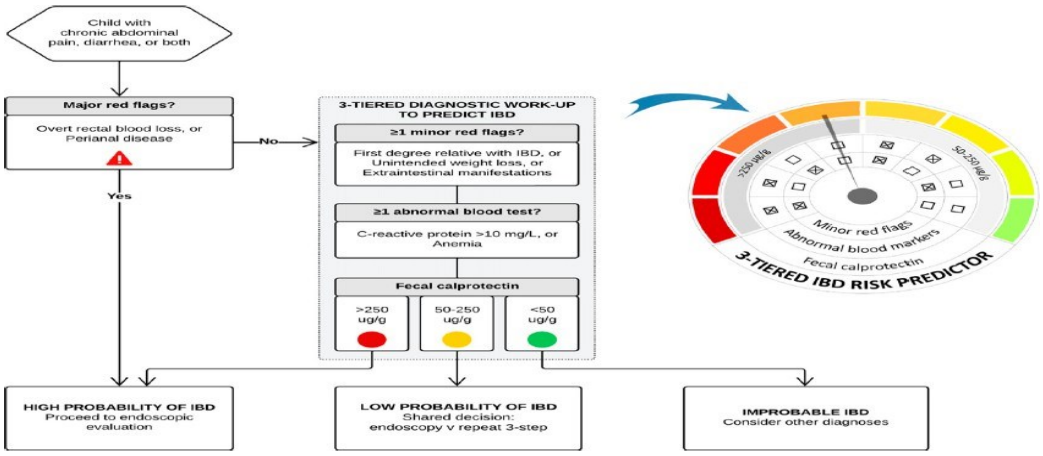

Figure 4: If there is a high suspicion of IBD, should we scope? By using this approach, you can determine if your patient should have an endoscopy to confirm if they have IBD, be monitored to see if latent IBD manifests, or have their complaints checked for other reasons. A visual aid for interpreting the three-tiered diagnostic workup is provided by the insert.

Treatment of Pediatric Inflammatory Bowel Disease

Over the past 15 years, the objectives for treating IBD in children have undergone a significant shift. The primary objective was to lessen symptoms when there were few other therapy choices. Biologics that target tumor necrosis factor (TNF) have the potential to alter the disease's natural course by promoting the development and healing of the mucosa. As a result, the current therapeutic objectives are to: (1) restore normal growth and quality of life; (2) eradicate symptoms; and (3) eliminate problems.

1- Corticosteroids

Children's CD and UC can be clinically remitted with the help of corticosteroids. Nonetheless, over 50% of patients need surgery or depend on corticosteroids, when using corticosteroids [61,62]. Because of their well-established, panoptic side effects, corticosteroids are not appropriate for supportive care. The systemic bioavailability and adverse effects of budesonide, a highly intended corticosteroid, are limited by its considerable metabolism in the first transit of the liver. Formulations of controlled-release budesonide are useful for causing UC and CD to go into remission. They don't work well as maintenance therapy, either [36, 37].

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2- Food therapy in burial

For the induction of clinical remission in children with CDs, treatment with an exclusive enteric diet (EEN), which is defined as providing nearly 100% of the required calories using a liquid formula, is just as successful as corticosteroid therapy. EEEN therapy typically lasts eight to twelve weeks. This method has advantages over corticosteroids, such as EEN's ability to promote growth, the avoidance of side effects linked to corticosteroids, and improved mucosal healing [63,64]. The main drawback of EEN is its stringent liquid formula diet, which necessitates a nasogastric tube placement every evening for a continuous nighttime meal for many patients. A popular guided therapy on the first European path, exclusive gut nutrition is also becoming more popular in the US. There have been some documented successes with a variety of partial in-laws, including support therapy, a nasogastric diet for one to four months, and night food with a regular daily meal [65,66].

3- Aminosalicylates

Aminosalicylates have been found to have a topical anti-inflammatory action on the intestinal mucosa. They can be given topically with an enema or suppository, or taken orally using formulations that release the active component 5-aminosalicylic acid (5-ASA) in the colon and ileum. For almost 40 years, sulfasalazine has been used to treat IBD; however, many patients are unable to handle the side effects of sulfa, which include fever, rash, headache, and nausea [67]. The only 5-ASA medication prescribed for children by the US Food and Drug Administration is balsalazide. 40 According to a major observational study, using 5-ASA medications alone will keep 30% of children with UC in remission [68].

4- Immunomodulators

Thiopurine medications, such as azathioprine sodium and its active metabolite mercaptopurine (6-MP), have been used to treat IBD for about 30 years. Thiopurines are suitable for maintenance treatments because of their several-week delayed onset of action. Early (6-MP) administration (within 8 weeks of diagnosis) dramatically lowers corticosteroid exposure and enhances the maintenance of clinical remission in children with CD, according to a ground-breaking multicenter, randomized clinical study 44. Similarly, observational studies back up the use of thiopurines in kids with UC who don't react to 5-ASA medications [69]. Myelosuppression, increased transaminase levels, and

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pancreatitis are among the side effects linked to thiopurines. Thiopurines have been linked to a slight increase in the incidence of lymphoma; in Children on thiopurines, the risk for all pediatric patients is 0.6 per 10,000 patient years [70].

5- Anti-TNF Therapy

Following extensive study in carefully planned trials, the US Food and Drug Administration has authorized Infliximab, the first anti-TNF drug created in 1998, for the management of children's moderately to severely active CD and UC. 56% of children with CD are in remission after a year, and 88% of them respond to infliximab. After a year, 39% of UC patients are in remission, and 47 (73%) of them respond. 48 Adalimumab has shown potential in treating children with moderately to highly active CD, and the US Food and Drug Administration has granted a license for this use. 49 Children with IBD who are not responding to corticosteroids or who remain dependent on corticosteroids even after receiving immunomodulator therapy are usually treated with anti-TNF medications. In adults, azathioprine and infliximab function better together than either medication alone, and they are occasionally used in conjunction with immunomodulators [71].

6- Surgery

Surgery is a crucial therapeutic option for the all-encompassing treatment of children's UC and CD. An ileal pouch-anal anastomosis in conjunction with a total colectomy may be beneficial for children with UC who are not improving with pharmaceutical treatment [72].

Conclusion

The "disease of the century" is inflammatory bowel disease, a complicated illness that affects millions of people globally. IBD is influenced by a variety of factors, such as genetics, lifestyle, and gut microbial ecology. It is uncertain, therefore, how microbes contribute to the development and management of disease. With an emphasis on CMV, EBV, EV, and HBV, we examined the data regarding viral infections and IBD. According to the studies covered here, people with IBD may be more susceptible to viral infections. On many levels, including the pathophysiology, outcomes, and management of the disease as well as a stand-alone treatment, viral infections and IBD are closely related. In patients with IBD, infections continue to be a major cause of death, which is extremely concerning. Future studies should be carried out to ascertain the relationship between

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viral infections and IBD as well as the most effective course of treatment for those who are afflicted with these viruses. The impact of the environment and microbiota on IBD must also be clarified and integrated, and we need to learn more about the mechanisms behind important elements of IBD, including viral composition and transmission pathways, immunogenicity, and horizontal gene transfer

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