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ABOUT COVER

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REVIEW

Secondary causes of inflammatory bowel diseases

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Abstract

Inflammatory bowel diseases (IBD), conventionally consist of Crohn's disease (CD) and ulcerative colitis. They occur in individuals with high risk genotype for the disease in the setting of appropriate environmental factors. The pathogenesis of IBD involves a dysregulated autoimmune response to gut dysbiosis, which in turn is triggered due to exposure to various inciting environmental factors. But there is no clearly defined etiology of IBD and this type of disease is termed as "idiopathic IBD", "classic IBD", or "primary IBD". We reviewed the current medical literature and found that certain etiological factors may be responsible for the development of IBD or IBD-like conditions, and we consider this form of *de novo* IBD as "secondary IBD". Currently known factors that are potentially responsible for giving rise to secondary IBD are medications; bowel altering surgeries and transplantation of organs, stem cells or fecal microbiome. Medications associated with the development of secondary IBD include; immunomodulators, anti-tumor necrosis factor alpha agents, anti-interleukin agents, interferons, immune stimulating agents and checkpoint inhibitors. Colectomy can in some cases give rise to *de novo* CD, pouchitis of the ileal pouch, or postcolectomy enteritis syndrome. After solid organ transplantation or hematopoietic stem cell transplantation, the recipient may develop *de novo* IBD or IBD flare. Fecal microbiota transplantation has been widely used to treat patients suffering from recurrent *Clostridium difficile* infection but can also causes IBD flares.

Key words: *De novo* inflammatory bowel disease; Secondary inflammatory bowel disease; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

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Core tip: Inflammatory bowel diseases (IBD) are chronic illnesses of the gastrointestinal tract with no clearly defined etiology and are traditionally termed as primary IBD. It is generally believed that IBD results from abnormal immune response to dysbiosis of gut microbiota in a genetically susceptible individual. IBD or IBD-like conditions may also be caused by well-defined etiologies; such as medical, surgical, and organ transplantation. These conditions are coined as secondary IBD. In this review we attempted to highlight some etiological factors, pathogenetic pathways, and clinical features of secondary IBD.

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INTRODUCTION

Inflammatory bowel diseases (IBD) are idiopathic chronic diseases of the gastrointestinal (GI) tract that are traditionally divided into ulcerative colitis (UC) and Crohn's disease (CD) based on their respective phenotypic presentation. Sometimes there is an overlap in clinical presentation, colonoscopic findings and histopathological features between UC and CD; which is termed as indeterminate colitis[1,2]. UC is the most predominant type of IBD with a prevalence of 7.6 to 246.0 cases per 100000 per year, followed by CD which has a prevalence of 3.6 to 214.0 cases per 100000 per year[3]. The worldwide distribution of IBD is skewed towards being more prominent in North America and Europe, although in the past two decades its prevalence has risen in developing countries like China and India[4,5]. This change in trends has paralleled with changes in dietary habits like inclusion of processed foods, increased intake of sugars and fats, overutilization of antibiotics and an overall improvement in hygiene.

The diagnosis of IBD is made by correlating clinical presentation, endoscopic findings and histopathological features of diseased tissue specimens. There is no single test to diagnose IBD or to distinguish between the CD and UC, although use of perinuclear anti-neutrophil cytoplasmic antibody and anti-saccharomyces cerevisiae antibody titers can sometimes be helpful in distinguishing the two[6]. Gut inflammation in UC is limited to the mucosal layer (epithelium, lamina propria and muscularis mucosa) and may extend up to the superficial submucosa. On the other hand, CD is characterized by the presence of non-caseating granulomas, transmural inflammation of the gut and formation of strictures and fistulas. In rare circumstances, CD can manifest solely as a perianal disease without bowel involvement[7]. The main differentiating features distinguishing CD from UC are the presence of granulomas, transmural disease, rectal sparing, and formation of strictures and/or fistulas. Although UC can occasionally manifest with strictures and perianal abscess or fistulas[8], Classic UC is expressed as a contiguous inflammation almost always involving the rectum and extending proximally to the left colon or entire colon, *i.e.*, extensive colitis or pancolitis. Sometimes the disease can extend into distal 10-15 cm segment of the terminal ileum, which is termed as backwash ileitis. CD on the other hand can arise in any part of the GI tract with a segmental distribution. It usually involves the ileocecal region, sparing the rectum. Smoking is considered as a risk factor for CD, but a protective factor for UC. These features of UC and CD suggest that their etiopathogenesis may not completely overlap. In addition, there are extra-intestinal manifestations such as erythema nodosum, pyoderma gangrenosum, and primary sclerosing cholangitis (PSC).

The etiology and pathogenesis of IBD remain unclear with several speculations suggesting the role of genetic factors, gut microbiome, and immune dysregulation. The interaction between these aforementioned factors gives rise to various immunogeneic types and clinical phenotypes of disease state. We term this type of traditional disease state as "idiopathic inflammatory bowel disease", "classic inflammatory bowel disease" or "primary inflammatory bowel disease" due to its unclear or idiopathic etiology and pathogenesis. However, certain identifiable factors like medications, bowel-alternating surgery, and transplantation of organs, stem cells or fecal microbiota appear to induce IBD or IBD-like changes in the GI tract. The affected individuals

essentially present with the fitting clinical symptoms and signs supported by endoscopic, histopathologic, and radiologic findings of IBD. We have termed this specific type of disease as "secondary inflammatory bowel disease (SIBD)" (Table 1).

Pathogenesis of conventional IBD

Genetic mutations or acquiring variants of certain genes have been proposed to be a pre-disposing risk factor for developing IBD. Genetic alteration in the gene coding for nucleotide-binding oligomerization domain 2 has been found to be associated with CD in about 20% of cases[9]. This mutation is associated with reduced response to bacterial lipopolysaccharides leading to increased survivability of certain gram negative bacteria that translocate into the bowel epithelium and induce inflammation. A loss of function mutation in the alleles coding for fucosyltransferase 2 and thereby absence of secretion of this enzyme in the intestinal tract is associated with an increased risk of alterations in the microbiome[10]. Genetic defects leading to abnormal T-cell function and macrophage activity can induce immune-mediated gut injury[11]. These cellular alterations induce dysregulated cytokine production and release, which recruits more inflammatory cells and continues the process of immune-mediated inflammatory response. Genetic linkage analysis has shown that mutations in the IL-10/IL-10R signaling pathway has been associated with infancy or early childhood onset IBD[12,13].

The GI tract along with the mesentery consist of a vast number of immune cells making it a highly immunogenic organ. The gut microbiome lives in harmony with the host defense system that protects the host from invasive GI pathogens. This tolerance to the gut microbiome is mediated by the homeostasis of intestinal microbiota, gut epithelial cell, stromal cells of the intestines, antigen presenting cells (dendritic cells, tissue macrophages) and inflammatory cells (neutrophils, lymphocytes)[14]. Alteration in the gut microbiome and a dysregulated response by any of these cells can shift the delicate balance of host defense and immune tolerance leading to development of IBD[15]. There is decreased biodiversity in the microbiome of individuals diagnosed with IBD[16]. Although a study in monozygotic twins showed the opposite results among individuals diagnosed with CD[17].

Dysbiosis plays an important role in the pathogenesis of classic IBD. The *Phyla Firmicutes* and specifically the family of Gram negative enteric organisms, *i.e.*, *Enterobacteriaceae*, have been found to be abundant in the diseased state of IBD[18,19]. Short-term antibiotic therapy has shown to improve gut inflammation, likely by affecting gut bacteria and regulating dysbiosis[20]. Another mechanism of microbial effect on the GI tract is the ability of the gut bacteria to adhere to mucosal surface and invade the deeper submucosal layers inducing an inflammatory reaction[21,22]. Subsequently mucosal breakdown occurs due to inflammatory cell-mediated tissue injury and the damaged mucosa further exposes the sub-epithelium to more colonies of bacteria leading to a vicious cycle of antigenic exposure and mucosal injury.

In short, the pathogenesis of IBD involves a dysregulated autoimmune response to gut dysbiosis which is precipitated by exposure to environmental factors among individuals who have a pre-existing high-risk genotype. Proinflammatory factors like tumor necrosis factor (TNF) alpha, interleukins-12/23 and cell adhesion molecules (integrins/intercellular adhesion molecules) play a key role in immune activation and recruiting immune cells[23]. Modern biological therapy has been designed to block these mechanisms or pathways, with TNFα blockers like infliximab and adalimumab being examples. These agents have also been effective in treating other autoimmune or rheumatological conditions. Interestingly, IBD often coexist with some of the systemic autoimmune disorders, and some of them are classified as extra-intestinal manifestations of IBD. In addition, genetic linkage analyses have shown an overlap of mutations in gene loci for IBD and these other autoimmune conditions[24]. These conditions include ankylosing spondylitis, lupus and rheumatoid arthritis. There could be a common pathogenic mechanism or a relationship at genomic level existing between IBD and other immune-mediated conditions.

DRUG-INDUCED SECONDARY IBD

Environmental factors influence the disease course in IBD patients. Two such well-studied factors are smoking and appendectomy, which are associated with an increased risk of developing CD, and a decreased risk for UC[25]. However, there are several other factors highlighted in this article that appear to induce IBD (Table 1). The pathogenesis of IBD is centered on dysregulated immunity, as described earlier. Hence it is not surprising to find that medications which alter the host immunity can

Table 1 Classification of secondary inflammatory bowel diseases based on etiology

Classification	
Drug-induced secondary IBD	Immunomodulators: Azathioprine, 6-mercaptopurine, tacrolimus, mycophenolic acid, cyclosporine; Anti-TNF agents: Infliximab, adalimumab, etanercept; Anti-interleukin agents: Secukinumab, tocilizumab; Interferons: Interferon α; Immune stimulating agents: GM-CSF (sargramostim), G-CSF (filgrastim); Checkpoint inhibitors: Ipilimumab, nivolumab, pembrolizumab
Post-surgical secondary IBD	Post-colectomy enteritis syndrome; Post-colectomy ileal pouchitis; Post-colectomy *de novo* Crohn's Disease of the Pouch; Post-bariatric surgery: Roux-en-Y gastric bypass
Post-transplant secondary IBD	Fecal microbiota transplantation related IBD; Post- hematopoietic stem cell transplant IBD: cord colitis; Post-solid organ transplant IBD: liver, kidney

IBD: Inflammatory bowel disease; GM-CSF: Granulocyte monocyte-colony stimulating factor; G-CSF: Granulocyte-colony stimulating factor.

sometimes lead to the development of *de novo* IBD, which we have termed as "drug-induced secondary IBD"[26]. These medications mainly include immunomodulators and biological agents. A newer class of drugs called the checkpoint inhibitors used in treating melanoma and other malignancies have also been implicated in precipitating IBD. There is a similar but weak association with the use of immune stimulating agents as well.

Immunomodulators

Immunomodulators alter the immune system mainly by inhibiting lymphocyte function. These medications consist of, but are not limited to azathioprine, 6-mercaptopurine (6-MP), tacrolimus, cyclosporine A, and mycophenolate mofetil (MMF). They are commonly used to prevent graft rejection after kidney and liver transplantation. Azathioprine and 6-MP have a well-established role in achieving long-term disease remission in the management of IBD. Cyclosporine A has also been used for the treatment of refractory IBD, including during acute UC flares[27].

Immunomodulators may induce IBD or IBD-like conditions. Studies have shown that the post-organ transplant use of immunomodulators causes a down-regulation of regulatory T-cells in the colonic mucosa[28]. This may create a propensity to develop immune-mediated inflammation in the colon, as regulatory T-cells prevent activation of B and cytotoxic T-lymphocytes. Tacrolimus is a routinely used immunosuppressant for organ transplantation due to its predictable side-effect profile and the availability of tests for monitoring its serum level. The use of tacrolimus has been reported to induce a flare of pre-existing IBD among individuals with solid organ transplantation[29]. Its use has also been shown to be associated with the development of *de novo* IBD[29,30]. In an observational study of 53 patients without a diagnosis of IBD who underwent liver transplantation, 6 (11%) of them developed *de novo* IBD during a median follow up of 3.9 years[29].

The use of MMF as an immunosuppressant is mainly seen in kidney or liver transplant recipients. One of its common side effects is diarrhea, and in about 9% of cases it causes "MMF-induced colitis"[31,32]. This type of colitis presents with IBD-like features of endoscopic and histologic changes in the colon[31]. The colonoscopic appearance of MMF-induced colitis is similar to that seen in classic IBD or graft-versus-host disease. But it exhibits mucosal eosinophilic predominance with the lack of apoptotic microabscesses and endocrine cell aggregates in lamina propria on histology[33]. This disease can sometimes persist even after discontinuation of MMF, taking up to 4-6 m for endoscopic resolution[34]. There have been multiple reported cases of individuals who developed *de novo* CD after exposure to MMF, followed by improvement of disease after stopping the medication[32,35,36]. There was a reported case of rapid resolution of MMF-induced colitis with a single dose of infliximab, suggesting the role of TNF in its pathogenesis[37]. One can speculate that MMF-induced colitis represents a variant of IBD. Paradoxically, there is some evidence to support the use of MMF for treating active IBD[38]. In a study of 25 patients with steroid-dependent disease unresponsive to biologics, MMF therapy achieved a clinical response in nearly 50% of cases[39]. Two small studies have shown that MMF induced steroid-free clinical remission in about 25% of cases[39,40]. Its therapeutic effect may help achieve long-term disease remission[41]. Therefore it appears to be effective in treating IBD while it can induce colitis resembling IBD or lead to SIBD[42]. This shows that interference with our complex immune system may be beneficial or detrimental for either treatment or induction of disease.

Anti-TNFα agents

Anti-TNFα inhibitors are molecules directed against the proinflammatory TNFα and they alter TNFα-mediated immune signaling in inflammatory pathways. Some examples of these agents are infliximab, adalimumab, and etanercept. They have been used for treating various immune-mediated rheumatological disorders, IBD, or IBD-related extra-intestinal manifestations, such as ankylosing spondylitis, uveitis, erythema nodosum, and pyoderma gangrenosum[43]. Treating one autoimmune condition can sometimes precipitate another due to alteration in the immunological homeostasis. Interestingly, individuals who are exposed to an anti-TNF agent, may develop *de novo* IBD or a form of drug-induced SIBD[44,45]. Along the same lines, new-onset psoriasis or eczema has been reported after exposure to the anti-TNF agents[44,46]. For example, the administration of infliximab for the treatment of IBD-related and non-IBD related inflammatory arthropathies has shown to induce autoimmune conditions like drug-induced lupus, autoimmune hepatitis and multiple sclerosis[47-49]. In some cases a paradoxical response is encountered after its administration, where previously arthritis-free individuals with IBD develop new-onset IBD-related arthropathy[50].

Etanercept, an anti-TNFα agent, has been extensively used to treat rheumatoid arthritis, while being ineffective in treating IBD. In fact, the use of this agent has shown to be associated with development of *de novo* IBD in multiple clinical observations[45,51-53]. In a large case series of patients who received etanercept for various rheumatological disorders, 49 individuals developed *de novo* IBD[52]. The average duration of therapy before the onset of symptoms was 3.58 mo. Its use has also been associated with precipitating pre-existing UC[51]. In a French study, the average frequency of etanercept-related *de novo* IBD was approximately 0.15%. In the same study, two patients who were treated with infliximab developed IBD[45]. In another large study of 17018 patients with auto immune disorders, several patients were on etanercept, infliximab, or adalimumab. The ones on etanercept showed a significantly increased risk of developing *de novo* UC or CD, yet no such effect was seen with infliximab or adalimumab[53]. In a case report, a 56-year-old male with psoriasis who was treated with adalimumab developed *de novo* UC[54]. His UC responded to the anti-IL-12/ 23 agent, ustekinumab.

The phenomenon of paradoxical response to agents like infliximab, adalimumab, or etanercept leading to the development of *de novo* IBD needs to be further explored. We hope that ongoing research may be able to identify individualized pathogenetic pathways for each patients which will aid in selecting their appropriate therapeutic agent, and pave the way to personalized medicine in IBD care. Another emerging aspect of IBD therapy is the use of biosimilars, which needs to be further studied in regard to their ability to induce *de novo* IBD resulting in SIBD.

Anti-interleukin agents

Anti-TNFα agents like infliximab and adalimumab have become the preferred therapies for treating IBD. Recently an anti-interleukin agent, ustekinumab (anti-IL-12/23) has been approved for the treatment of CD and UC[55,56]. The agent has been successfully used for treating psoriasis and other rheumatological conditions for the past decade. Other anti-interleukin agents have been created for their anti-inflammatory effects; and these include, but are not limited to; secukinumab, an anti-IL-17A agent used for treating psoriasis, and tocilizumab an anti-IL-6R inhibitor used for treating rheumatoid arthritis[57,58]. In a separate study, both these agents have been found to be associated with exacerbation of pre-existing IBD[59,60]. These agents may even induce *de novo* IBD in individuals at risk. Therefore we recommend that new agents, which could have the potential for therapy in immune-mediated disorders like IBD, need to be thoroughly studied for the immunogenicity and their association with the development of *de novo* IBD.

Interferon

Interferons (IFNs) are glycoprotein molecules which are secreted by host cells in response to viral infections and act as cytokines in inflammatory cascades. They have a role in inhibiting viral replication by inducing an immunological response through the activation of antigen-presenting cells, natural killer cells, neutrophils, and lymphocytes. IFNs have been investigated as potential immunological agents for treating IBD, but the studies showed no considerable clinical benefits[61-63]. IFNα has been used for treating hepatitis B or hepatitis C infection. With the current use of highly effective direct acting antiviral agents, the use of IFNs has been largely out of practice. Nevertheless, IFNs are still used for treating multiple sclerosis, certain types

of lymphomas, and leukemias.

There have been multiple reported cases of chronic hepatitis C-infected individuals who developed *de novo* UC after receiving IFNα-based therap[64-66]. There was one reported case in which CD developed after IFN therapy for an HCV and HIV co-infected individual[67]. All of these reported cases responded to 5-aminosalicylic acid compounds or corticosteroids. There have been several reported cases of UC flare during IFN therapy for chronic HCV infection[68,69]. IFNα has a tendency to stimulate T helper-1 cells which play a key role in the pathogenesis of several immune-mediated disorders[70]. This immune response in the gut may be responsible for the development of *de novo* IBD.

Immune stimulating agents

It has been proposed that CD in some individuals is related to a state of immune deficiency rather than over-activity. The immunodeficiency hypothesis can be used to explain the higher propensity of developing IBD among individuals with inherited immune disorders like Wiskott-Aldrich syndrome and glycogen storage disorders[71]. Cellular cytokines like granulocyte monocyte-colony stimulating factor (GM-CSF) and granulocyte-colony stimulating factor stimulate the hematopoietic stem cells in the bone marrow to induce production and maturation of granulocytes and monocytes, which play a role in innate immunity. Animal studies have shown that mice with an increased level of anti-GM-CSF antibodies had a reduced neutrophilic phagocytic capacity. The defect in the innate mucosal defense mechanism of the gut can lead to an increased risk of developing bowel inflammation[72]. The deficiency in GM-CSF along with nucleotide-binding oligomerization domain 2 mutations, impairs the innate immune response resulting in bacterial invasion of the lamina propria, and these bacteria in turn stimulate gut-specific T-lymphocytes[9]. These activated T-cells produce several inflammatory markers which may lead to development of IBD among predisposed individuals.

Several lines of clinical evidence suggest an association between GM-CSF and IBD. An Australian study of patients with IBD found that the level of antibody to GM-CSF was higher in the CD cohort than that in the UC cohort[73]. The higher levels were associated with more penetrating or stricturing disease, which in turn is associated with an increased risk of bowel surgery. Overall, the antibody level was significantly higher in the IBD group than the control group. The presence of anti-GM-CSF antibody suggests a disease state and the antibody titer could be used as a prognostic marker for disease activity, especially in case of CD[74]. A familial association with this antibody production has been described among those who have a family history of UC or CD[75]. The anti-GM-CSF antibody was found to be associated with an increased intestinal permeability and bacterial translocation, which was in turn correlated with a higher likelihood of developing IBD flares[76]. The use of immune stimulating therapy has been proposed for the treatment IBD. The use of recombinant GM-CSF (sargramostim) and granulocyte-colony stimulating factor (filgrastim) for treating CD has shown some therapeutic effect[77,78]. The studies demonstrated an improved steroid-free survival and reduction in the Crohn's disease Activity Index score[78,79].

Among individuals with CD, low immunoglobulin levels have been associated with an increased risk for undergoing surgeries[80]. Based on immunodeficiency hypothesis, individuals with lower immunoglobulin levels are at risk for developing severe CD. We can also speculate that such individuals could be susceptible for developing *de novo* IBD or IBD-like conditions in the presence of underlying high-risk genotype. Intravenous immunoglobulin therapy is used for various autoimmune disorders like myasthenia gravis, systemic sclerosis, and multiple sclerosis[81-83]. Studies have also demonstrated therapeutic benefits of IVIG in treating refractory IBD[84,85].

Checkpoint inhibitors

Checkpoint inhibitors include, but are not limited to, ipilimumab, nivolumab, and pembrolizumab. These medications are used for treating multiple malignant conditions including melanoma[86]. Ipilimumab is a monoclonal antibody directed against the cytotoxic T-lymphocyte antigen-4 which helps in downregulating the T-cell function[87]. Nivolumab and pembrolizumab are monoclonal antibodies which act on the programmed cell death-1 receptor. Studies have shown that approximately 30% of individuals treated with ipilimumab develop IBD-like gut inflammation[88]. This phenomenon has been observed since its early human trials in 2009[86,89]. Ipilimumab alters the immunological homeostasis, which could lead to the development of autoimmune conditions. It can precipitate an IBD-like disease state and also worsen pre-existing autoimmune disorders like rheumatoid arthritis, psoriasis and lupus[90,91]. It may even permanently alter the immune system which could give rise to IBD[92].

Ipilimumab-associated colitis shares many endoscopic and histologic features of classic IBD. The affected individuals have increased CD4 + T-lymphocytes and plasma cells in the gut mucosa, resembling that seen in IBD[93]. There are upregulated inflammatory pathways with an increased number of inflammatory cells which in turn stimulate other surrounding inflammatory cells causing further release of cytokines and inducing mucosal injury. Increased inflammatory markers or cells in the affected colonic mucosa include granzyme B, FoxP3, and CD8 + lymphocytes[88]. It commonly presents in the form of an inflammatory colitis, followed by an enteritis[94]. Severe forms of the disease are susceptible to develop bowel perforation. Extreme precautions should be taken if diagnostic colonoscopy is performed in these patients with severe disease[95,96].

The principle of treating such inflammatory conditions of the bowel is, like in case of classic IBD, to inhibit immune-mediated injury. Suppressing immunity with the use of steroids is the first-line therapy. Severe cases that do not respond to steroids, have shown to be effectively treated with infliximab, especially those with deep colonic ulcerations[97,98]. Vedolizumab (anti-integrin molecule) has also shown to induce remission among patients with ipilimumab-induced colitis[96,99]. With the advent of programmed cell death-1 inhibitors, the use of ipilimumab could be avoided especially due to its strongly associated adverse events and toxicities[100]. Some experts also suggest the prophylactic use of budesonide along with ipilimumab. In a published double-blinded randomized controlled trial (RCT), prophylactic use of budesonide was most beneficial if the severity of diarrhea was grade 3 or 4, and the authors recommended its use for grade 2 diarrhea or higher[101]. Discontinuation of the medication followed by steroid therapy seems to be an effective strategy for treating ipilimumab-induced colitis. Once the symptoms resolve it is reasonable to restart therapy, since the recurrence rate of colitis is about 6% and this is independent of the duration of steroid treatment[102].

The use of ipilimumab among patients with pre-existing IBD could induce a disease flare. As a general rule, it may be best to avoid it among patients who have an existing diagnosis of IBD[103]. But one could make an argument for treating those patients in long-term disease remission, especially when administered in combination with corticosteroids. In this situation, we recommend to approach it on a case-by-case basis. Combination therapy of nivolumab and ipilimumab is more effective in treating melanoma than ipilimumab alone but it can increase the risk of developing colitis. In a head-to-head analysis of the two treatment options, combination therapy was associated with a higher incidence of adverse events (54%) than ipilimumab monotherapy (20%)[104]. The most common severe adverse event was colitis, seen in 13% of overall combination treatment group compared to no cases of colitis in ipilimumab monotherapy group. Cases of nivolimumab monotherapy-induced colitis have also been reported resembling characteristics like those of UC[105].

Currently there are no randomized clinical trials in the evaluation of therapies for checkpoint inhibitor induced colitis, although a majority of them are treated with various steroid formulations[106]. Another approach for its treatment is the use of fecal microbiome transplantation, where stool from healthy donors is transplanted into the gut of individuals suffering from checkpoint inhibitor-induced colitis[107]. A small case series has demonstrated the benefit in this therapy. This may also suggest the role of fecal microbiome in pathogenic mechanisms of *de novo* IBD[108].

POST-SURGICAL SECONDARY IBD

Abdominal and pelvic surgeries are commonly performed in IBD patients, especially among those with CD. Studies have shown that bowel altering surgeries can have an effect on the microbiome in the GI tract, creating an environment for IBD remission or flare[109]. For example, surgical ileocolonic resection in patients with isolated CD resulted in 10-year disease remission in 50% of cases[110]. But some patients developed postoperative recurrence of bowel inflammation following the same surgery. A murine study showed that ileocolonic resection can alter the microbiota not just in the colon but also in the jejunum, which could precipitate IBD in the large and small bowel[111]. Animal studies have shown that surgical changes alter the gut microbiome, which can make the commensals virulent and cause anastomotic leaks[112,113]. These chronic mucosal lesions may represent an IBD-like phenomenon in the post-surgical bowel segments. Individuals with IBD with an abundance of bacterial species like *Bacteroides vulgatus*, *Clostridium perfringens* and *Ruminococcus gnavus* in the gut are at an increased risk for the development of CD of the pouch if they undergo

proctocolectomy with ileal pouch-anal anastomosis (IPAA)[114].

Post-colectomy enteritis syndrome

Patients with UC that undergo total colectomy or total proctocolectomy can develop a chronic inflammatory state of the small bowel called post-colectomy enteritis syndrome[115,116]. It is characterized by diffuse chronic enteritis which usually develops several months after the surgery. When suspected, an upper GI endoscopy, ileoscopy *via* stoma, or enteroscopy should be performed[117]. It appears to be distinct from CD in terms of its non-segmental involvement, superficial mucosal inflammation, absence of fistulas/strictures and the absence of granulomas. This condition can present with severe ulcerations and may even lead to a fatal outcome[117,118]. This has been speculated to be a form of UC of the small bowel due to its lack of typical features of CD. It is usually treated with immunosuppressive therapy like corticosteroids especially during the initial presentation or a flare, followed by a long-term use of immunosuppressants like azathioprine or infliximab[117].

Post-colectomy ileal pouchitis

Surgical resection of diseased bowel can be curative among individuals with severe forms of IBD which is unresponsive to medical treatment. Total proctocolectomy with IPAA is considered a definitive treatment for those with UC, since the entire colon with almost complete rectum is removed, leaving no available organ to manifest the disease. CD on the other hand is a segmental disease that can involve any part of the GI tract, hence resection of the diseased segments can be curative in many cases but disease recurrence is not uncommon[119,120]. Patients with refractory UC or UC with colitis-associated neoplasia require colectomy. Restorative proctocolectomy with IPAA has become the surgical treatment of choice in those who require total colectomy. This standard bowel reconstruction surgery can be associated with pouchitis or CD of the pouch. Pouchitis, a chronic inflammation of the ileal pouch after IPAA is speculated to occur due to fecal stasis, dysbiosis, altered mucosal immunity, and surgery-associated ischemia. It is commonly treated with antibiotics but some cases do not respond to long-term antibiotic therapy and is termed as chronic antibiotic-refractory pouchitis. Therefore, pouchitis represents a disease spectrum ranging from acute antibiotic-responsive phenotype to chronic antibiotic-refractory entity. The latter form of pouchitis resembles classic IBD in clinical, endoscopic, and histologic features, often requiring immunosuppressive therapy, including biologics[121,122].

In cases that are refractory to medical therapy, fecal diversion, away from the diseased segment of the bowel is an effective modality of treatment[123]. Experts consider chronic antibiotic-refractory pouchitis as an independent entity of IBD. Another type of pouchitis is called "diversion pouchitis". Diversion pouchitis responds to short chain fatty acids therapy[124]. It is important to differentiate this type of inflammation from ischemic changes which are frequently seen near the stoma and is related to the surgical technique.

Fecal diversion with the construction of a stoma can be performed to treat downstream bowel or perianal diseases in IBD. In some cases, fecal diversion may induce *de novo* IBD in an uninvolved segment of the bowel[125]; *i.e.*, postcolectomy enteritis syndrome as outlined above. This suggests that surgery is a trigger which influences the immune function in the uninvolved segment, leading to the development of inflammation.

Post-colectomy de novo CD of the pouch

Proctocolectomy with IPAA in patients with a preoperative diagnosis of UC has been shown to induce *de novo* CD among 2.7%-13% of patients who undergo the surgery for an initial diagnosis of UC or indeterminate colitis[126]. The new disease can develop weeks to even years after the surgery. It is believed that the bowel reconstructive surgery for UC creates a CD-friendly environment. After colectomy the GI transit of consumed food is quick, altering the gut microbiome and creating a CD inducing environment. This along with areas of ischemia due to surgical alteration can give rise to *de novo* CD or induce a disease flare[126]. The development of new disease may occur in those individuals who already have an underlying high-risk genotype for developing IBD and surgery only acts as a trigger that precipitates its phenotypic expression. The role of other environmental factors like peri-operative use of antibiotics and non-steroidal anti-inflammatory drugs, ischemia, obesity, and anxiety related to the surgical intervention may have a significant contributing effect in giving rise to this disease state.

De novo IBD after bariatric surgery

Morbid obesity is a chronic illness which can increase the risk of developing other comorbidities like diabetes, hyperlipidemia, cardiovascular diseases and several types of cancers including colon cancer. Interventions to treat obesity are mainly directed towards lifestyle changes like adopting a low-calorie diet and adequate exercise. Following these interventions can be a challenge to many and a growing number of obese individuals instead choose to undergo bariatric surgery[127]. There are several types of bariatric procedures performed in the United States, the commonly performed ones are Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and laparoscopic gastric band placement[128,129].

One of the most effective surgeries for morbid obesity is RYGB and it has been shown to induce *de novo* CD[130,131]. There have been several reported cases of individuals who developed new-onset IBD after undergoing a bariatric surgery[132-135]. A recently published case series of 44 patients who developed *de novo* IBD after surgery, demonstrated that there seems to be a higher incidence of developing the disease after RYGB[133]. The majority of cases were females and CD was the most common type of disease (n = 31), followed by UC (n = 12) and one case of indeterminate colitis. The median time to develop the disease after undergoing surgery was 7 years. Similar findings were observed in another series of 15 patients, suggesting a possible role of bariatric surgery in the development of SIBD[136].

It is suspected that the alteration in microbiota or nutritional status could have a role in precipitating the disease in these individuals. Similarly, development of celiac disease after undergoing pancreaticodudenectomy[137], Billroth II procedure[138], pyloroplasty[138] or IPAA[139] has been reported. This could suggest an immunogenic response to the surgery leading to immune-mediated gluten sensitivity and therefore giving rise to celiac disease. Individuals who undergo bariatric surgery have shown to develop an alteration in their gut microbiota[140,141]. This change could lead to colonic dysbiosis which plays an important role in pathogenesis of IBD[15,16]. In addition, there is alteration in the nutritional parameters in these individuals due to artificially induced malabsorption which could play a role in the disease process, for example vitamin D deficiency and hypoglobulinemia have been linked to pathogenesis of IBD[84,142]. Interestingly, when the surgery is performed in individuals with well controlled IBD, it has shown to be safe and effective, with an acceptable risk of post-operative complications[143-145]. Our understanding of these mechanisms is limited[146].

POST-TRANSPLANT SECONDARY IBD

The immune system plays a central role in the pathogenesis of IBD. Hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT) is performed with the use of steroids and immunomodulators. These agents suppress the immunogenic response of the recipients lymphocytes against transplanted human leukocyte antigens, to prevent immune-mediated rejection[147]. Therefore appropriate cross-matching is carried out prior to transplantation to prevent human leukocyte antigens-mismatch[148]. The alteration in the immune system with the use of immunosuppressant's or introduction of foreign antigens could lead to a dysregulated immune response and subsequent development of autoimmune disorders. One such autoimmune conditions is IBD that can develop after HSCT or SOT. Another type of transplantation is that of a healthy donor's fecal material, which is used to treat individuals with recurrent *Clostridium difficile* infection (CDI)[149]. If the donor suffers from IBD then their gut microbiome may carry the microbiota that is proinflammatory and could lead to development of *de novo* IBD in the recipient[150,151]. Additionally, the alteration in the gut microbiome may induce an exaggerated immune response to the newly introduced bacteria which can precipitate immune-mediated gut inflammation.

Post-hematopoietic stem cell transplant IBD

HSCT is an effective treatment in several hematopoietic disorders including leukemia. Recipients of stem cell therapy are immunosuppressed and are at risk for developing various GI infections, like infectious enterocolitis. Umbilical cord blood of newborns is a good source of harvesting stem cells which are used for HSCT[152]. The recipients can develop a unique type of colitis, which is clinically and histologically distinct from the typical infectious colitis or colitis associated with graft-versus-host disease[153,154]. This condition is termed as "cord colitis" and the affected individuals usually present with non-bloody diarrhea several months after the transplantation[153]. Colonic biopsies demonstrate chronic active colitis with non-caseating granulomas and the disease can

involve the upper or lower GI tract, a pattern resembling that of CD[154,155]. They also tend to have high loads of the bacteria *Bradyrhizobium enterica* in their gut. Some speculate that the alteration in gut microbiome has a role in the pathogenesis of this disease[156]. This is also supported by the fact that antibiotic therapy is effective in the treatment. Cord colitis could be a variant of IBD which develops in the setting of altered immunity due to the use of cord blood stem cells or the use of immunomodulators.

Post-solid organ transplant IBD

Individuals who undergo SOT are immunosuppressed during the peri-transplant and post-transplantation periods. There is increased risk of developing diarrhea after transplantation, commonly due to infections or due to side effects of medications, but there are other conditions that could cause diarrhea in these patients. Two such conditions are the onset of an IBD flare in those with a pre-existing diagnosis of IBD or the development of *de novo* IBD[157]. This phenomenon is more common after orthotopic liver transplantation than other SOT, like kidney or heart[158]. IBD in general and UC in particular are associated with concomitant PSC, for which the mainstay of treatment is OLT. This is probably the reason for encountering higher number of OLT than SOT of other organs in the IBD population[159,160]. The incidence risk of developing *de novo* IBD in SOT recipients versus general population is 206 and 20 respectively per 100000 person-years[161]. In a study of post-renal transplant recipients, it was found that the incidence risk of developing IBD was twice than that for general population[162]. In a retrospective chart review of 6800 liver and/or kidney transplant recipients that received some form of immunosuppression, it was found that 14 individuals developed *de novo* IBD[161]. Post-OLT patients who develop *de novo* IBD had a tendency to have underlying PSC or develop PSC in the future[160,163].

The etiopathogenesis of *de novo* IBD after SOT is likely related to the use of immunosuppressants like steroids, immunomodulators, and anti-thymocyte globulin; that alter the "immune thermostat" leading to a dysregulated immune response to gut microbiome[157]. This in turn can lead to development of *de novo* IBD among at risk individuals. This is a paradoxical response to immunosuppression, a key principle in treating IBD with agents like azathioprine and 6-MP. Details regarding effects of various immunomodulators in precipitating IBD have been described in the previous section of this review. In a recently published retrospective study of 373 patients suffering from PSC, with or without concurrent IBD, the 10-year cumulative risk of developing a disease flare or *de novo* IBD was about 25%[42]. These risks were higher with the use of MMF and lower with azathioprine in the post-operative period. The use of azathioprine after SOT seemed to be protective against the development of IBD flare or *de novo* IBD[29,42].

Interestingly, there is evidence suggesting that immunosuppression with organ transplantation may be beneficial in patients with IBD. In a study of 41 IBD patients that underwent OLT the rate of clinical remission was higher than 42 IBD patients who did not undergo OLT (54% *vs* 33%, $P = 0.03$)[164]. Transplant recipients who received MMF had better outcomes than those with other immunosuppressants. This variable response to immunotherapy by different individuals illustrates the complex nature of the immunological processes at play where alteration in immunity causes a disease flare in some while in others it could be protective against flaring. One could argue that the transplant recipients were monitored closely and were more compliant with medications, therefore had lesser incidence of disease flare.

Fecal microbiota transplantation-associated IBD

Gut microbiome consists of trillions of organisms which include bacteria, fungi and viruses. In patients with IBD there is a state of gut dysbiosis which plays a role in its pathogenesis[150,151,165]. Individuals with recurrent CDI have a significant alteration of their colonic microbiota leading to gut dysbiosis, which can be successfully treated with fecal microbiome transplantation (FMT) from healthy donors[149]. The fecal material is introduced *via* upper delivery methods (oral capsules or naso-gastric/jejunal tube) or lower delivery methods (colonoscopy or enema). Among individuals with IBD who develop CDI, FMT has shown to be successful in treating 87%-91% of cases after a single transplantation[166,167]. Interestingly, this rate of success is slightly lower when compared to individuals without IBD[168]. Since gut dysbiosis is seen in IBD as well, investigators have utilized FMT for treating IBD flares with good response, especially in case of UC[169,170]. There are few reported cases of CD flare that responded successfully to FMT[171,172]. It may also have a role among patients with active disease that is not responding to biologic therapy[172]. Fecal transplantation has also shown to modestly improve disease severity in case of chronic pouchitis[173].

It is interesting to note that individuals treated with FMT for CDI appear to have an alteration of gut microbiome mirroring the donor's microbiome and with a higher microbial biodiversity[174]. But in patients with IBD the microbiome after FMT resists this change and rater tends to retain the pre-transplant type of gut microbiome. This may suggest that the microbiome by itself may not be an influential pathogenic mechanism in IBD but rather a source to stimulate the immune system that drives the disease process and which in turn influences the gut microbiome. This may also explain the lack of consistent response of FMT in treating IBD. A meta-analysis of nine cohort studies, eight case studies and one RCT showed that FMT appears to be safe in IBD but its efficacy was not consistent[169]. In a more recent meta-analysis of four RCT's comparing FMT versus placebo for the treatment of active UC, showed that clinical remission was achieved in 28% of patients in FMT group when compared to only 9% in placebo group[170]. Rates of clinical response were 49% and 28% in the FMT and placebo groups, respectively. Well-designed RCT's are needed to further study the role of FMT in the treatment of IBD[175].

Use of FMT is not a completely safe procedure and is associated with few adverse events, especially infections and in rare cases death[176,177]. There have been multiple reported cases of individuals with IBD and CDI who developed an IBD flare after treatment with FMT[176,178,179]. Studies have shown that the rate of developing a disease flare after FMT is about 15%-25%, higher among those who were transplanted *via* lower delivery method than peroral method[168,180]. Based on these observations, we can speculate that FMT could also induce development of *de novo* IBD among individuals who carry the preferential genotype for the disease. This may be more likely if the donors themselves have active IBD. As a part of screening process for donors, several experts that FMT continue to exclude those who have IBD, even though we have not had any direct evidence that shows that such donors with IBD could cause adverse effects in the recipient[181-183]. Perhaps the alteration of gut microbiome may be more harmful in certain individuals and further studies are needed to recognize the factors that influence the development of FMT-induced IBD flare up.

CONCLUSION

IBD have a complex pathogenesis which consists of an interaction between immune system, gut microbiome and genetic factors. These three components can be influenced by several environmental factors which could tip the balance towards an immune mediated proinflammatory state in the gut and in certain extra-intestinal tissues. In a normal state there is immune tolerance towards host microbiome. External influences can alter this balance by inducing a hyper-immune response, leading to mucosal injury of the GI tract. This type of *de novo* IBD due to specific external causes is termed as secondary inflammatory bowel disease (SIBD). These external factors have been categorized into three main groups: Drugs, surgery and organ/fecal transplantation. Drugs that can influence immunity and potentially alter it, have been implicated with the development of drug-induced SIBD; these include immunomodulators, biologics, interferons, immune stimulators, and immune checkpoint inhibitors. Bowel altering surgery can influence the microbiome and lead to malabsorption, especially in case of bowel resection and bariatric surgery. Surgeries that are used to treat one type of disease, like UC with proctocolectomy followed by ileal pouch-anal anastomosis, have shown to precipitate new forms of diseases like chronic pouchitis or CD of the pouch. This type of *de novo* chronic gut inflammation after surgery is termed as post-surgical SIBD. The role of immunosuppressants in organ transplant recipients has been key in preventing immune-mediated rejection. These immunosuppressants can paradoxically induce an autoimmune mediated gut inflammation. The donor's foreign organs or stem cells could also induce an immune reaction causing immune mediated tissue injury. Both these factors can lead to post-solid organ/stem cell transplant related. The interaction between microbiota and host immune system is complex process, and factors altering bowel anatomy and gut homeostasis may reset host's immune thermostat, triggering the development of IBD or SIBD.

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