Diagnosis and Management of Irritable Bowel Syndrome-Like Symptoms in Ulcerative Colitis

Desislava Dimitrova-Yurukova¹, Nikola Boyanov¹, Ventsislav Nakov², Radislav Nakov²

¹ Department of Gastroenterology, Pulmed University Hospital, Plovdiv, Bulgaria
² Clinic of Gastroenterology, Tsaritsa Yoanna University Hospital, Medical University of Sofia, Sofia, Bulgaria

Corresponding author: Radislav Nakov, Clinic of Gastroenterology, Tsaritsa Yoanna University Hospital, Medical University of Sofia, 8 Byalo more St., Sofia, Bulgaria; Email: radislav.nakov@gmail.com; Tel.: +359 889 807 558

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Abstract

Both ulcerative colitis (UC) and irritable bowel syndrome (IBS) are chronic gastrointestinal (GI) conditions that show some typical features. Persistent GI symptoms typical for IBS are observed in patients with diagnosed UC. Both IBS and UC are characterised by dysregulation of the enteric nervous system, alterations in the gut flora, low-grade mucosal inflammation, and activation of the brain-gut axis. Therefore, it appears that there may be some overlap between the two conditions. It is rather difficult to tell if the lower gastrointestinal symptoms are secondary to coexisting IBS or a hidden UC condition.

Given the disruptions in gut microbiota in UC and the likely role of the brain-gut axis in the production of such symptoms, treatments such as probiotics, fecal microbiota transplantation, antidepressants, and psychological therapy would appear to be sensible options to use in both illnesses. They are both chronic, causing patients to have a worse quality of life and everyday suffering, as well as incurring significant expenses for the health-care system.

The aim of this review article was to give an up-to-date perspective on the diagnosis and management of IBS-like symptoms in UC.

Keywords
diagnosis, irritable bowel syndrome, ulcerative colitis

INTRODUCTION

IBS has been estimated to affect about 10% of the general population globally, but the prevalence rates are highly variable.[1,2] They range from country to country from 1.1% to 45.0% but has been estimated to be 12% (95% CI 7%, 17%) generally in North America[2], with a similar prevalence specifically in Canada[3]. Rates also vary according to diagnostic criteria.[1,3-5] Studies have revealed that IBS is more common in women than in men. As for the IBS subtype, IBS with constipation is significantly more prevalent among women than among men.[6]

The prevalence of irritable bowel syndrome (IBS) in Bulgaria estimated from a population-based study is approximately 20%, which was comparable to that in the Middle East and developed Asian countries.[5] According to a 2012 meta-analysis, the pooled global prevalence of the disorder was 11.2%, ranging from 1.1% to 45.0%.[7] Recently, a global epidemiological study of functional gastrointestinal disorders (FGID) has reported that IBS has a prevalence rate of 4.1%.[8] The study concluded that the African continent, the Arab world, and Eastern Europe are severely underrepresented in IBS prevalence studies.[8]

Ulcerative colitis (UC) has an incidence of 8–14 per 100,000 people, and a prevalence of 120–200 per 100,000 people in Western populations.[9] Among quiescent UC patients, a higher prevalence of IBS-like symptoms than expected was reported more than...
30 years ago by Isgar et al.\textsuperscript{[10]} These conclusions have since been repeated in several studies in UC patients and patients with Crohn’s disease (CD).\textsuperscript{[11–13]}

There is considerable variation in the reported prevalence rates, ranging from 9% to 46% in UC patients with quiescent disease.\textsuperscript{[14]} This could be explained by different criteria used for remission in UC patients, different criteria for the diagnosis of IBS, or various study designs. Recently, the IBSEN study reported that the overall prevalence of IBS-like symptoms in UC was 27%, and in patients in deep remission, the prevalence was 29%.\textsuperscript{[15]} No difference in the prevalence of IBS-like symptoms was found between UC patients with ongoing inflammation and patients in deep remission. IBS-like symptoms in UC patients were quite frequent after 20 years of the disease.\textsuperscript{[15]}

In this review, we make an up-to-date overview of the diagnosis and management of IBS-like symptoms in UC. We focus on the overlapping symptoms, pathological overlaps, and current therapies.

**DIAGNOSIS**

IBS presents with chronic abdominal pain and changed bowel habits. Unfortunately, most people who meet diagnostic criteria for IBS do not have a formal diagnosis. Moreover, quite a small percentage of those affected seek medical help. It is proven that IBS is associated with increased healthcare costs and is the second-highest cause of work absence.\textsuperscript{[16]}

The Rome IV criteria define IBS as a FGID characterised by recurrent abdominal pain, on average, at least one day per week over the last three months. It should be associated with two or more of the following criteria: the pain is related to defecation; the pain is associated with a change in frequency of stool and/or with a change in the appearance of stool.\textsuperscript{[17]} The cause is unknown, and the pathophysiology is not entirely understood. The administered treatment depends on the leading symptom, consisting of dietary management and drugs, including anticholinergics and agents active at serotonin receptors.\textsuperscript{[16]}

Ulcerative colitis is a chronic inflammatory disease of the gastrointestinal (GI) tract that affects the colorectum.\textsuperscript{[18]} The pattern of disease activity is characterised by periods of active inflammation alternating with periods of remission. It is characterised by relapsing episodes of inflammation limited to the mucosal layer. The rectum is usually affected, and inflammation may proceed proximally and continuously to involve other parts of the colon.\textsuperscript{[19]} UC often presents in young adulthood and is more common in developed countries. Extraintestinal symptoms, particularly arthritis, may occur. Although the etiology of the condition is not yet fully understood, it is believed to be a result of immunological dysregulation, host genetic factors, environmental variables, altered mucosal permeability, and disturbances in the gut microbiome. No definitive cure has been created. Even so, medical treatment is crucial for UC patients. It defines their quality of life and well-being. The aim of treatment is to induce remission and prevent relapse of disease activity by using a combination of certain types of drugs: glucocorticosteroids, oral and topical 5-aminosalicylic acids, thiopurines, cyclosporine, and biologicals.\textsuperscript{[18,19]}

In contrast to ulcerative colitis, IBS is a highly prevalent condition. Patients are divided into subtypes in addition to the predominant stool pattern they report:

- IBS with diarrhea (IBS-D);
- IBS with constipation (IBS-C);
- mixed IBS (IBS-M) – constipation followed by diarrhea or the opposite;
- Unclassified IBS (IBSU) – the bowel habit is none of the above mentioned.

As IBS is a FGID, without any known organic explanation, the condition is diagnosed by using symptom-based diagnostic criteria, with the current gold standard being the Rome IV criteria.\textsuperscript{[17]}

The following symptoms are shared by two different health conditions (UC and IBS):

- Chronic symptoms of abdominal pain, cramping;
- Diarrhea;
- Mucus in stool;
- Bowel urgency.

Although the two disorders have traditionally been seen as distinct in terms of both presentation and cause, some researchers are putting forth theories that perhaps the two diagnoses are actually at different ends of the same spectrum. Some studies have demonstrated that people who have IBS are at higher risk of being eventually diagnosed with IBD (UC or Crohn’s disease). A group of researchers found that the higher risk might be associated with having experienced infectious gastroenteritis (stomach “flu” caused by infectious bacteria or viruses).\textsuperscript{[1]}

**OVERLAPPING SYMPTOMS**

**Pain, diarrhea, constipation**

The original history of UC is that of quiescent symptoms, intermingled with episodes of flare-ups, which can be classified as follows. A flare-up is mild when the patients have four or fewer stools per day with or without blood, no signs of systemic toxicity, and a regular erythrocyte sedimentation rate (ESR); mild pain, tenesmus, and periods of constipation are also common. On the other side, severe abdominal pain, profuse bleeding, high temperature, or weight loss are not part of mild disease symptoms. In the case of a moderate flare-up, patients have loose, bloody stools (>4 per day), mild anemia, and abdominal pain. They show minimal signs of systemic toxicity, including a low-grade fever. Adequate nutrition is usually maintained, and weight loss is not associated with moderate clinical disease. The clinical presentation of the severe episode of UC is more than 6 bloody stools per day, not well-formed, severe cramps orab-
dominal pain, high temperature (more than 37.5°C), heart rate more than 90 beats/minute, anemia, laboratory markers for inflammation (high leucocytes, CRP), and rapid weight loss. Patients with a severe clinical presentation typically have frequent loose, bloody stools (≥6 per day) with severe cramps and symptoms of systemic toxicity as demonstrated by fever (temperature ≥37.5°C), tachycardia (HR ≥90 beats/minute), anemia (hemoglobin <10.5 g/dL), or an elevated ESR (≥30 mm/hour). Patients may have rapid weight loss.[14] Usually, bloody diarrhea with different intensity and duration has been alternated by asymptomatic intervals. It is quite often accompanied by increased urgency to defecate, mild lower abdominal cramps, blood, and mucus in the stools. IBS usually begins in adolescence and the 20s, causing bouts of symptoms that recur at irregular intervals. Patients have abdominal discomfort, which varies in the high range but is often located in the lower abdomen, steady or cramping in nature, and relieved by defecation. Moreover, abdominal discomfort is temporally associated with alterations in stool frequency (increased in diarrhea-predominant IBS and decreased constipation predominant-IBS) and consistency (i.e., loose or lumpy and hard).[20]

Regarding patients with UC, the “gold standard” for diagnosis is colonoscopy. UC should be distinguished from Crohn’s disease (CD) but, more importantly, from other causes of acute colitis (e.g., infection; in elderly patients, ischemia). The diagnosis is reached after lower gastrointestinal investigation confirms diffuse, continuous, and superficial inflammation in the large bowel, and biopsies show changes in keeping with the disorder.[18] Non-invasive methods such as fecal calprotectin measurement may be considered reliable and inexpensive in assessing disease severity or treatment change strategy.[21]

For diagnosing IBS, we use the Rome IV criteria, which are standardized symptom-based criteria. A recent systematic review and meta-analysis, which pooled data from many cross-sectional surveys and case-control studies, concluded that around one in three UC patients stated symptoms compatible with IBS, with the odds for announcing these types of symptoms four times higher in patients with UC in clinical remission, compared with controls without UC.[22]

Pathological overlaps

Although the cause of IBS is still unclear and no organic cause can be found on laboratory tests or biopsies, nowadays, there is much evidence that proves the multifactorial cause of this condition. Some typical features could be found regarding the development of IBS and UC. It is proven that low-grade mucosal inflammation, an altered microbiome, increased intestinal permeability, and genetic factors play a crucial role in the pathogenesis of them both.[23–25]

Visceral hypersensitivity

Visceral hypersensitivity is a multifactorial process that may occur within the peripheral or central nervous systems and plays a leading role in the etiology of IBS symptoms.[26] It is an increased sensation in response to different triggers. Perception in the GI tract is a result of the stimulation of various receptors in the gut wall. They transmit signals with the help of afferent neural pathways to the dorsal horn of the spinal cord and, therefore, to the brain.[26] A few studies have focused on selective hypersensitisation of visceral afferent nerves in the gut, stimulated by bowel distention or bloating, as a possible cause for IBS symptoms.[27] Studies showed that the severity of IBS complications in patients with hypersensitivity IBS is dramatically higher than in other IBS patients.[26]

Rectal distension in patients with IBS also increased cerebral cortical activity more than in controls. However, in one study involving balloon distension of the descending colon, increased colonic sensitivity was affected by a psychological tendency to report pain and urgency rather than increased neurosensory sensitivity.[27] Bloating is common in patients with IBS.[28] Almost half of IBS patients report a sensation of abdominal fullness and gases. These symptoms have a significant impact on their everyday function. Bloating is often described as one of the more distressing symptoms connected with IBS.[29] Bloating may happen from increased gas production from bacterial fermentation of undigested food, retarded gas transit, and heightened sensitivity of the gut to average luminal gas volumes, or impaired abdominal wall musculature.[28,30]

Mucosal inflammation

Increased mucosal barrier permeability and mucosal inflammation may play a crucial role in the development of IBS symptoms. Studies have shown more significant levels of circulating proinflammatory cytokines in peripheral blood and higher levels of the proinflammatory cell infiltrate in the intestinal mucosa of IBS patients than in patients in the control group. The exact origin of this inflammation is uncertain; however, it may be related to a modification in the gut microbiota, with evidence of a dysbiosis in IBS, and a relative abundance of proinflammatory species compared with healthy controls without IBS.[7,19,31] Higher levels of plasma proinflammatory interleukins have been noted in patients with IBS. Moreover, IBS patients’ peripheral blood mononuclear cells produce higher amounts of tumour necrosis factor than healthy controls.[31] There is an association between gut microbial diversity and composition and the development of some GI diseases such as IBD, colorectal cancer (CRC), and IBS.[32]

The immunohistologic investigation has revealed mucosal immune system activation characterised by alterations in particular immune cells and markers in some patients with IBS (those with diarrhea-predominant IBS and patients with presumed postinfectious IBS) and UC.

Increased numbers of lymphocytes have been described in the colon and small intestine in patients with IBS.[21] A study in which full-thickness jejunal biopsies were obtained in ten patients with severe IBS found increased lym-
phocyte infiltration in the myenteric plexus in nine patients and neuron degeneration in six patients.\cite{27}

Mast cells are the effector cells of the immune system. An increased number of mast cells have been demonstrated in the terminal ileum, jejunum, and colon of IBS patients. Studies have demonstrated a correlation between abdominal pain in IBS and activated mast cells in proximity to colonic nerves.\cite{27}

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**Alteration in fecal microbiota**

The complex ecology of the fecal microbiota has led to speculation that changes in its composition could be associated with diseases, including IBS. Recent data suggest that the fecal microbiota in individuals with IBS differ from healthy controls and vary with the predominant symptom.\cite{33} This concept was supported by a study demonstrating that colonic hypersensitivity in IBS patients could be assigned to germ-free animals by inoculating the animals with gut microbiota from IBS patients but not from healthy individuals. More studies are needed to validate these conclusions.\cite{33}

Because of potential microbiota alterations in IBS, it is possible that patients with IBS-D would profit from probiotics, which affect the structure and metabolism of the microbiota.\cite{33} One placebo-controlled randomized trial found that the administration of *Lactobacillus plantarum* did not significantly influence the gut microbiota of patients with IBS. However, patients who received the probiotic had a decrease in symptoms of flatulence. Similar findings were described in a study in which a probiotic yogurt consisting of a mixture of *B. animalis* subsp lactis Bb12 and *K. marxianus* B0399 improved symptoms but did not alter intestinal microbiota in IBS patients. More data on the mechanisms of action of probiotics in IBS are needed.\cite{27}

**Psychosocial factors**

Various studies have shown a negative influence of IBS-like symptoms on both mood and quality of life in patients with IBD. Psychological distress is prevalent among patients with IBS and UC, especially in those who want to see a physician. Some patients have anxiety disorders, depression, or somatization disorder. Sleep disorders may also be reported by patients.\cite{9}

**THERAPIES**

**Probiotics**

Probiotics reduce pain and symptom severity in IBS patients. In their updated systematic review, Tina Didari et al. demonstrated the beneficial effects of probiotics in IBS patients compared with placebo.\cite{34} Probiotics are supposed to affect the gut microbiota, anti-inflammatory properties, and the ability to modulate visceral hypersensitivity. The nature of probiotics explains their beneficial role in intestinal function as they can protect against pathogenic bacteria via their antimicrobial properties. Probiotics also amplify the intestinal tight junctions and stabilise the permeability. Moreover, probiotics stimulate goblet cells to produce mucus to enhance the intestinal barrier function, normalise bowel movements, and reduce visceral hypersensitivity.\cite{35} In their meta-analysis, Li-Xuan et al. concluded that probiotic treatment was more effective than placebo in maintaining remission in UC.\cite{36} Probiotics can improve the metabolic activity of the intestinal microbiota and its components by preventing bacterial overgrowth and by maintaining the integrity of the intestinal mucosal barrier, thereby adjusting and stabilizing the intestinal environment.\cite{37}

**Diet**

Regarding the diet, standard recommendations include adhering to a regular meal pattern, reducing intake of insoluble fibers, alcohol, caffeine, spicy foods, and fat. It is recommended that people should drink at least 1.5-2 litres of water per day in order to ensure proper hydration. The second-line dietary approach should be considered as the symptoms are still available. It includes following a diet low in fermentable oligo-, di-, mono-saccharides and polyols (FODMAP). It is crucial to be delivered only by a healthcare professional with expertise in dietary management. A growing body of evidence supports the efficacy of this diet. On the contrary, the role of lactose or gluten dietary restriction in the treatment of IBS remains subject to future research and a lack of high-quality evidence.\cite{37} Avoiding raw fruits and vegetables limits trauma to the inflamed colonic and may lessen symptoms in patients with UC. A milk-free diet also may help but need not be continued if no benefit is noted.\cite{39} Patients should have light meals; eating should be slow and effective. Reducing the amount of sugar-consistent foods and sweeteners may relieve flatulence, bloating, and diarrhea.\cite{37}

**Psychological therapies and antidepressants**

Patients with IBD and persistent GI symptoms associated with a mood disorder (e.g., depression, anxiety) may benefit from behavioural modification in conjunction with antidepressants, similar to the approach to patients with IBS, which is discussed separately. Reducing stress is crucial, as it is one of the most potent triggers that unlock the symptoms. Moreover, psychological stress can affect the degree of intestinal inflammation. This fact also supports psychological strategies for treating the symptoms in patients with quiescent IBD or IBS.\cite{39}
Physical activity

Mild to moderate intensity exercises are recommended. They refresh and improve well-being in patients with IBD, but no evidence-based data suggests an anti-inflammatory effect. Therefore, exercising may positively affect functional GI symptoms, but this statement has not been studied enough.[39]

Complementary and alternative medicine

Complementary and alternative medicine remedies (e.g., herbal preparations, homeopathy, Bach’s remedies) may help and reduce symptoms such as abdominal pain and anxiety in both IBS and IBD patients. However, more studies are needed to prove their role in the treatment of these conditions.[39]

Fecal microbiota transplantation (FMT)

The data published to date suggest that FMT has the potential to be an effective treatment for UC and IBS when standard treatments could not help. However, FMT is associated with potential risk for transmission of infectious agents, and the optimal dosing schedule and delivery method for FMT are still unclear. Strategies to reduce infection risk and the appropriate patients’ selection should be discussed in details.[31,33,40]

Future perspectives

Reducing costs by improving treatment strategies is a great challenge for future perspectives. Many investigational therapies have been examined for treating patients with UC and IBS. Unfortunately, none has been sufficiently studied to recommend its routine use. Prevention and early diagnosis are also crucial. Very often, patients with UC have IBS-like symptoms, which can make the differential diagnosis challenging. It is crucial to keep in mind that CRC must always be excluded in case of bloody stool or weight loss. That is why more studies about its prevalence, gender predisposition, and misleading symptoms should be done. Patients should be well aware of both conditions – IBS and UC. For this purpose, handbooks and leaflets raising awareness could be written and distributed.

CONCLUSIONS

IBS and UC are chronic lifelong conditions with periods of remission and relapse. They affect young and active people, leading to impaired quality of life. IBS-like symptoms are often present in UC. Scepticism remains regarding the cause of these symptoms, although low-grade mucosal inflammation secondary to subclinical UC activity remains a distinct possibility. Both conditions present with a combination of impaired intestinal immunity, low-grade mucosal inflammation, and altered microbiome. It seems that stress is an enormous trigger factor for flare-ups of disease activity via the brain-gut axis. This feature determines the treatment of IBS, but still, many therapeutic strategies need to be improved for both IBS and UC. More studies and research are required to reduce the costs and improve the quality of life of these patients.

Author contributions

R.N. conceived the manuscript, D.DY, V.N., and N.B. wrote the manuscript. All authors approved the final version of the manuscript. R.N. supervised the whole process.

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Диагностика и лечение симптомов, подобных синдрому раздражённого кишечника, при язвенном колите

Десислава Димитрова-Юрукова1, Никола Боянов1, Венцислав Наков2, Радислав Наков2

1 Кафедра гастроэнтерологии, УМБАЛ „Палмед“, Пловдив, Болгария
2 Клиника гастроэнтерологии УМБАЛ „Царица Йоанна“, Медицинский университет – София, София, Болгария

Адрес для корреспонденции: Радислав Наков, Клиника гастроэнтерологии УМБАЛ „Царица Йоанна“, Медицинский университет – София, ул. „Ягелло наме“ № 8, София, Болгария; Email: radislav.nakov@gmail.com; Тел.: +359 889 807 558

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Резюме

И язвенный колит (ЯК), и синдром раздражённого кишечника (СРК) являются хроническими заболеваниями желудочно-кишечного тракта (ЖКТ), для которых характерны некоторые типичные признаки. У больных с диагностированным ЯК наблюдаются стойкие гастроинтестинальные симптомы, типичные для СРК. И СРК, и ЯК характеризуются нарушением регуляции энтеральной нервной системы, изменениями кишечной флоры, вялотекущим воспалением слизистой оболочки и активацией оси мозг-кишка. Таким образом, представляется, что между этими двумя состояниями может быть некоторое совпадение. Довольно сложно сказать, являются ли симптомы нижних отделов желудочно-кишечного тракта вторичными по отношению к сосуществующему СРК или скрытому ЯК.

Учитывая нарушения кишечной микробиоты при ЯК и вероятную роль оси мозг-кишка в возникновении таких симптомов, такие методы лечения, как пробиотики, трансплантация фекальной микробиоты, антидепрессанты и психологическая терапия, по-видимому, являются разумными вариантами применения при обоих заболеваниях. Они оба носят хронический характер, вызывая у пациентов ухудшение качества жизни и повседневные страдания, а также влекут за собой значительные расходы для системы здравоохранения.

Цель этой обзорной статьи состояла в том, чтобы дать современный взгляд на диагностику и лечение СРК-подобных симптомов при ЯК.

Ключевые слова
диагностика, синдром раздражённого кишечника, язвенный колит