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Allergic and Immunologic Perspectives of Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD) is a chronic immune-mediated inflammatory condition primarily involving the gastrointestinal tract. It includes Crohn's disease (CD), ulcerative colitis (UC), and a less common phenotype—indeterminate colitis. It is thought to result from a complex interplay of environmental, microbial, and host factors including genetic factors, although the exact mechanism is not known. Dietary factors have been shown to play a role in the pathogenesis of IBD and can potentially alter the intestinal microbiota as well as disrupt the immune function in the gut. CD is characterized by transmural inflammation, sometimes associated with granulomatous lesions, and involves the entire gastrointestinal tract but often spares the rectum. UC is characterized by mucosal inflammation typically confined to the colon and rectum. Although IBD is mostly seen in western world, recent data suggests that the incidence and prevalence are increasing worldwide. Enteral nutrition has been shown to be effective in inducing remission in pediatric population with CD; however, there is mixed data in adult population. Nutritional deficiencies such as vitamin D and zinc deficiency are often noted in IBD patients. Several extraintestinal manifestations are noted in patients with IBD. Some of them parallel with the disease activity and others are independent of the disease course. Assessment of IBD disease activity clinically, radiologically, if indicated, biochemically and endoscopically is important to guide therapy in IBD. To ensure comprehensive care, it is important to assess associated conditions such as nutritional and psychological well-being, as well as age appropriate health maintenance status prior to starting treatment for IBD. Several biologic agents including anti-tumor necrosis factor alpha (anti-TNF-α) drugs, anti-integrins, and antibodies to the p40 subunit of IL12/23 are approved for induction and maintenance of remission of IBD. Steroids are also often used for induction. Anti-metabolites and thiopurines are also useful either as monotherapy or in combination regimens. Potential side effects of anti-TNF-α drugs such as serious infections, malignancy, worsening of heart failure, and infusion-related reactions should be considered prior to starting these drugs. Anti-TNF-α drugs with or without immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) are often used for the induction and maintenance of remission. Treating to target of endoscopic and clinical remission provides the best long-term outcomes. Our knowledge and understanding of IBD has grown significantly. However, there are several unanswered questions on pathogenesis, disease behavior, and drivers of inflammation in various patient subgroups which require further research.

Keywords Colitis · Nutritional deficiencies · Enteral nutrition · Granulomatous cheilitis · Melkersson-Rosenthal syndrome · Tumor necrosis factor · Sweet syndrome

Introduction

Inflammatory bowel disease (IBD) is an immune-mediated condition primarily of the gastrointestinal tract, characterized by chronic inflammation. While there are several postulated mechanisms responsible for the pathophysiology, it is generally considered to be the result of dysbiosis of the gut microbiome resulting in an altered immunological balance in the intestinal mucosa [1].

The major phenotypes of IBD are Crohn's disease (CD) and ulcerative colitis (UC). A third less common clinical phenotype is indeterminate colitis, which accounts for 10–15% of all the IBD cases. CD is characterized by transmural inflammation with granulomatous lesions seen in varying proportions and can

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involve the entire gastrointestinal (GI) tract. UC is characterized by mucosal inflammation typically involving the colon and rectum. Indeterminate colitis meets criteria for IBD based on clinical, endoscopic, and pathologic data; however, it does not have characteristic features that allow classification into either CD or UC phenotypes. Recent studies show that the prevalence of CD and UC has been increasing worldwide including Far East [2].

Although the exact etiological mechanism of IBD is not known, several studies have shown a complex interplay of environmental, microbial, and host factors including genetic factors that predisposes to IBD. Environmental and microbial factors are usually considered modifiable, and theoretically, prevention of IBD could potentially be achieved by targeting these factors [3–5]. Diet is considered to be an important environmental factor as it can also affect the composition of intestinal microbiota [6]. Several genetic association studies have identified over 200 genetic risk loci in IBD and the role of immune dysregulation in the development of IBD [7].

In this review, we discuss the pathophysiology, role of immune system in the pathogenesis of IBD, dietary factors associated with IBD, and some extraintestinal manifestations that are likely allergy mediated. We also highlight the role of newer biologic therapies in the treatment of IBD and their potential side effects.

Epidemiology

A systematic review of over 200 population-based studies has defined the disease distribution worldwide [8]. The western world is considered to have highest distribution of the IBD with prevalence up to 0.5% of the general population and incidence ranging from 10 to 30 per 100,000 [9]. While the annual incidence of UC and CD in North America varies from 0 to 19.2 per 100,000 and 0–20.2 per 100,000, respectively, the prevalence of UC and CD in North America is 37.5–248.6 per 100,000 and 16.7–318.5 per 100,000, respectively [8]. When the adjusted prevalence rates for IBD in Olmsted County, Minnesota, USA from January 2011 are extrapolated to the most recent US Census, there are approximately 1.6 million persons with IBD in the USA [10]. CD and UC are equally distributed in North America; however, Europe has higher prevalence of UC than CD [8]. There is also disease variation in a geographical pattern with respect to latitudes, with a higher incidence of CD noted in northern latitudes than in southern latitudes [11]. Furthermore, IBD is also noted to be more common in urban population than the rural population.

Pathophysiology

While definitive/classic CD and UC colitis are at the respective ends of the spectrum of IBD, the clinical presentation of these two diseases may vary depending on the location and severity of the disease.

Crohn's Disease

CD can involve the entire GI tract from mouth to the perianal area. It is characterized by "skip" lesions with characteristic normal mucosa between the areas of inflammation. The most common area of involvement in the GI tract is the distal small bowel (ileum), which is seen in approximately 80% of patients. Approximately 50% of the CD patients have ileocolitis, another one third of the patients have perianal disease, and 5–15% of them have predominantly upper GI tract involvement typically the mouth or gastroduodenal area [12]. Although rectal sparing is considered typical of CD, the rectum is involved in about 20% of the CD patients. The clinical manifestations of CD are more variable and protean compared to UC. This may be attributable to the characteristic transmural inflammation of the GI tract and perhaps the varying locations of the disease throughout the GI tract [13, 14]. Common symptoms of CD include abdominal pain, fatigue, chronic diarrhea with or without bleeding, weight loss, anemia, and fever [15]. The chronic transmural inflammation in CD can lead to fibrosis, strictures, and fistulas.

Ulcerative Colitis

UC is characterized by inflammation of the colonic mucosa, commonly involving the rectum. It may extend in a proximal and continuous fashion to involve the entire length of the colon. UC involves only rectum in about 25% of the cases, and the entire colon (pancolitis) is involved in about 10% of cases. Disease not extending beyond the splenic flexure is described as left-sided disease, while disease extending more proximally is described as extensive disease. In contrast to CD, there are usually no skip lesions in UC. However, in cases of partial response to therapy in UC, some colonic areas may appear healed and look normal. The distal terminal ileum may appear inflamed, typically with superficial changes on histology. This phenomenon known as backwash ileitis may occasionally mimic CD. The colonic inflammation can eventually lead to ulceration, edema, bleeding, anemia, dehydration, infections, and electrolyte imbalance [16]. The chronic mucosal inflammation in the colon can lead to the formation of pseudopolyps and sometimes a rigid colon without haustral markings known as lead-pipe appearance, which is noted on a barium enema study.

Pathogenesis

Although the exact mechanism leading to the clinical manifestation of IBD is unclear, it is believed to be the result of

immune dysregulation in the GI tract as a result of a complex interplay between environmental and microbial factors in a genetically susceptible host. There is disruption of local immunity in the mucosal layer of the intestine, which is constituted by gut associated lymphoid tissue (GALT), in IBD patients. GALT includes lymph nodes, lymphoid follicles, and Payer's patches [17]. Several cells in the intestinal epithelial cell layer including Paneth cells, M cells, enterocytes, goblet cells, and neuroendocrine cells help separate the gut pathogens from the subepithelial lamina propria [18, 19].

A mucus layer covers the outer epithelial surface to protect the mucosa. This mucus layer is mostly composed of mucin produced by goblet cells, defensins produced by Paneth cells, and phosphatidylcholine (lecithin), which is abundant in the colon. The mucus layer has an outer loose permeable layer with commensal bacterial and an inner firm and sterile mucus layer that is in contact with the intestinal epithelium [20]. Any pathway with a genetic predisposition or environmental related stressful mechanism that leads to depletion of the mucus can lead to higher exposure of gut pathogens to intestinal mucosa. This can lead to increased chronic intestinal inflammation which is known to play a role in the pathogenesis of IBD, particularly in patients with UC [21].

The integrity of the intestinal epithelial barrier is maintained by adherens junctions, tight junctions, and desmosomes, which form the intercellular apical junction complex. Some studies have shown that increased intestinal permeability and defective epithelial barrier may play a role in the pathogenesis of IBD [22]. Other animal studies have showed that mice with defective intestinal epithelial barrier and permeability have increased tendency to develop spontaneous colitis [23–25]. The main components of adherens junctions and tight junctions in the intestinal epithelium that potentially play a role in the pathogenesis of IBD, in particular UC, include E-cadherin encoded by CDH1, LAMB1 (a laminin), and GNA 12 (encodes for a GTPase) [26, 27].

Intestinal epithelial cells, in addition to formation of a physical barrier, secrete several anti-microbial peptides such as α-defensins (produced by Paneth cells) and β-defensins both intra- and extracellularly. A defective or decreased expression of these peptides has been shown to occur in the inflamed colon and ileum of CD patients [28, 29]. Paneth cells also secrete NOD2, which is encoded by a gene that is strongly associated with CD. This was the first gene to be identified to confer risk for the development of CD [30, 31].

In addition to the intact intestinal epithelium as an effective barrier, the innate and acquired immune systems play a major role against toxins or pathogens. The innate immune system provides the initial foreign body response by activating the myeloid-derived cells, lymphoid cells, and natural killer cells. Myeloid-derived cells are composed of neutrophils, monocytes, macrophages, and dendritic cells (DCs). The adaptive immune system confers specific immunity against foreign antigens by activating the B lymphocytes (humoral immunity) and T lymphocytes (cell-mediated immunity) in association with antigen-presenting cells (APCs) and the major histocompatibility complex (MHC) [21]. Autophagy is a cellular process of clearing the degraded organelles such as mitochondria, endoplasmic reticulum, peroxisomes, and intracellular pathogens. It involves antigen processing and cell signaling with T cell homeostasis [32]. Any alterations in the autophagy can lead to reduced clearance of gut pathogens that can potentially contribute to IBD in genetically susceptible hosts [33]. Stress or starvation can trigger autophagy, which helps to reutilize essential amino acids and cellular proteins. Mutations in ATG16L1 and IRGM genes, involved in autophagy, have shown to be associated with CD [34, 35].

Innate immunity is non-specific and confers the first line of defense against foreign antigens. It initiates rapid inflammatory response by activating specific cells. The dendritic cells are a type of APCs which activates T cells and in turn the adaptive immune response. Increased levels of cytokines are produced in the lamina propria by myeloid cells with "inflammatory" phenotype in the IBD patients [36–38].

The adaptive immune system on the other hand is highly specific and consists of B and T lymphocytes. It confers long-lasting immunity. B lymphocytes mediate humoral immunity within the gut and secrete antibodies, mostly immunoglobulin A (IgA). T lymphocytes mediate cellular immunity which is a key player within the adaptive immune system. It responds to toxins or pathogens by working in conjunction with the "professional" APCs (including dendritic cells, macrophages, etc.) and the major histocompatibility complex (MHC). In order to clear specific pathogens, Th0 cells are activated and can differentiate into Th1 or Th2 or Th17 cells. While the clearance of intracellular microorganisms is regulated by Th1 cells, extracellular pathogens are cleared by Th17. Th2 cells mediate allergic reactions and are also protective against foreign toxins [39, 40]. Any abnormal T cell response with overproduction of cytokines and chemokines by the activated T cell subsets can lead to chronic intestinal inflammation. The main target of immunomodulating drugs in the treatment of IBD is the adaptive immunity.

Several pro-inflammatory cytokines have been identified in the inflamed intestines of patients with CD and UC. The primary mechanism of corticosteroids in the treatment of IBD is the suppression of pro-inflammatory cytokines, such as tumor necrotic factor-α and IL-1β, and regulation of T helper cell differentiation and type 1 interferon production [41].

Various cytokines are produced by the T cell subsets which help in the triggering of immune response against foreign pathogens or toxins. IL-12 induces Th1 cells, which in turn produce large quantities of interferon (IFN)-gamma and tumor necrosis factor (TNF), which has been noted in both human studies and mouse models of chronic colitis [39, 42–44]. This finding led to the development of anti-TNF therapy for CD

[45]. Increased mucosal levels of IL-12 can lead to abnormal Th1 immune response, which may cause intestinal inflammation in CD [46, 47]. Th17 cells facilitate production of several cytokines such as IL-17A, IL-17F, IL-21, and IL-22 [48]. IL-21 and IL-2 that are produced by Th17 are shown to be in high concentrations in the inflamed mucosa of IBD patients [49, 50].

There are several genetic susceptibility markers identified in patients with CD. A combination of genetic susceptibility, interplay of environmental factors, and alterations in the intestinal microbiome all contribute to the development of CD.

Intestinal Microbiota

Gut microbes are important in the regulation and development of the immune system as has been shown in several animal models. Intestinal microbial colonization starts at birth, rapidly changes during the first year of life, and becomes relatively functionally stable at the age of about 2 years [51]. A high microbial concentration is noted in the distal ileum and colon. The fecal microbiota is usually fairly stable over a period of time in adulthood; however, it can change in response to environmental factors and certain diseases [52]. Dietary factors, antibiotic usage during childhood, and helminth exposure are the important environmental factors that have been shown to influence the intestinal microbiota [53–55]. Any dysregulation in the bidirectional host-microbial interaction can lead to intestinal inflammation [56, 57].

Alterations in the diversity, density, and function of intestinal microbiota have been described in the patients with IBD [58, 59]. Some studies have shown that there is significant reduction in the diversity of the stool microbiome, particularly during the early course of Crohn's disease in the pediatric population [60, 61]. Moustafa et al. showed that IBD patients had significant stool microbiome dysbiosis compared to healthy controls. There was loss of a diversified core microbiome, depletion of specific bacteria, and enrichment of specific bacteria and virulence factors in the stool microbiome [62]. However, it is not clear if this alteration in the microbiome is the primary driver of the development of IBD or the result of the intestinal inflammation in IBD. This phenomenon has also been noted in the pediatric population early during the course of the disease.

Few studies have shown increased concentrations of the bacteria with pro-inflammatory properties such as enteroadherent and invasive *Escherichia coli* in the fecal microbiota of patients with IBD compared to healthy controls [51, 63]. The microbiota in patients who have undergone an ileal pouch-anal anastomosis (IPAA) surgery for UC and its association with pouch inflammation (pouchitis) has also been studied [64, 65]. Patients with familial adenomatous polyposis who undergo IPAA never develop pouchitis, unlike patients with UC. The exact cause of this is unknown although changes in the dynamics of the intestinal microbiota in these two groups of patients may possibly play a role.

Dietary Factors in IBD

The role of food in IBD pathogenesis and treatment has been extensively studied in several epidemiologic studies. Some of these studies have shown that enteral nutrition can induce clinical and endoscopic remission [66]. Dietary nutrients studied in IBD are usually classified in to fats, proteins, carbohydrates, vitamins, and minerals. Several dietary nutrients such as vitamins, amino acids, and fatty acids (short-chain fatty acids, SCFAs) have been shown to help regulate the mucosal immune function. These nutrients are influenced by the gut microbiota [67]. Patients with CD are at increased risk of malnutrition even when the disease is quiescent; however, UC patients develop malnutrition only when there is active disease [68]. Hence, it is very important to assess the nutritional status of CD patients at a regular interval and treat nutrient deficiencies to prevent malnutrition and its complications such as osteoporosis, anemia, and growth failure. There is also the risk of vitamin and micronutrient malabsorption secondary to disease location with or without surgical resections in patients with CD. Patients with distal ileal stricturing disease and or surgical resections of the distal ileum are at risk of vitamin B12 deficiency.

Several observational studies have been performed to assess the dietary patterns that are associated with increased risk of IBD. Dietary changes accompanied by a westernized lifestyle could be an important environmental factor in the development of CD. Although the exact mechanism of interaction between various foods and the development of IBD is not known, patients on high sugar, low fiber, and high fat are found to be more susceptible to IBD [6].

The role of nutrition in pediatric IBD has been extensively studied. Pediatric IBD patients are at increased risk of delayed development and nutritional deficiencies. Breast feeding is the only nutritional intervention that has been shown to decrease the risk for CD and UC [69]. Breast milk potentially alters the intestinal microbiota in the neonates.

Although enteral diet has been recommended and shown to be effective in pediatric CD patients, corticosteroids are more effective than enteral diet therapy in adults [70]. Enteral therapy has been used as a primary therapy for the treatment of CD although the major disadvantage is its unpalatability leading to non-compliance. The role of enteral therapy in CD is discussed in the later sections of this article.

A nested matched case–control study, within a large prospective multinational EPIC (European Prospective Investigation into Cancer and Nutrition) study with 366,351 participants, showed that a diet with high consumption of sugar and soft drinks and low consumption of vegetables was associated with an increased risk of developing UC.

[71]. Another nested case–control analysis among the participants within the EPIC study showed that higher docosahexaenoic acid (DHA) intake was inversely associated with the development of CD [72].

IBD developed in 77 subjects in a large French prospective study of 67, 581 middle-aged women with a mean-time follow-up of 10.4 years [73]. In this study, a higher risk of IBD was associated with high total animal protein intake, specifically meat, fish, and seafood, but no increased risk with eggs or dairy products. There was also a positive association between total polyunsaturated fatty acid (PUFA) consumption and the risk of developing IBD [73].

The risk of UC and CD was assessed among 170, 805 women enrolled in Nurses' Health study where Cox proportional model was used for adjusting for potential confounders [74]. A greater intake of long-chain n-3 PUFA was associated with a lower risk of UC; however, higher intake of trans-unsaturated fatty acids was associated with increased risk of UC. In contrast, intake of total fat, saturated fats, unsaturated fats, and n-6 and n-3 polyunsaturated fatty acids (PUFA) were not associated with the risk of CD or UC [74].

Nutritional Deficiencies

Patients with IBD are at increased risk of nutritional deficiencies. This is particularly true in patients with CD. This may be due to decreased nutrient intake associated with sitophobia or increased losses and/or decreased absorption. The common micronutrient deficiencies noted in IBD include water-soluble and fat-soluble vitamins and several minerals including iron, zinc, selenium, and calcium.

The common water-soluble vitamin deficiencies noted in IBD patients include folate deficiency and vitamin B12 deficiency. Folate deficiency is mostly attributed to the drugs used in the treatment of IBD. Culprit drugs include sulfasalazine and methotrexate. These drugs often exacerbate the preexisting folate deficiency resulting from decreased oral folic acid intake [75]. The sulfa moiety in sulfasalazine can bind folate in the gut lumen, thereby decreasing its absorption. Patients on sulfasalazine should be supplemented with oral folic acid 1 mg daily. Pregnant women receiving sulfasalazine should receive higher doses of folic acid at 2 mg daily. Methotrexate is a folic acid antagonist, which is absolutely contraindicated in pregnancy. In a study of IBD patients with hyperhomocysteinemia, folate deficiency was associated with increased risk of colorectal cancer [76].

Vitamin D is the most common fat soluble vitamin deficiency seen in IBD patients. A large meta-analysis showed that patients with IBD had 64% higher odds of vitamin D deficiency than controls (OR = 1.64; 95% confidence interval, 1.30–2.08; $I = 7\%$; $P < 0.0001$) [77]. Patients with UC had two times higher risk of vitamin D deficiency than normal controls [77]. Vitamin D has been shown to play an important role in the innate immunity [78]. Vitamin D receptors (VDR) have been found in several immune cells including T cells (CD4+ and CD8+), B cells, neutrophils, macrophages, and antigen-presenting cells. It enhances the anti-inflammatory properties such as phagocytosis, chemotactic response, and production of anti-microbial proteins (such as cathelicidin) and also helps to downregulate the production of pro-inflammatory cytokines including IL-1, IL-6, IL-8, and TNF-α [79, 80]. Garg et al. reported that vitamin D may have an important immunomodulatory role in IBD as their levels had strong inverse correlation with intestinal inflammation, which was independent of potential malabsorption, sunlight exposure, total vitamin D intake, and obesity [81]. A recent 5-year follow-up longitudinal study with 965 IBD patients showed that 30% had low mean vitamin D levels, which was associated with higher morbidity and mortality [82]. Whether vitamin D deficiency is a precursor of IBD or a result of ongoing intestinal inflammation in IBD is a question of ongoing research.

Zinc is an essential trace element that is absorbed in the small intestine. Zinc deficiency is often seen in patients with chronic diarrhea and IBD. Zinc serves as a cofactor for several enzymes and plays a crucial role in tissue healing and immune function. An experimental human model showed that zinc deficiency leads to decreased products of Th1 cells, i.e., interferon-gamma and IL-2 [83]. Zinc deficiency often occurs in IBD patients due to decreased oral intake, malabsorption, and/or previous small bowel resections. The prevalence of zinc deficiency in IBD ranges between 15 and 40% [84, 85]. A large prospective single center cohort study involving 773 CD patients and 223 UC patients showed that serum zinc deficiency in IBD patients is more likely to have adverse disease-specific outcomes, which improve with normalization of the zinc levels [86]. Another prospective cohort study from Nurses' Health Study 1 and Nurses' Health Study II involving 170,776 women, who were followed for 26 years, showed that zinc intake was inversely associated with CD but not UC [87]. The association was stronger in patients with CD for dietary zinc (hazard ratio, HR 0.63, 95% CI, 0.43–0.93) compared to zinc supplements [87]. A total of 269 incident cases of CD and 338 incident cases of UC were noted in this study.

Other common vitamin deficiencies noted in IBD include vitamin A, vitamin B12, vitamin E, and vitamin K deficiencies. Other mineral deficiencies that have been reported include iron, magnesium, and selenium. The clinical manifestations of these nutritional deficiencies are listed in Table 1.

Enteral Nutrition for the Treatment of IBD

Data on the use of enteral nutrition (EN) for induction and remission of active CD in children remains controversial. Several of the studies on the use of enteral nutrition (EN) have compared their efficacy to steroids. In this section, we review

Table 1 Nutritional deficiencies and their clinical manifestations in IBD

Nutritional deficiency	Common clinical manifestations
Vitamin B12	Macrocytic anemia, pancytopenia, glossitis, neuropsychiatric changes—paresthesias, gait disturbances, subacute combined degeneration of the spine, depression, dementia, psychosis
Vitamin D	Osteomalacia, bone fractures, secondary hyperparathyroidism, bone pain, muscle weakness
Vitamin A	Night blindness, corneal xerosis, Bitot's spots, keratomalacia, poor bone growth
Vitamin K	Hypocoagulable state (easy bruisability, mucosal bleeding, etc.)
Vitamin E	Hemolytic anemia, Brown bowel syndrome, neuromuscular disorders—ataxia, hyporeflexia, skeletal myopathy, pigmented retinopathy
Folate	Macrocytic anemia
Zinc	Diarrhea, acrodermatitis enteropathica, night blindness, glossitis, depression, immune dysfunction, nystagmus, hypogonadism, delayed wound healing
Selenium	Cardiomyopathy (Keshan disease), skeletal muscle dysfunction, macrocytosis, immune dysfunction
Iron	Microcytic anemia, impaired neurocognitive development
Magnesium	Refractory hypokalemia, neuromuscular disturbances, ventricular arrhythmias

IBD inflammatory bowel disease

the available literature on use of EN in both pediatric and adult patients with CD.

Steroid therapy may have a role in the treatment of patients with acute CD. Its use is limited by significant side effect profile especially in children in whom it has been associated with developmental delay and delayed puberty. A meta-analysis involving 11 randomized control trials (RCTs) with 394 children studied the efficacy of corticosteroid therapy and EN for induction of remission in active CD in pediatric patients [88]. In this meta-analysis, seven RCTs ($n = 204$) compared EN with corticosteroid therapy and four RCTs ($n = 190$) compared total EN regimen with partial EN regimen. Analysis of the pooled results of four RCTs ($n = 144$) showed no significant difference in the remission rates between EN and corticosteroid groups (relative risk, RR 0.97, 95% CI 0.7–1.4, random effect model). One RCT ($n = 50$) showed a significant higher remission rates in patients receiving total EN compared to those receiving partial EN.

A large Cochrane database meta-analysis involving 15 trials compared different formulations of EN and 8 trials compared EN to steroid therapy for the induction of remission of active CD [66]. The results showed that corticosteroids were more effective than EN at inducing remission of active CD, and protein composition in the EN formulas did not influence the effectiveness of EN in the treatment of active CD. Several biologic therapies and immunomodulatory agents have been used effectively to induce and maintain remission in CD either as monotherapy or as part of combination therapy.

The role of EN in maintaining remission is still unclear. Another systematic review of two RCTs showed that supplementary EN may be effective for maintenance of remission in CD [89]. EN could be considered an alternative or as an adjunct to drug therapy for maintenance of remission in CD. Furthermore, a review of seven prospective cohort studies including three RCTs showed that EN is useful for the maintenance of remission in patients with quiescent CD [90]. There was similar efficacy between elemental and polymeric diets for the maintenance of clinical remission and for allowing tapering and cessation of steroid therapy [88].

EN is recommended as primary therapy as part of the European guidelines for the treatment of active CD in children [91]. A recent Japanese retrospective study on 58 newly diagnosed pediatric CD patients showed that EN with aminosalicylates is effective for maintaining remission and decreasing the rate of intestinal surgery [92]. None of the patients in this study received corticosteroids, immunomodulators, or biologic therapy until relapse, which occurred in 43% of the patients with a median duration of remission of 32.4 months. A retrospective single-center analysis of 94 pediatric patients with active CD showed that exclusive EN induces remission; however, the efficacy of EN tends to decrease with a second course of EN [93]. The presence of NOD2 genotype has been shown to be a predictor of higher relapse rates in this study [93].

Although there is data to support the use of exclusive EN as a primary therapy to treat active CD in pediatric patients, this intervention is not routinely utilized in adults. A review of 11 studies directly comparing exclusive EN and corticosteroid therapy in adults with active CD showed that exclusive EN may only benefit a subset of adult patients with newly diagnosed and treatment naïve active CD, although poor compliance with exclusive EN due to unpalatability was noted in half of these studies [94]. A recent study on 41 adult patients with active CD with complications including intestinal fistula, abscess, or strictures showed that exclusive EN is effective in inducing early clinical remission, mucosal healing, promoting fistula closure, and decreasing the abscess size [95].

Overall, the data on the use of EN for CD shows more favorable results in the pediatric population. In adults, it may have some benefits in specific circumstances if tolerated; more vigorous studies are needed in adult patients with CD.

Extraintestinal Manifestations of IBD

There are several extraintestinal manifestations (EIMs) of varying severity associated with IBD. The mechanism and exact prevalence of these EIMs have not been extensively studied. Some of the EIMs parallel to the disease activity and others run an independent course (Table 2).

A population-based cohort study showed that a total of 6.2% of the IBD patients had at least one of six major EIM, and 0.3% had multiple EIMs [96]. Although the exact pathogenesis of EIMs in IBD is unknown, it has been suggested to be an immune-complex-mediated inflammation and often associated with major histocompatibility complex loci [97, 98].

In this section, we highlight aspects of the more challenging EIMs and discuss the available literature.

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis characterized by an inflammatory papule or pustule progressing to a painful necrotic ulcer with a violaceous undermined border and a purulent base (Fig. 1). The incidence of PG is estimated to be 3–10 cases per million per year [99], occurring most commonly between ages 20 and 50 years. It occurs in patients with IBD, hematological disorders, and arthritis. A large National Inpatient Sample database analysis of 2273 adult patients with pyoderma gangrenosum (PG) showed that a total of 74 patients (3.2%) died during the hospitalization [100]. The primary factors associated with the

Table 2 Activity of EIMs in relation to the IBD activity

EIM	Parallel course of IBD	Independent of IBD activity
Erythema nodosum	XXXX	
Pyoderma gangrenosum		XXXX
Peripheral arthropathy	XXXX (type 1 arthropathy, ≤ 6 joints involved)	XXXX (type 2 arthropathy, polyarticular)
Axial arthropathy		XXXX
Uveitis	X	XXXX
Episcleritis	XXXX	
Primary sclerosing cholangitis	X	XXXX
Oral aphthous ulcers	XXXX	
Sweet syndrome	XXXX	

EIM extraintestinal manifestations, *IBD* inflammatory bowel disease, *X* strength of association

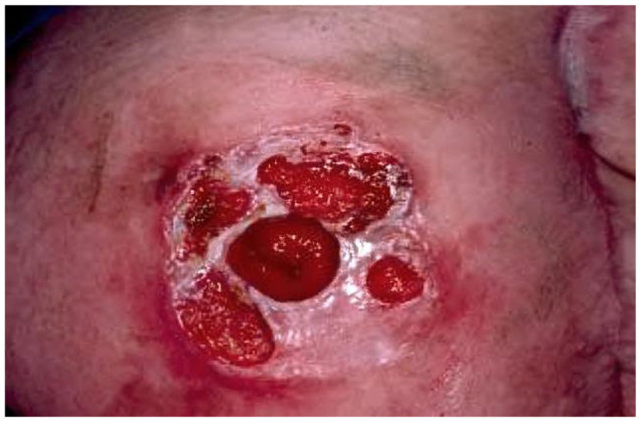

Fig. 1 Peristomal pyoderma gangrenosum. Image reproduced with permission from Jeffrey P Callen, MD, University of Louisville School of Medicine, published by Medscape Drugs & Diseases (https://emedicine.medscape.com/), Pyoderma Gangrenosum, 2017, available at: https://emedicine.medscape.com/article/1123821-overview

pathogenesis of PG include neutrophil function abnormalities, genetic alterations based on the reports of familial PG cases, and systemic inflammation with dysregulation of the innate immune system.

The major subtypes of PG are ulcerative PG (classic), bullous PG (atypical), pustular PG, and vegetative PG [101]. IBD patients usually develop pustular PG characterized by painful pustules surrounded by erythema. Other disease states or syndromes associated with PG are PAPA syndrome (autosomal dominant disorder characterized by Pyogenic Arthritis, PG, and Acne), PAPASH syndrome (Pyogenic Arthritis, PG, Acne, and Suppurative Hidradenitis), and PASH syndrome (PG, Acne, and Suppurative Hidradenitis). PAPA and PAPASH have been reported to have the gene mutation in PSTPIP1 [102, 103].

Diagnosis is based on clinical, pathologic, and laboratory findings, although there are no definite characteristic or pathognomonic findings for PG. A rapidly progressive painful, necrotic ulcer with a violaceous, and undermined border should raise the suspicion for PG once other cutaneous disorders are ruled out. Pain is often out of proportion to the size and appearance of the ulcer, and it can be associated with fever. PG is often associated with pathergy, which is an exaggerated skin injury in response to minor inciting trauma, either iatrogenic or accidental. A retrospective study of 103 PG patients showed that 31% had pathergy, 34% had IBD, and the mortality rate during the 8-year study period was 16% [104].

A recent retrospective study compared several procedures to 166 PG patients. It showed that compared with skin biopsy, small open surgical procedures [adjusted odds ratio (aOR) of 8.65 (95% confidence interval, 1.55–48.33)], large open surgical procedures [aOR of 5.97 (95% CI, 1.70–21.00)], Mohs micrographic surgery/skin excision [aOR of 5.97 (95% CI, 1.70–21.00)], and chronicity of PG at the time of procedure [aOR of 4.58 (95% CI, 1.72–12.22)] are associated with

recurrence or exacerbation of PG [104]. Immunosuppression, time elapsed since the original PG diagnosis, and procedure location did not significantly influence the risk of PG recurrence or exacerbation [105].

A novel diagnostic tool, the PARACELSUS score, has been proposed recently for PG based on a retrospective study of 60 PG patients and 50 controls [106]. Major diagnostic criteria include rapidly progressing disease, assessment (absence) of relevant differential diagnoses, and reddish-violaceous wound border. Minor criteria include amelioration by immunosuppressant drugs, characteristically irregular shape of ulceration, extreme pain > 4/10 on visual analogue scale, and localization of lesion at site of trauma. Three additional criteria include suppurative inflammation in histopathology, undermined wound margins, as well as concomitant systemic disease. A total score of ten points or higher indicates a high likelihood of PG and differentiates PG from chronic venous leg ulcers [106].

Treatment of PG is best done in a multidisciplinary and multimodality approach based on the size and severity of the lesion. Local wound care should be used to facilitate healing of the lesion. Surgery is performed only in select cases due to the risk of pathergy. Infliximab has been reported to suppress pathergy in a PG patient allowing for a successful tendon surgery [107]. Local corticosteroids (clobetasol propionate) and calcineurin inhibitors (topical tacrolimus) are often used as primary and adjunctive therapies in limited PG [108]. While systemic corticosteroids are the first-line agents for treatment of extensive PG, systemic cyclosporine can be used as an alternative first-line agent in patients who cannot tolerate or fail corticosteroid therapy [109].

A randomized, double-blind, placebo-controlled trial of 30 patients showed that infliximab infusion at 5 mg/kg was superior to placebo in the treatment of PG [110]. Although the efficacy data is limited, intravenous immune globulin (IVIG) has been shown to be a treatment option in refractory PG that does not respond to other medications [111].

Pyostomatitis–Pyodermatitis Vegetans

Pyostomatitis–pyodermatitis vegetans (PPV) is a rare mucocutaneous inflammatory disease associated with inflammatory bowel disease. The oral manifestations are referred to as pyostomatitis vegetans (PSV) and the skin manifestations as pyodermatitis vegetans (PDV) (Fig. 2). PPV has a strong association with IBD [112]. A retrospective review of seven PPV cases showed that PPV was associated with IBD and primary sclerosing cholangitis and may precede gastrointestinal symptoms of IBD [113]. Although it resembles pemphigus vegetans, histology of PPV lesions typically shows eosinophilic spongiosis with eosinophilic microabscesses and pseudoepitheliomatous hyperplasia. In addition, there is a negative direct immunofluorescence. These unique

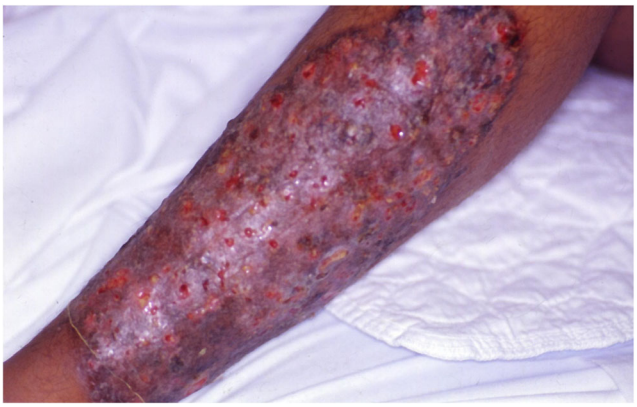

Fig. 2 Pyoderma Vegetans. Image reproduced with permission from Robert A Schwartz, MD, MH, Rutgers New Jersey Medical School, published by Medscape Drugs & Diseases (https://emedicine.medscape.com/), Pyoderma Vegetans, 2017, available at: https://emedicine.medscape.com/article/1055728-overview

characteristics can help differentiate it from pemphigus vegetans [114]. Furthermore, acanthosis and hyperkeratosis of the epithelium with underlying connective tissue containing a dense lymphocytic, neutrophilic, and eosinophilic infiltrate can be seen as well [115].

The exact pathogenesis of PPV is not known. Postulated etiological pathways including microbial infections as the cause of this condition have been proposed. However, cultures obtained from the oral and/or skin lesions are usually negative [116]. An immunological component with a rise in peripheral blood lymphocytes and eosinophils has been proposed in the pathogenesis of PPV [115]. However, there is lack of data supporting this line of thinking.

Treatment of co-existing IBD medically or surgically (colectomy) usually helps in controlling the oral and skin lesions of PPV. In the absence of IBD, topical corticosteroids are often helpful in treating these lesions [117]. Systemic corticosteroids [118], dapsone [112], sulfasalazine [119], and sulfamethoxypyridazine [116] may be useful in the treatment of PPV, although the supportive data for these drugs is only based on case reports.

Sweet Syndrome

Sweet syndrome is a neutrophilic dermatosis characterized by acute fever, neutrophilia, painful erythematous and edematous papules, plaques, or nodules of the skin (Fig. 3). It is a rare extraintestinal manifestation of IBD [120]. It has also been associated with other conditions such as infections (upper respiratory and gastrointestinal) [121], pregnancy [122], malignancy (hematologic or solid tumors) [123], and drugs (most common—granulocyte-colony stimulating factor) [124]. High erythrocyte sedimentation rate (ESR) [125], low hemoglobin levels [125], and vesiculobullous lesions [126] could

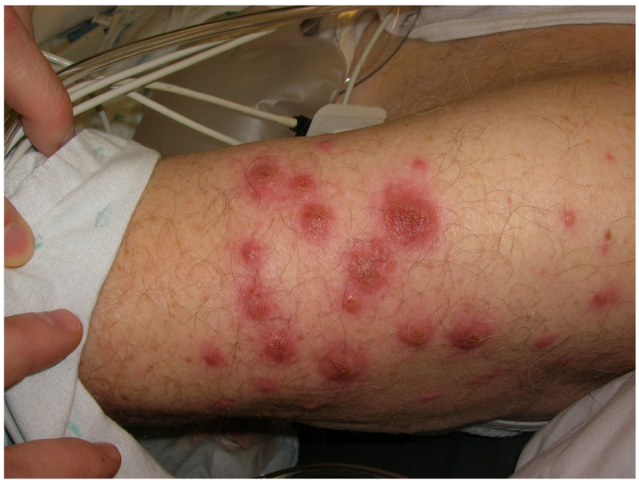

Fig. 3 Sweet syndrome. Image reproduced with permission from Galen Foulke, MD, Department of Dermatology, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA

be markers of underlying malignancy in Sweet syndrome and may need further work up in these patients.

The exact pathogenesis of Sweet syndrome is not well understood. Several interleukins such as IL-1, IL-3, IL-6, and IL-8 have been postulated to contribute to the pathogenesis of Sweet syndrome. Th1 cytokines (IL-2, IFN-gamma) rather than Th2 cytokines (IL-) may play a role in the pathogenesis of Sweet syndrome [127]. Other possible factors in the pathogenesis of Sweet syndrome include hypersensitivity reactions from microbial antigens leading to neutrophil activation and infiltration by cytokines [128] and genetic susceptibility (chromosome 3q abnormalities and HLA-B54, MEFV gene mutations) [129–131].

Corticosteroids are the first-line treatment for Sweet syndrome**.** Topical and intralesional corticosteroids may be used as an adjunct to systemic corticosteroids in widespread lesions [132]. A retrospective study of 90 patients with Sweet syndrome showed that colchicine was an effective drug and can help reduce corticosteroid usage in the treatment of Sweet syndrome [126]. Less frequently used drugs include dapsone and potassium iodide. Few case reports suggest the utility of rituximab in the treatment of refractory Sweet syndrome [133, 134]. Agarwal A et al. reported a case of successful treatment of refractory subcutaneous Sweet syndrome with adalimumab [135].

Granulomatous Cheilitis

Granulomatous cheilitis (GC) is characterized by chronic swelling of one or both lips due to granulomatous inflammation, first described by Miescher in 1945. It is considered to be an incomplete variant of Melkersson-Rosenthal Syndrome (MRS), which is a triad of recurrent orofacial edema, recurrent facial nerve palsy, and fissuring of the tongue [136]. The exact mechanism of GC is unknown. Proposed mechanisms include allergic reactions, autoimmune causes, chronic dental infections, and an association with CD. Skin prick tests are often positive in almost half of these patients. Several case reports of GC associated with the CD are reported in the medical literature [137, 138].

Although definite treatment is not available, treatment options include avoidance of the allergen [139] and antibiotics [140] with or without intralesional corticosteroids [141] . Treatment of underlying psychiatric comorbidity often helps to decrease relapses [142].

Therapies in IBD

Anti-tumor Necrosis Factor Alpha Therapy

Anti-tumor necrosis factor-alpha (anti-TNF-α) drugs—infliximab, adalimumab, golimumab, and certolizumab pegol—are Food and Drug Administration (FDA) approved for the treatment of IBD in the USA [143]. These drugs are commonly used for the induction and maintenance of remission in patients including but not limited to those with moderate to severe CD and/or those who do not respond to a course of steroid therapy or unable to wean off the steroids. Significant side effects related to anti-TNF-α drugs include serious infections, malignancy, worsening of heart failure, dermatological manifestations (such as psoriasis), and infusion-related reactions.

Serious infections include reactivation of latent tuberculosis (TB), invasive fungal infections, bacterial, viral infections, and other opportunistic pathogens, including Legionella and Listeria [144]. Reactivation of hepatitis B can occur in patients who were exposed to the infection in the past. Patients should always be tested for latent TB and hepatitis B immune status prior to initiating biologic therapy. Serious infections are more likely to occur if patients are on concomitant immunosuppressant, such as methotrexate, azathioprine, or corticosteroids. The risk appears to be highest in patients with concomitant steroid therapy.

Malignancies such as lymphoma, particularly a rare type of T cell lymphoma—hepatosplenic T cell lymphoma, have been reported with anti-TNF-α drug in children and younger adults [145–147]. Reactivation of melanoma has also been reported in patients on anti-TNF-α drug [148]. Other potential side effects of anti-TNF-α drug include detection of anti-nuclear antibody titers after initiation of the therapy, and rare cases of lupus-like syndrome have also been reported [149]. New diagnosis or worsening of underlying demyelinating disorders (such as multiple sclerosis, optic neuritis) has also been reported with anti-TNF-α drugs [150]. These drugs can also worsen underlying heart failure.

Although anti-TNF-α drugs are effective in the treatment of psoriasis, they can paradoxically cause psoriasis as a side effect. It is usually more common in women and often localized to palms, soles, and scalp, a phenomenon that has been described

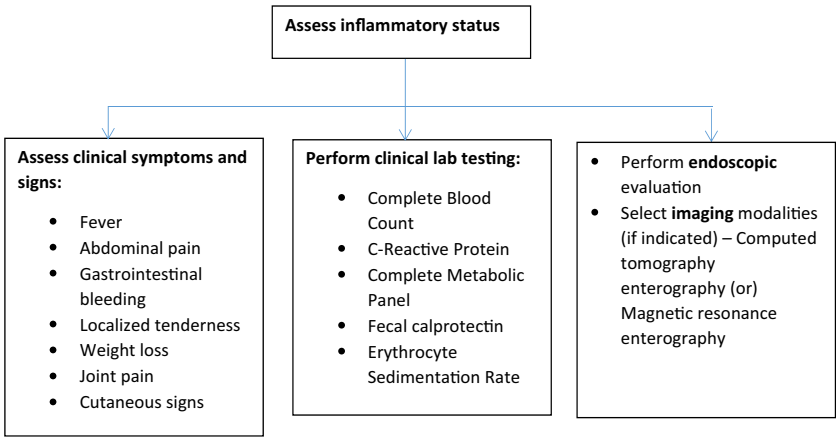

Fig. 4 Algorithm for diagnosis of CD and UC. Modified based on the American Gastroenterological Association (AGA) recommendations

as inverse psoriasis [151]. A recent nationwide cohort study of 7415 IBD patients in Spain showed an incidence of psoriasis of 0.5% per patient year with anti-TNF-α drugs [152].

Infliximab is chimeric IgG1 monoclonal antibody and is highly specific against tumor necrosis factor-alpha, which is a major mediator of gastrointestinal inflammation in IBD. It is administered at a dose of 5 mg/kg infusion at 0, 2, and 6 weeks and then every 4–8 weeks for IBD patients. The dose may be increased to 10 mg/kg, if needed, based on the clinical response.

There are adverse reactions associated with infliximab and may need to stop the medication in patients who develop severe reactions. Premedication with anti-histamine, acetaminophen, and/or corticosteroids should be considered to prevent mild infusion related reactions such as flushing, mild rash, fever, or mild wheezing. Other common side effects associated with infliximab include head ache (18%), upper respiratory infections (flu-like illness), and opportunistic infections.

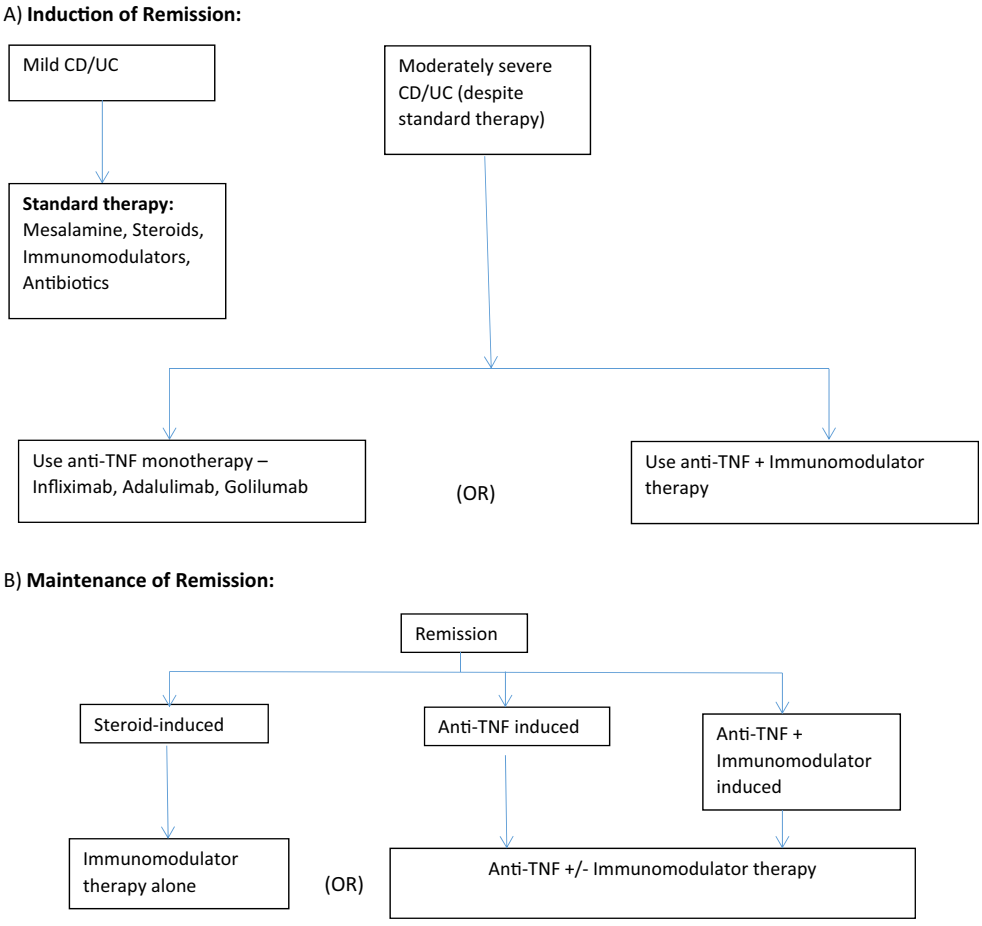

Fig. 5 Algorithm for the medical management of CD and UC. Modified based on the American Gastroenterological Association (AGA) guidelines—Jonathan P. Terdiman, Claudia B. Gruss, Joel J. Heidelbaugh, Shahnaz Sultan, Yngve T. Falck–Ytter the AGA Institute Clinical Practice and Quality Management Committee Published Online: March 04, 2014

A single-center retrospective study of 336 IBD patients treated with infliximab showed that 8.9% of the patients developed systemic adverse reaction to infliximab and 50% of them who developed the adverse reaction had to discontinue the medication [153]. More recently, there is data on infliximab desensitization which can be safely performed by gradually increasing doses starting at a dilution of 0.1 mg/mL to reach the full treatment dose over approximately 4 to 6 h [153]. This allows patients who are responding to the medication to continue after an initial reaction to infusion.

Adalimumab is a recombinant monoclonal antibody that binds to human tumor necrosis factor alpha and in turn decreases the gut inflammation. It is administered at a dose of 40 mg subcutaneously every 2 weeks for maintenance of IBD. It has the same side effect profile as the infliximab.

Certolizumab pegol is another anti-TNF-α drug that is FDA approved for the treatment of CD. It is a pegylated humanized Fab' fragment of the tumor necrosis factor alpha monoclonal antibody [154]. It is not a complete antibody as it lacks the Fc region. It is administered at a dose of 400 mg subcutaneously every 4 weeks for maintenance. The pegylated molecule may have a unique advantage in pregnancy as it does not cross the placental barrier in any significant way [155].

Other medications used in the treatment of IBD include immunomodulators (azathioprine, 6-mercaptopurine), vedolizumab, and ustekinumab. Algorithms for the approach to diagnosis and management of CD and UC are shown in Figs. 4 and 5.

Conclusion

IBD is a complex, chronic, immune-mediated condition primarily of the gastrointestinal tract. Our understanding of the immunology and pathophysiology is evolving, and with that are opportunities to further explore other therapeutic pathways.

There are several immune-mediated conditions associated with IBD. These manifest either as extraluminal manifestations of IBD or as separate disease entities. The clinical course of the extraluminal manifestations of IBD does not always mirror the clinical activity of the bowel disease. This is a further indication that the clinical pathways of the two conditions are not always driven by the same immunological or pathophysiological mechanism.

Some associated conditions including inverse psoriasis are manifested after treatment, typically with anti-TNF alpha drugs. Further studies are needed to better understand the predisposing factors in subgroups of these IBD patients.

The past few years have seen significant advances in the treatment of IBD. In addition to traditional medications including 5'ASA, thiopurines, steroids, and anti-metabolites, several biologic agents have come to market. Although this provides broader therapeutic choices, not all patients respond similarly to these drugs and those who do so may lose response over time. Explanations for this observation include the complexity of the innate and adaptive immune systems and our realization that pathways of inflammation are varied in various clinical phenotypes of IBD. Recent treatment strategies include dual/combination treatment to help improve durability of response by reducing antibody formation and perhaps by attacking the disease by different pathways. Side effects of the treatment and the significant cost burden remain a challenge for these patients.

IBD patients especially patients with CD are at increased risk of nutritional deficiencies. This may be due to decreased nutrient intake associated with sitophobia, increased losses, and/or decreased absorption. Micronutrient deficiencies noted in IBD include vitamins and several minerals including iron, zinc, selenium, and calcium deficiencies. Simple interventions including replacement of vitamins have been shown to reduce associated co-morbidities in IBD. There is conflicting data on the potential benefits of enteral nutrition on disease course, especially in children. There is a window of opportunity to further investigate the effects of the nutritional adjustments on the intestinal microbiome.

Over the next several years, our understanding of the immunological basis of IBD will continue to develop. It is our expectation that this will lead to a better understanding of potential safer therapeutic targets with better outcomes. In addition, there is an opportunity to explore therapies that may target other associated conditions and perhaps get us closer to a cure.

Compliance with Ethical Standards

Conflict of Interest There are no conflicts of interest relevant to this manuscript. However, for full disclosure, Dr. Clarke is on the speakers' bureau for AbbVie, Takeda, and Janssen. In addition, he has served on an Ad Board for Pfizer.

Ethical Approval and Informed Consent This is a review article; no patients were involved, and informed consent was not required. Permission was obtained for all images used and appropriate attribution/acknowledgement stated.

Disclosures Speakers Bureau for Abbvie, Janssen and Takeda; Ad Board for Pfizer.

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