

Behcet's Disease: An In-Depth Review about Pathogenesis, Gastrointestinal Manifestations, and Management

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Keywords

Behcet's disease · Gastrointestinal involvement · Inflammatory vascular disorder · Management · Pathogenesis

Abstract

Background: Behcet's disease (BD) is a complex inflammatory vascular disorder that follows a relapsing-remitting course with diverse clinical manifestations. The prevalence of the disease varies throughout the globe and targets different age-groups. There are many variations of BD; however, intestinal BD is not only more common but has many signs and symptoms. **Summary:** BD is a relapsing-remitting inflammatory vascular disorder with multiple system involvement, affecting vessels of all types and sizes that targets young adults. The etiology of BD is unknown but many factors including genetic mechanisms, vascular changes, hypercoagulability, and dysregulation of immune function are believed to be responsible. BD usually presents with signs and symptoms of ulcerative disease of the small intestine;

endoscopy being consistent with the clinical manifestations. The mainstay of treatment depends upon the severity of the disease. Corticosteroids are recommended for severe forms of the disease and aminosalicylic acids are used in maintaining remission in mild to moderate forms of the disease. **Key Messages:** In this review, we have tried to summarize in the present review the clinical manifestations, differential diagnoses, and management of intestinal BD. Hopefully, this review will enable health policymakers to ponder over establishing clear endpoints for treatment, surveillance investigations, and creating robust algorithms.

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Introduction

Behcet's disease (BD) is an inflammatory vascular disorder with multiple system involvement, affecting vessels of all types and sizes. The clinical path follows a relapsing-remitting course with diverse clinical manifestations. The etiology of BD is unknown; however, a sturdy correlation with

human leukocyte antigens, especially HLA-B51, has been found [1]. The International Criteria for Behçet's Disease (ICBD) was developed from the collaboration of experts from 27 nations to take up the diagnostic quandary and the shortcomings of the preceding criteria, namely International Study Group (ISG) [2]. In ICBD criteria oral ulcer, genital ulcer, and ocular manifestations each get 2 points, and others (skin lesions, neurological manifestations, vascular manifestations, and positive SPT) get 1 point. A score of ≥ 4 points is required for a diagnosis of BD. The performance of ISG criteria versus ICBD criteria has been checked in multiple cohorts. These studies point out that ICBD criteria have greater sensitivity, and therefore, diagnosis may become easier with the use of these criteria. However, ICBD criteria are less specific than the ISG criteria, which might result in overdiagnosis [3]. Countries with a high prevalence of BD are found along the silk route. Young adults between the ages of 20–40 years are most commonly affected, with BD being more common and more severe in males compared to females [4, 5]. During the previous 3 decades in Korea, rates of BD in male patients, and complete type disease have declined, and patterns of organ involvement have shifted such that the major presenting features (genital ulcers, ocular involvement, and skin lesions) have lessened whereas the mean patient age rose progressively, as did the frequencies of joint, gastrointestinal (GI) and central nervous system manifestation [6]. GI manifestations of BD are associated with notable morbidity and mortality. Abdominal pain, nausea, vomiting, diarrhea, and GI bleeding are the most common symptoms. BD may involve any portion of the alimentary tract and different GI organs [7]. The present study aims to focus on intestinal BD, including its diagnoses, clinical manifestations, and management.

Epidemiology of BD

Countries with a high prevalence of BD are found along the silk route, in the Mediterranean region (especially in Turkey), in the Middle East, and the Far East. Countries with the most prevalence to the least prevalence include Turkey and Iran followed by Saudi Arabia, Iraq, Italy, Israel, China, Japan, Egypt, Spain, France, USA, Sweden, Portugal, Germany, and UK [8]. The male-to-female ratio in Iran was 1.19, Japan 0.98, China 1.34, Korea 0.63 and, Germany 1.40 to 1.00 [8]. The mean age of onset in years was 25.6 in Iran, 38.87 in Korea, 25.8 in the Azeri population of Iran, 33.8 in China, 26 in Germany, 25.6 in Turkey, and 29.3 in Saudi Arabia, and 29.4 in Iraq [6, 9–11].

Epidemiology of BD and GI/Extra-GI Involvement

In Irani patients with BD, the most common manifestations of BD included oral ulcers seen in 97.5% of patients, followed by genital ulcers seen in 65.7% of patients [12]. Skin manifestations were seen in 64.6% of patients. The prevalence of GI disease is illustrated in Figure 1 [11, 13].

Pathogenesis and Pathophysiology

A summary of the pathogenic mechanisms involved is presented in Figure 2 [14–37]. Patients with Behçet syndrome have higher levels of antibodies to mycobacterial heat shock protein epitopes, some of which have strong homology to human heat shock proteins. T-cells and/or antibodies may recognize epitopes shared by both host and the infectious organism's heat shock proteins, causing Behçet syndrome to develop and/or persist [30]. Specific bacteria, particularly streptococci, may also play a role in the immune response in patients with Behçet syndrome [30]. The innate immune system's mannose-binding lectin (MBL) activates the complement cascade after binding to carbohydrate structures on microorganisms. Behçet syndrome, as well as other autoimmune disorders, has been linked to low MBL serum levels and MBL gene mutations [31]. Behçet syndrome has been linked to changes in toll-like receptor patterns, particularly increased activity of toll-like receptors 2, 4, and 8 [32].

Autoreactive T-cells tend to play a critical role in the pathogenesis of Behçet syndrome [33]. Additionally, Th17 cells, which produce IL-17, have been found to be increased and activated in Behçet syndrome patients, which may explain some of the seemingly contradictory results about Th1 and Th2 activity in this disorder [35]. Gamma-delta T-cell activation can be polyclonal, with different antigenic stimuli eliciting different responses [37].

Behçet syndrome has been linked to changes in cellular signaling pathways. In a study comparing 9 patients with Behçet syndrome to 9 healthy controls, the JAK1/STAT3 pathway was activated in CD14(+) monocytes and CD4(+) T-cells in 9 patients with Behçet syndrome [36].

A number of molecules that interact to mediate endothelial dysfunction in Behçet syndrome have been identified. Increased serum, erythrocyte, synovial, and aqueous humor NO concentrations, as well as elevated levels of NO metabolites in Behçet syndrome, have been reported

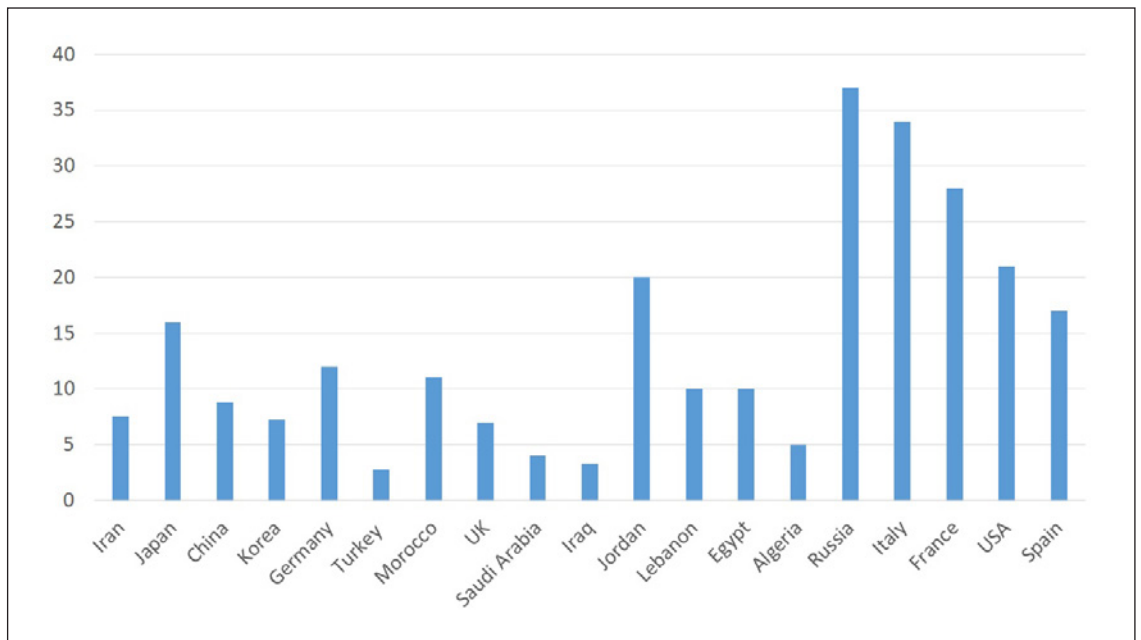


Fig. 1. Prevalence of GI manifestations of BD globally. GI, gastrointestinal; BD, Behcet's disease.

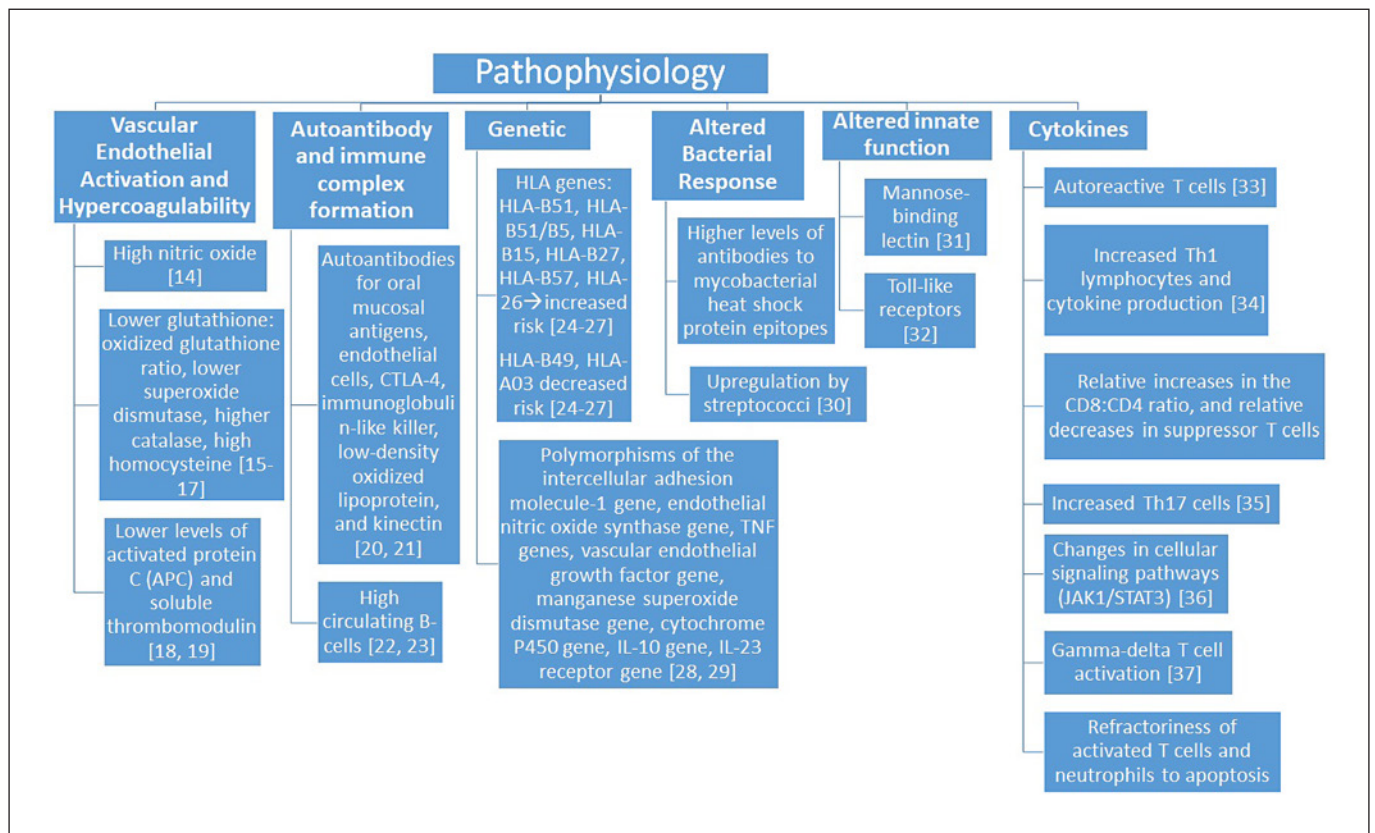


Fig. 2. Pathophysiology of BD. BD, Behcet's disease.

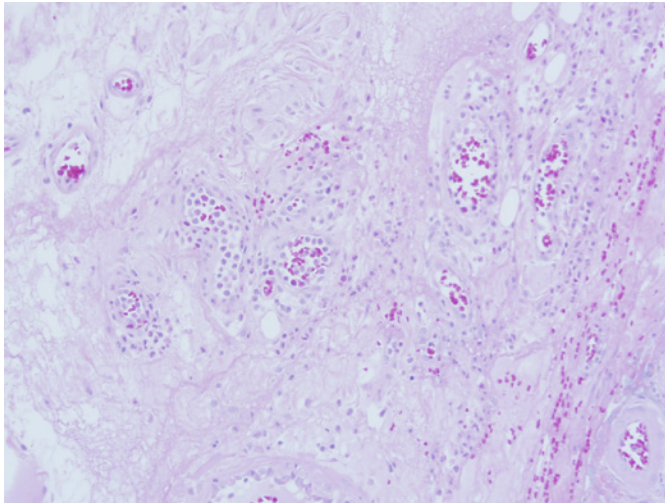


Fig. 3. Submucosa of the bowel demonstrating acute and chronic vasculitic changes of the small vessels and venules with perivascular chronic inflammation (H&E).

[14]. Patients with Behçet syndrome have higher levels of oxidative stress, lower glutathione: oxidized glutathione ratio, lower superoxide dismutase, and higher catalase have all been discovered [15–17]. In Behçet syndrome, elevated mean plasma homocysteine levels have been found to be associated with NO concentrations and reduced flow-mediated vessel dilatation [15–17]. The majority of evidence indicates that thrombosis in Behçet syndrome is caused by vascular damage caused by inflammation or intrinsic endothelial dysfunction, which can serve as a source of thrombogenic stimuli in and of itself (Fig. 3).

Polymorphonuclear motility is increased in Behçet syndrome. Increased levels of cytokines like IL-8 and TNF-alpha in the blood cause polymorphonuclears and the endothelial surface to become activated [38]. Increased E-selectin on the luminal surface encourages neutrophil adhesion and migration through the affected vessel's wall and beyond [39]. These present as indicators of inflammation (Fig. 4, 5).

Other mechanisms include a genetic predisposition for low IL-10 expression because many models suggest that this reduction is linked with inflammation; a similar theory has been associated with ulcerative colitis. These interactions of low expression and inflammation have also been noted for the IL23R/IL12RB2 genes in the vicinity of IL-10 genes as revealed in samples from Japanese and Turkish population [40].

Histopathology

BD has many features on histopathology. Oral and genital ulcers are relatively not specific with a mixed dermal inflammatory infiltrate at the base of the ulcer [41]. There might be erythema nodosum-like lesions with vasculitis and necrobiosis [41]. There can also be perivascular infiltrate of mononuclear cells, mast cell infiltrate, or neutrophilic vasculitis [41]. In some papulopustular lesions, there might be evidence of spongiosis, basal keratinocyte vacuolization, intraepidermal pustules, and suppurative folliculitis [41] (Fig. 3–5).

Patterns of GI Involvement in BD

GI manifestations of BD may involve any segment and/or organ of GI tract [42]. Usually, the intestinal segment is involved, with mural findings. These findings are most commonly mural ulcerations with a polypoid mucosal surface followed by involvement of the terminal ileum and ileocecal valve. Rarely, the mesentery might be involved as well in form of fibrofatty proliferation [43]. GI BD can result in neutrophilic phlebitis causing mucosal ulcerations or it can involve large vessels such as mesenteric arteries causing ischemia and infarction of the GI segments [44].

Anatomic Distribution of GI Involvement and Symptoms

The highest frequency of GI involvement of BD is reported in Russia, Italy, and France [8, 11, 13]. We discuss various effects of BD on alimentary canal and GI organs in detail below.

Esophagus

Esophageal involvement is uncommon. Esophageal BD also presents with involvement of another part of GI tract in >50% of the cases [4]. It can present as ulcers, stenosis, perforation, varices, and decreased motility [7, 45–47]. Clinical symptoms include retrosternal chest pain, dysphagia, odynophagia, hematochezia, and melena [48].

Stomach and Duodenum

The stomach is presumably the least involved GI organ in BD. Gastroduodenal involvement is found to be most common in people of Chinese descent in a study conducted in Taiwan [49]. Common symptoms include dys-

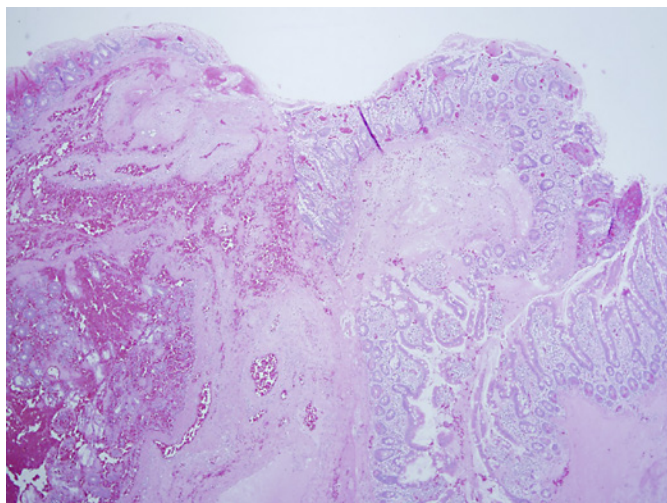


Fig. 4. Low-power view of a hemorrhagic focus of bowel with transmural defect demonstrating minimal inflammatory change and ulceration with adjacent preserved villi of the ileum (H&E, $\times 2$).

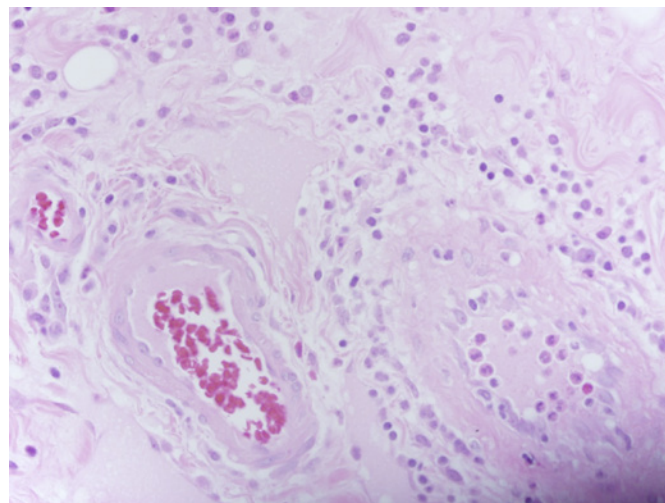


Fig. 5. High-power view of bowel submucosa with acute and chronic inflammation of the small vessels (H&E stain, $\times 40$).

pepsia and epigastric abdominal pain, and ulcers can be found in stomach or duodenum alone as well as in both organs concurrently [7]. Rare manifestations include gastric Non-Hodgkin's lymphoma, pyloric stenosis, and gastroparesis [50, 51]. In a study, 13 patients with BD demonstrated that the number and size of oral and genital ulcers diminished significantly and various clinical manifestations regressed after the eradication of *Helicobacter Pylori*, suggesting that the bacterium may be involved in pathogenesis of BD [52].

Jejunum, Ileum, and Colon

In a study by Neves et al. [53], video capsule endoscopy revealed small intestinal manifestations of Behcet disease in a group of 10 individuals with jejunum being the most affected segment [54]. Most common complication of intestinal BD was found to be perforation (12.7%), followed by fistula (7.6%), stricture (7.2%), and abscess (3.3%) [55]. The most common location of perforation is reported to be terminal ileum, ileocecal valve and ascending colon, risk factors being age <25 at diagnosis, history of laparotomy and volcano-shaped ulcers [56, 57].

Pancreas, Liver, and Biliary System

BD is an exceptionally rare cause of pancreatitis. Only a few case reports have been published on this subject [58, 59]. Pancreatic involvement in patients with BD can be attributed to this disease being a form a vasculitis, as there

have been few cases of acute pancreatitis demonstrated in patients having other vasculitis such as Wegener granulomatosis [60]. It is possible that pancreatic involvement in BD is subtle and does not have clinical manifestations which may require diagnostic studies to evaluate for this condition; this is suggested by an autopsy series done in Japan which revealed pancreatic involvement in 2.9% individuals in a sample of 170 cases [61].

The most prominent complication of hepatobiliary system in BD is Budd Chiari syndrome (BCS), as a result of underlying endothelial dysfunction [62]. The prevalence rate is 1.3%–3.2%, and it is associated with poor prognosis [63, 64]. Patients have typical symptoms of BCS including ascites, right upper quadrant pain, and hepatosplenomegaly and can present in an acute, subacute, or chronic setting. Patients can also have isolated or concurrent inferior vena cava and portal vein thrombosis as well [65]. Some authors suggest BCS screening with duplex ultrasonography for all patients with BD given its high prevalence and mortality in BD patients [63]. Other less common hepatobiliary manifestations of BD include aseptic abscess, chronic hepatitis, and sclerosing cholangitis [65–67].

Extra-GI Manifestations

Unlike inflammatory bowel disease, BD primarily presents with widespread manifestations of other organ systems. It is classically characterized by recurrent oral and genital

Table 1. Common GI and extraintestinal manifestations of intestinal BD, intestinal TB, and Crohn's disease

	GI manifestations					Extraintestinal manifestations		
	Oral	Esophagus	Stomach	Small intestine	Large intestine	Pancreaticobiliary	Lesion quantity/distribution	
Behcet's disease	Aphthous ulcers	Rare	Rare	Ileocecal ulcers (most common)	Rare	Rare	Grouped/localized, oval/round shaped deep ulcers, <6 ulcers	Genital ulcers, uveitis, erythema nodosum-like lesions
Intestinal TB	Rare	Rare	Rare	Ileocecal ulcers	Rare	Rare	Round/oval/ring shaped, punched out lesions, focal distribution, <5 ulcers	Ascites, lymphadenopathy, pericardial effusion, vertebral osteomyelitis, renal tuberculosis
Crohn's disease	Aphthous ulcers	Rare	Rare	Common, transmural inflammation	Perianal fistula, fissures common	Rare	Irregular, longitudinal ulcers w/ cobblestoning appearance, diffuse, multisegmental	Aphthous ulcers, pyoderma gangrenosum, uveitis, PSC, arthritis, ankylosing spondylitis

TB, Tuberculosis; PSC, Primary Sclerosing Cholangitis; GI, gastrointestinal; BD, Behcet's disease.

ulcer, uveitis, and characteristic skin lesions. The oral aphthous ulcers recur at least 3 times in a year, they can be single or multiple and can present after trauma or dental procedures [68]. Genital ulcers are the second most commonly observed initial manifestation of BD, they are large, multiple, and deep with irregular borders [69]. Other mucocutaneous findings include papulopustular and erythema nodosum-like lesions. Other extra-GI manifestations include arthritis, central nervous system, and vascular lesions [69].

Diagnostic Evaluation

A recent Japanese article described the algorithm that could be used for evaluation of the disease. BD should be suspected in patients with right-sided lower abdominal pain and blood-filled stool [70]. Intestinal form of the disease is usually confirmed if a volcano-shaped ulcer is visualized on endoscopy [70]. Combined with other symptoms of recurrent ulcers, oral, and ocular findings, systemic BD may be diagnosed [70].

Diagnostic Modalities

According to Hamdulay et al. [71], wireless capsule endoscopy is a useful investigation in patients with BD having prominent GI symptoms and negative conventional evaluations. Capsule endoscopy has a major role in detecting small bowel lesions including reddened lesions, erosions, and ulcers. It also has a role in following up and detecting the efficacy of remission [72]. Endoscopic findings include single or multiple ulcers. Routine endoscopy is not recommended in patients with BD [73]. Patients with upper GI symptoms may be referred for upper endoscopy and/or esophageal manometry [7]. Typical colonoscopic findings of intestinal BD were found to be single or multiple deep ulcers with discrete margins found at ileocecal area or anastomotic sites in patients with previous GI surgeries, the disease was further classified as localized single, localized multiple, multisegmental and diffuse based on the site and distribution of lesions with localized single type being the most common finding [74].

Differential Diagnoses

Intestinal Behcet's has been called the "great mimicker" due to its clinical and extraintestinal similarities to inflammatory bowel disease (specifically Crohn's disease)

Table 2. Treatment modalities for Behcet's syndrome

Disease severity (DAIBD score)	Medical therapy	Highest level of evidence
Mild-moderate (20–74)	ASA	Retrospective Cohort Study, Expert Opinion
Moderate-severe (40–>75)	CS	Retrospective Cohort Study, Expert Opinion, Case Reports
Moderate-severe (CS resistant)	Anti-TNF agent (adalimumab, infliximab)	Retrospective Cohort Study, Qualitative Systematic Review (Meta-Synthesis), Expert Opinion, Case Reports
Moderate-severe (CS and anti-TNF resistant)	Immunomodulators (AZA, MTX, thiopurines)	Retrospective Cohort Study
Other	Thalidomide, tacrolimus	Thalidomide (Case Series) Tacrolimus (Case Report)

DAIBD, Disease Activity Index of Behcet's Disease; CS, corticosteroids; ASA, aminosalicylates.

and intestinal tuberculosis. Although IBD and intestinal TB are the most commonly cited on the differential diagnosis, other less commonly cited diagnoses include NSAID-induced small intestinal ulcers and simple ulcers of the GI tract [70]. Table 1 describes the most and least common GI manifestations of intestinal BD, intestinal TB, and Crohn's disease as well as common extraintestinal manifestations.

Management

The management of BD is complicated by a lack of clearly defined and standardized guidelines and also because most medical therapies lack robust evidence to support their use. The goal of management of BD is to tailor medical therapy to the level of clinical severity in order to achieve and maintain remission as well as to prevent surgical intervention. A clinical scoring tool known as the Disease Activity Index of Behcet's Disease was developed in 2011 by Cheon et al. [75] which utilized a combination of mainly clinical symptoms (i.e., fever, abdominal pain, and extraintestinal manifestations) to separate patients into varying levels of clinical severity ranging from quiescent (least severe) to severe. The different medical therapies and the evidence for their use are described in Table 2.

Medical Management

In mild to moderate cases, 5-ASA, or the class of aminosalicylates and sulfasalazine (prostaglandin-inhibitor) are frequently used to maintain remission once it has already been established. A 2012 Korean retrospective study found that when treated with either sulfasalazine or 5-ASA monotherapy, patients experienced clinical relapse ~32% of the time. They found that risk factors for

clinical relapse included earlier age of diagnosis, elevated CRP, and higher disease activity index scores (Disease Activity Index of Behcet's Disease). Another retrospective study conducted by Kinoshita et al. [76] had similar results, with 57% of patients treated with 5-ASA monotherapy maintaining clinical remission after 1 year of treatment. Both studies concluded that 5-ASA and sulfasalazine should only be used in patients with mild to moderate disease, as the risk of relapse on ASA or sulfasalazine monotherapy increased significantly at higher disease activity levels.

In moderate to severe cases, corticosteroids are generally recommended as the first-line treatment for BD per the 2020 Japanese consensus statements [48]. Treatment response to steroids generally induces remission in over 40% of cases and responsiveness to treatment was found to be independently associated with a decreased risk of surgery [77]. TNF-inhibitors such as infliximab or adalimumab are considered second-line treatment for patients that are corticosteroid dependent. A retrospective cohort study conducted by Sugimura et al. [78] showed that TNF-inhibitor agents induced both clinical and endoscopic remission in patients with intestinal BD. A 2019 study conducted by Miyagawa et al. [79] also found that when corticosteroids are used in combination with TNF-inhibitor agents that there was a significantly increased ulcer healing rate on endoscopy which could be another option prior to moving onto 3rd line agents.

Immunomodulating agents such as azathioprine and methotrexate are recommended as third-line agents in patients with moderate to severe BD that are resistant to both corticosteroids and TNF-inhibitors [74]. Thiopurines also have some utility in reducing rates or recurrence after surgery [80]. Etanercept is also another promising modality.

A trial studied 19 patients who did not respond to conventional therapy by treating with etanercept. There was significant improvement in the healing rate of buccal and genital ulcers, the remission rate of ocular lesions, skin lesions, and abdominal symptoms, the healing rate of intestinal ulcers, and the recovery rate of ESR and CRP. The relapse rate in the etanercept therapy was also reduced significantly [81]. Adalimumab has also been known for both achieving clinical response and complete remission without use of corticosteroids [82]. Golimumab has been known to show a more promising result with DMARDS [82]. Other agents such as thalidomide, mycophenolate, certolizumab pegol, and tacrolimus are only supported by case reports/series and are not part of the most recent consensus statements for medical therapy.

Surgery

Intestinal Behcet's Disease might require surgical management. Perforation and massive GI bleeding are absolute indications for surgery, whereas abdominal abscess, fistula, and stricture can be possible indications. Other indications include patients who are refractory to medical treatment. Additionally, patients who have a high risk of recurrence are more likely to end up receiving surgical management, including patients with GI symptoms at the initial presentation, patients with volcano-type and deep intestinal ulcers, and patients who failed to achieve complete remission during the initial treatment [83].

Prognosis and Follow-Up

BD is classically a multi-organ disease and the rate at which GI manifestations occur is highly variable and has been reported as being as high as 50% with highest rates occurring in Far East [84]. Although the rate of GI involvement is variable, its occurrence is generally an indicator of poor prognosis with increased morbidity and mortality as compared to cases of BD without GI involvement. GI involvement can lead to severe complications such as intestinal perforation, fistulas, and hemodynamically significant GI bleeds that often require surgery, with many patients requiring repeat surgery [85]. Given the multi-organ involvement in BD, studies have been conducted to characterize clinical and biochemical risk factors for developing GI involvement which found that gender (male), elevated ESR, CRP, IL-6 and decreased hemoglobin were all independent risk factors for developing intestinal BD. Risk of relapses has also been studied in a study focusing on Chinese patients. The relapses were

more likely to occur in patients with intestinal ulcers in the ileocecal and colorectal regions or in patients with poor compliance. Recent study reported a relapse rate of about 20% in case of long-term follow-up irrespective of treatment modality [86, 87].

Advancements/Future Developments

As of now, the majority of medical therapies for BD are supported by low-level evidence such as case reports, retrospective cohort studies, and expert opinion. As further evidence is developed, the treatment algorithm and guidelines for BD will likely become more robust.

Currently, endpoints for treatment are not well established in regard to whether the goal should be to aim for ulcer healing on endoscopy or simply clinical remission. Studies have been conducted that show some correlation (albeit weak correlation) between endoscopic ulcer healing and clinical improvement [79]. Kinoshita et al. [76] also proposed an endoscopic scoring system to attempt to predict postsurgical relapse in patients who had required surgery for their disease and found that there was a relationship between patients with endoscopic relapse and clinical relapse. Given that endoscopic ulcer healing and recurrence both correlates with clinical improvement and also may have predictive value in risk stratifying postsurgical patients for relapse, conducting regular surveillance endoscopy may have utility in determining which patients may require escalation in medical therapy; however, currently there are no established guidelines for surveillance. Further studies in regard to these correlations could be useful to determine this.

Conclusions

BD is a chronic inflammatory disorder that involves many systems, especially the GI tract. Although there are some rare GI manifestations, small intestine is commonly involved. The foundation of treatment depends on severity, but there is a need to provide robust management protocols for treating the disease. Additionally, endoscopic investigations should be considered in surveillance for healing and recurrence of intestinal ulcerative lesions.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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