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Review

REVIEW

Care of inflammatory bowel disease patients in remission

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Abstract

Inflammatory bowel disease (IBD) comprises two distinct conditions: ulcerative colitis and Crohn's disease, both of which are chronic, relapsing disorders carrying significant morbidity, mortality and healthcare costs. With growing attention to coordinated healthcare for patients with chronic systemic diseases, this review focuses on the care of IBD patients in remission, their concerns, quality of life, follow-up, the role of primary care physicians and the IBD-specific aspects of long-term care. We did an extensive PubMed search for articles pertaining to IBD patients in remission and, along with the authors' experience, formulated a comprehensive review. The difficulties faced by IBD patients in remission include but are not limited to education and employment concerns, psychosocial issues, problems related to health insurance, nutrition, fertility and infections. This review also addresses newer treatment modalities, the debatable effects of smoking on IBD and the importance of vaccination. IBD in remission can be a challenge due to its multifaceted nature; however, with a coordinated approach by gastroenterologists and other involved practitioners, several of these issues can be addressed.

Key words: inflammatory bowel disease; remission; long-term care

Introduction

Coordinating healthcare for patients with multifaceted chronic diseases is receiving increasing attention. Inflammatory bowel disease (IBD) comprises two distinct chronic conditions—ulcerative colitis (UC) and Crohn's disease (CD)—both of which carry significant morbidity, mortality, compromise in quality of life and costs [1–3]. Both UC and CD are lifelong, relapsing disorders for which therapy to induce remission (inductive therapy) is followed by therapy to maintain remission (maintenance therapy). Typically, 5-aminosalicylic acid (5-ASA) agents and budesonide are used in patients with mild disease, while corticosteroids, immunomodulators and antitumor necrosis factor (TNF)-α agents are used in patients with more severe disease [4]. These medical therapies are complemented by various endoscopic (i.e. dilation and surveillance biopsies) and surgical interventions (i.e. resection, ileo-anal pouch and ileostomy) [5].

This review focuses on patients with IBD who are in remission and who have become asymptomatic after medical, endoscopic or surgical therapies. Once in remission, patients with IBD look forward to a normal life but, because of the chronicity of maintenance therapy and the possibility of disease recurrence, still face difficult physical and emotional transitions and social and financial challenges [6]. Since many IBD patients in remission may be treated by non-specialists, we discuss aspects of broader care that may be disregarded but play an important role in the preservation of general health and quality of life (**Figure 1**). When IBD patients are transitioned by their gastroenterologists to primary care or other specialty providers for

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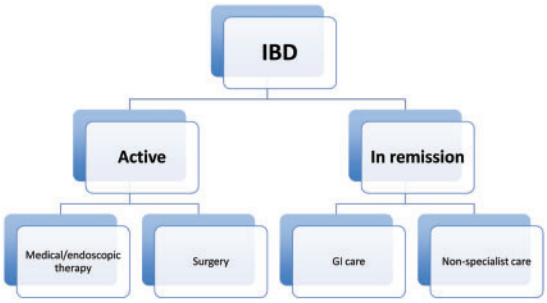

Figure 1. IBD may be active (requiring medical, endoscopic or surgical therapy) or inactive after effective induction of remission. Patients with IBD in remission may remain under the care of a gastroenterologist or may transition to other non-specialist providers. Coordinated care to cover all patient healthcare needs is essential.

follow-up, those providers should have sound understanding of the risks for long-term and late effects related to IBD and/or its therapy, especially those resulting from the use of biologics and immunosuppressive agents or surgery.

Definition of IBD in remission

For UC, remission is defined as S0, using the Montreal classification [7]. Remission by Mayo score is defined as having a normal number of daily stools (0 points) with no rectal bleeding (0 points) and normal or inactive colitis on endoscopy (0 points) [8]. For CD, remission implies a corticosteroid-free clinical remission with CD activity index (CDAI) <150) [9] or a Harvey–Bradshaw Index <4 and endoscopic evidence of mucosal and fistula healing [10].

Essential components of chronic IBD follow-up care (Figure 2)

Caring for the IBD patient in remission can be complicated, challenging and sometimes suboptimal. Gastroenterologists often provide such care, but patients who live in rural settings have to travel a great distance for their IBD follow up, or are discharged by their gastroenterology or surgery teams and may subsequently seek care from family practitioners, general internists, or other providers. These practitioners need to navigate through various medical and surgical treatments, their late and sometimes indolent effects, surveillance options and schedules for follow-up care. Referral to physical and occupational therapy, other services (i.e. stoma therapists, counseling), pain management teams and social services must also be considered to ensure that all needs are addressed.

Transition and coordination

It is unclear if, how and when IBD patients should transition to primary care or other providers after induction and maintenance of disease remission or surgery, and one particular approach may not work for every patient or clinical setting. Most IBD patients in remission are followed in gastroenterology practices where the focus of follow-up visits is medication refills, surveillance for disease recurrence or detection of complications. Other patients are followed up at specialized IBD centers that engage a multidisciplinary team of care providers.

Compared with other chronic medical conditions such as asthma or diabetes, fewer IBD patients are followed only by primary care physicians. In one survey, only 37% of primary care physicians were found to be comfortable providing care to IBD

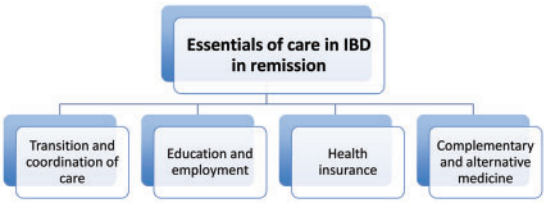

Figure 2. The care of IBD patients in remission entails a coordinated transition to non-specialist care (if necessary) as well as attention to other issues such as education, employment, health insurance and use of complementary and alternative medicine resources. Outside of specialty centers, integrated IBD care can be greatly enhanced by use of digital information technologies.

patients across a range of illness severity [11]. There is no current consensus on when the care of an IBD patient can be transitioned from specialty to primary care. Nevertheless, patients with an established diagnosis for >2 years who have been stable for >1 year could be considered candidates for transition. The availability of specific tools and written action plans for primary care providers would help make this transition much easier, safer and more effective [12].

The decision for transition and to whom is often based on the risks and severity of disease at baseline. Gastroenterologists are more likely to transition patients with mild disease or disease that has been surgically controlled (i.e. resection or colectomy). Because the risk for late effects of therapy or disease recurrence increases, transitioning IBD patients to other providers becomes less likely and more complex. Some IBD patients transition over time, which generally involves seeing their primary care provider for health maintenance and consulting their gastroenterologist only for IBD care and surveillance. Less often, gastroenterologists manage comorbid conditions as well as cancer surveillance and treatment-related or postoperative issues. Regardless, communication between providers and patients is essential. In the shared care model, IBD specialists or gastroenterologists should take the lead in coordinating among various providers to ensure that IBD-specific laboratory, endoscopic and imaging studies are indicated to evaluate whether the patient has a recurrence or a treatment-related adverse effect (Table 1).

Information technology may improve the quality, safety, efficacy and coordination of care among the various providers delivering care to IBD patients in remission and may also help engage patients in accessing their health records and monitoring their disease and its therapy. Electronic reminders can optimize blood count and liver panel monitoring in patients receiving thiopurines, surveillance colonoscopies in patients with UC, nutritional monitoring or periodic bone density assessments [13]. Computerized orders may decrease medication errors, highlight drug interactions or monitor the frequency of various tests such as colonoscopy. Such digital means not only enhance management and reduce costs but improve the patient's quality of life, adherence and knowledge about the disease [14].

Education and employment

Despite disease severity and chronicity, the majority of patients with IBD manage to stay in the work force and succeed in overcoming the obstacles imposed by their disease. However, females in white-collar occupations have an increased risk for disability [15]. Despite loss of schooling and physical inconveniences faced by students, teachers have a favorable attitude towards them. Students with IBD seem to require more time, but

Table 1. Various aspects of managing inflammatory bowel disease (IBD) in remission

Prevention of IBD recurrences, cancer or other late effects
Surveillance for disease spread, recurrence or cancer development
Assessment of medical, postsurgical and psychosocial effects
Intervention for consequences of IBD and its treatments
Coordination between gastroenterologists and primary care providers to ensure meeting all health needs

they eventually attain the same level of education as the overall population [16].

Most IBD patients maintain the same employment positions over a period of years but tend to use more sick leave. They also favor disclosing their diagnosis to their employers without facing discrimination. Most employers also seem to have fair attitudes against discrimination and toward the compensation provided to their employees with IBD [17]. Sex, age, duration of illness, having a stoma or pouch, comorbidity, vitality, pain and perceived personal control are significant predictors of the number of hours worked. Thus, strengthening the perception of control over illness in IBD patients is important and results in significant changes in productivity [18].

Risk factors for temporary work disability include sex, disease duration, disease activity, C-reactive protein levels, smoking, depressive symptoms, fistulas, extra-intestinal manifestations and use of steroids/antibiotics [19]. Examples of areas that require further focus include patients with IBD who develop primary sclerosing cholangitis (PSC) and may require subsequent liver transplantation as well as patients with CD and short bowel syndrome with or without the requirement for home parenteral nutrition [17]. A critical question is whether certain jobs pose risks that predispose patients to IBD or whether patients with IBD choose particular occupations because of the practical restrictions that the illnesses present.

Health insurance

Physical disability and functional limitations caused by IBD have resulted in work and insurance discrimination for some patients. In one study, IBD patients had an 87-fold increased risk of encountering difficulties when applying for life insurance and facing heavy premiums as compared with controls. Patients of high educational status with continuous disease activity and those who smoke have the highest odds of encountering such problems. Medical insurance difficulties were 5-fold more common in IBD patients compared with controls [20]. The rate of uninsured IBD admissions has risen disproportionately relative to the privately insured or general populations. In view of the recent advances in therapy and promising survival data on IBD patients, evidence-based guidelines for risk assessment of IBD patients by insurance companies should be drawn up to prevent possible discriminatory practices.

Complementary and alternative medicine

With IBD being a chronic, relapsing and remitting disease with prolonged courses of treatment, patients often look to complementary and alternative medicine (CAM) for further benefits. Multiple forms of CAM are used to treat IBD, and patients often use many of them together with conventional medical therapies. Patients using CAM report benefits that extend beyond simply improving disease control. CAM allows patients to exert a greater degree of control over their disease and its management than they are afforded by conventional medicine. There is limited evidence on the efficacy of CAM therapies in IBD [21]. A discussion regarding their CAM use and knowledge about what they are using is important for establishing a good physician-patient relationship and for understanding patients better [22].

Table 2. Inflammatory bowel disease (IBD)-specific aspects of long-term care

Steroid sparing
Cardiovascular issues
Smoking
Sexual and reproductive issues
Infections
Vaccinations
Lymphoma and other malignancies
Psychosocial issues
Cognitive issues
Subclinical inflammation
Monitoring thiopurine therapy
Delayed effects of treatment or disease
Surgical outcomes and sequelae
Nutrition
Gut microbiota
Ostomy issues
Extra-intestinal manifestations

IBD-specific aspects of long-term care (Table 2)

Steroid sparing

Corticosteroids are effective for inducing remission in IBD but are not helpful for long-term maintenance [23]. Because of their poor safety profile and tolerability, their prolonged use should be avoided and substituted with steroid-sparing agents such as immunomodulators and anti-TNF-α agents [24,25]. Despite the well-established risk factor for osteoporosis with extended steroid use, the majority of IBD patients do not get screened for metabolic bone disease [24].

Cardiovascular issues

Patients with IBD have a higher risk (up to 6-fold) of venous thromboembolism (VTE) and probably arterial disease, particularly mesenteric ischemia and ischemic heart disease [26]. Recurrence of thromboembolic events after discontinuation of anticoagulant treatment for the first VTE is more frequent (up to 30%) in IBD patients [27]. It is important to keep VTE in mind in patients with IBD (especially hospitalized patients) both with active disease and in remission. Apart from non-pharmacological measures, pharmacological prophylaxis should be considered. In postoperative IBD patients, reducing preoperative anemia, steroid use, malnutrition and anesthesia time may also reduce VTE [28]. Treatment is the same as in the general population, but its duration is not clearly defined [29].

The absolute risk of arterial thromboembolism is unknown. In one study, coronary artery disease was more frequent in IBD patients compared with age- and sex-matched controls [26]. CD patients seem to have lower levels of high-density lipoprotein; this could be due to the chronic inflammation as it is associated with disease flares [30]. A Danish nationwide study of IBD patients found a significantly increased risk of myocardial infarction, stroke and cardiovascular mortality as compared with matched controls. This risk was predominantly present in periods of IBD activity and not during remission [31]. In a recent meta-analysis there was no increased risk of cardiovascular or

arterial thromboembolic mortality [32]. Two retrospective studies failed to show increased risk of infarction or premature cardiovascular disease in patients with IBD [33,34]. There are limited studies on the effect of anti-inflammatory agents.

Analysis of a Danish cohort showed that TNF-α antagonists to have a protective effect on ischemic heart disease but an increased risk for cerebrovascular event [35]. In a smaller study comparing salicylates in IBD with steroids and azathioprine, the latter was found to decrease arterial stiffness [36]. In another study, the anti-inflammatory effect of statins significantly decreased steroid use in patients with IBD. There was also a trend towards decreased rate of anti-TNF agent use, abdominal surgery and hospitalization for overall IBD; after stratifying by disease type (CD *vs* UC), only the association between statin use and abdominal surgery in CD was statistically significant [37]. In another analysis, statin use was associated with a significant reduction in IBD-related colorectal carcinoma [38]. Randomized studies are required to substantiate the role of statins in patients with IBD, after which guidelines can be developed about when to start them and for whom.

Chronic inflammatory diseases such as IBD have also been linked with disturbances of the intestinal microbiome [39,40]. A recent study identified a novel pathway linking dietary lipid intake, gut microflora and atherosclerosis [41]. However, without large-scale studies, the link between enteric bacterial translocation in IBD and coronary artery disease remains elusive. The key to active and preventive therapy in IBD patients in remission is effective treatment of inflammation. Further, annual blood pressure screening, recording detailed family history to determine if they have any additional familial risk factors for cardiovascular disease, measuring weight and giving counseling should be performed. Diet and exercise should be encouraged for their overall health benefits.

Smoking

Cigarette smoking has a differential effect in patients with CD and UC, which seems to be due to an effect on dendritic cells [42]. In CD, current smokers have a more severe disease course when compared with former and non-smokers, requiring immunosuppression more often and in a dose-dependent fashion. Smokers with CD are also more prone to surgical recurrences (45.8% *vs* 37.8%) [43]. Active smoking is also associated with increased risk of extra-intestinal manifestations such as arthralgias [44] and a higher risk of relapse after discontinuating anti-TNF-α therapy [45]. In an intervention study for smoking cessation in CD, the need for steroids and for introduction or reinforcement of immunosuppressive therapy, respectively, were similar in patients who quit smoking and nonsmokers and increased in continuing smokers [46].

The protective effect of smoking on patients with UC is well established [47]. In UC, the disease course seems to be more benign in active smokers than former smokers, with lower rates of hospitalization, flares and need for steroids, while the risk of colectomy has been controversial [48]. Smoking may also prevent the development of primary sclerosing cholangitis (PSC) or pouchitis after colectomy and ileo-anal anastomosis [49]. However, other studies have failed to show the beneficial effect of smoking [50]. Current smokers with UC have demonstrated reduced corticosteroid utilization but no reduction in the rates of colectomy or hospital admission relative to nonsmokers [43].

A key challenge is the discussion regarding smoking cessation. Most patients are not aware of the effects of smoking on their disease activity. In a questionnaire study, three-quarters of smokers knew that tobacco was not beneficial for their CD, whereas all UC patients were aware that smoking had a beneficial effect [51]. The intent to quit smoking was superior in informed patients compared with those who were uninformed. Older patients and patients with UC were less likely to be informed [52]. Most smoking IBD patients (90.5%) claim never to have received any support for achieving smoking cessation, which is significantly more in UC compared with CD [53]. The beneficial effect of smoking needs to be weighed against the risks to the patient such as coronary artery disease or lung and colon cancer [47].

Sexual and reproductive issues

IBD may result in sexual dysfunction and impaired fertility; however, these issues are frequently ignored mainly due to lack of comfort discussing the topics despite recent advances in preserving fertility and managing sexual dysfunction. Sexuality is often affected in women with IBD, and many factors contribute to worsened intimacy. Both men and women with IBD show significantly lower scores in sexual function indices. Independent predictors of sexual dysfunction among IBD patients are the use of corticosteroids in women and the use of biological agents, depression and diabetes in men [54]. There are multiple important concerns for women with IBD including issues of body image and sexuality, menstruation, contraception, screening for cervical cancer, matters related to menopause and hormone replacement therapy [55]. Patients with quiescent IBD do not have decreased fertility as compared with the general population; for those who do conceive, the course of IBD is about the same as in non-pregnant patients.

Infertility in men with IBD can be caused by medications (i.e. sulfasalazine-induced oligospermia), by active inflammation or by poor nutrition. Sperm banking before therapy is recommended when possible. Sexual function can be adversely affected by some medications (i.e. methotrexate-induced erectile dysfunction), by the depression that can accompany active IBD and by proctocolectomy. There is no increased rate of adverse fetal outcomes when men with IBD father children, but methotrexate should be discontinued before attempting conception. Pelvic surgery may affect erectile and ejaculatory function temporarily or permanently. Screening for prostate cancer after proctocolectomy depends on the use of prostate-specific antigen monitoring. If further evaluation of the prostate is required, it can be accomplished using transperineal ultrasound and biopsy [56]. After proctocolectomy, only men demonstrate improved sexual function, while women only report improved sexual desire [57].

In women, pelvic IBD surgery (i.e. restorative proctocolectomy with ileo-anal anastomosis) has been associated with dyspareunia and can lead to infertility by reducing ovarian reserve or impairing conception through formation of adnexal adhesions [58]. In men and women, advances in fertility preservation have markedly improved the reproductive outlook for patients with IBD in remission, and embryo, oocyte and ovarian cryopreservation in women has resulted in preserved fertility. IBD patients in remission who are concerned about sexual function and infertility should be referred to the appropriate specialist for an evaluation that may include semen analysis, hormone level testing and discussion of various options. Referral to a professional counselor may also be indicated.

Infections

IBD makes patients more prone to infections, and the addition of steroids or immunomodulators increases the risk. Both the thiopurines and the anti-TNF-α agents have low rates of serious

infections. Nonetheless, the anti-TNF-α agents are associated with opportunistic infections with intracellular pathogens such as *Mycobacterium tuberculosis* [59]. Patients with active infections should not be started on anti-TNF-α therapy. Thiopurines and methotrexate have been associated with an increased risk of viral infections. Corticosteroids are associated with a greater risk of serious infections than immunomodulators and anti-TNF-α agents. Regardless of therapy, CD is associated with serious infections such as intra-abdominal and perianal abscesses [60]. Despite screening and treatment of latent tuberculosis, active disease may still develop during treatment with anti-TNF-α inhibitors. These patients are treated with standard antituberculosis regimens with prompt discontinuation of TNF-α antagonists [61]. Patients with IBD regardless of treatment status are also at increased risk of invasive pneumococcal disease and varicella zoster [62]; screening for cytomegalovirus, hepatitis C virus or Epstein-Barr virus is not necessary. IBD patients are also at increased risk for hepatitis B infection. Furthermore, immunosuppression medications—especially anti-TNF-α inhibitors—can reactivate hepatitis B. IBD patients should be tested for hepatitis B virus and, if positive, should be treated prior to starting an immunosuppressant [63].

Vaccinations

IBD patients must receive Tetanus-Diphtheria-Pertussis (Tdap), hepatitis A and B, pneumococcal and annual influenza vaccines, while HPV vaccine is recommended in young non-pregnant females. An important concern in patients with IBD is their ability to mount an appropriate response to vaccines, but the results of studies are mixed [64,65]. Most inactivated vaccines have been found to be safe in IBD patients—even those on immunosuppression—without causing significant disease flares [66]. Inactivated influenza vaccine is recommended in IBD patients. Due to their risk for complicated influenza infections and superimposed bacterial infections, post-exposure prophylaxis with oseltamivir may be considered in immunocompromised patients who come in contact with infected individuals [67]. Every newly diagnosed IBD patient should receive pneumonia vaccination. IBD patients are at an increased risk for pneumonia, and immunosuppressive medications further increase this risk. According to the Centers for Disease Control and Prevention guidelines, patients on immunosuppressive medications should be vaccinated once with pneumococcal conjugate vaccine, followed by pneumococcal polysaccharide vaccine after 8 weeks, a second dose of the same 5 years later, and then a third dose after 65 years [68]. A recent study indicated that among vaccinated IBD individuals, there was a 9-fold decrease in the incidence of influenza and an 8-fold decrease in the incidence of pneumonia [69]. Vaccination for hepatitis B is an important part of management of IBD patients. Anti-hepatitis B surface antigen titers should be checked and, if inadequate (< 10 IU/L), a vaccination regimen should be initiated [65]. Unfortunately, there are studies showing decreased immunogenicity of hepatitis B vaccine in IBD patients [70,71]. Live vaccines are not recommended when the IBD patient is immunocompromised; after live vaccination, an interval of at least 6 weeks to 30 months is required before initiating any biological agents.

Lymphoma and other malignancies

Patients with IBD have a higher risk of colon cancer, while CD patients are also at an increased risk of small bowel cancer. Further, a higher risk of skin cancers (i.e. melanoma), lymphomas and cervical abnormalities are seen in IBD patients, especially those on immunosuppressive agents. Although IBD has not been found to increase the risk of lymphomas [72], such risk arises from treatment. The first large prospective study showed that the overall multivariate hazard ratio for developing lymphoma from thiopurine used to be 5.28 [73]. A recent meta-analysis of 18 studies confirmed this observation and also showed that patients >50 years of age have the highest absolute risk of lymphoma per year on thiopurines [74]. Patients with UC have a 4-fold increase in risk of lymphoma while being treated with thiopurines [75]. In the case of anti-TNF-α agents, a definitive relation could not be stated since most of the patients were also on immunomodulators [72]. Combined treatment with thiopurines and TNF inhibitors significantly increases the risk of a rare hepatosplenic T-cell lymphoma, particularly in young male patients with CD. An increased risk of non-melanoma skin cancer is also observed when using thiopurines in IBD, whereas a slightly increased risk of melanoma is observed in those using anti-TNF-α agents.

The above observations trigger some important discussions regarding patients with existing or past history of cancers or the need for screening before starting immunomodulators. Some studies recommend that immunosuppressive agents be avoided, especially during the first 2 years after commencing cancer therapy. Other options for therapy such as 5-ASA, antibiotics, enteral nutrition, steroids alone or in combinations, Seton placement and curative or diverting surgery may be considered depending on the disease, type, location and severity; these alternative therapies may allow for a crucial drug-holiday period before re-administration of immunosuppressive agents. Preventive measures include smoking cessation, ultraviolet solar protection, annual skin examination and Pap test. If unavoidable, methotrexate should be the drug of first choice, followed by anti-TNF-α and thiopurines. Patients should be managed on a case-by-case basis by a multidisciplinary team of experts. A family history of cancer generally does not preclude initiation of immunosuppressive regimen [76,77].

Psychosocial issues

IBD is a chronic illness involving multiple clinic visits and hospitalizations and, in many patients, one or more surgeries. As such, it impacts psychosocial aspects of the patient's life and in turn affects quality of life, adherence to treatment or disease course. In a recent cross-sectional study of IBD patients, a higher level of perceived stress was found to be a strong predictor of lower health-related quality of life and lower adherence to provider recommendations [78]. Active disease is known to cause episodes of anxiety and depression, but disease-related concerns and worries are present even in patients in remission [79]. There is a need for interdisciplinary evidence-based guidelines to provide specific recommendations on the etiology and management of psychosocial issues in IBD [80].

Treatment options include medications and psychotherapy. Antidepressants have been used widely in patients with IBD, not only to help symptoms related to mood but also to reduce relapse rates, use of steroids and endoscopies [81]. Tricyclic antidepressants in particular may cause moderate improvement of residual gastrointestinal symptoms in IBD patients for whom escalation of therapy was not planned [82]. Successful immunosuppressive therapy also helps depression [83]. Psychotherapy may be of benefit and should be considered on an individual basis [84]. Thus IBD patients, both with active disease and in remission, should be screened for psychological distress, and preferably mental health professionals/psychological

services should be considered part of a multidisciplinary approach.

A substantial number of women believe that IBD also affects their personal relationships because they experience increased sexual problems, altered sexual satisfaction, body image and self-consciousness during intimacy. In turn, such illness perceptions have a significant direct influence on depression, anxiety and family functioning, and clinicians should be prepared to address them [85].

Cognitive issues

Cognitive changes related to long-term medical therapy, nutritional deficiencies or chronic pain may occur in patients with IBD in remission. Anemia, vitamin B12 deficiency and other extra-intestinal manifestations of IBD are commonly overlooked [86]. Mood disorders, particularly depression, may affect cognitive performance in specific tasks [87,88]. Neuropsychological testing may help define symptoms regarding executive functioning, work and related issues.

Subclinical inflammation

As a marker of neutrophilic intestinal inflammation, fecal calprotectin may be used as a filter to avoid unnecessary endoscopies in IBD, but larger studies are needed to confirm a correlation between fecal calprotectin with IBD extent, prediction of response to therapy or relapse [89]. Periodic assessment of sedimentation rate or C-reactive protein may also be used. Surveillance colonoscopy performed for cancer prevention can also assess mucosal inflammation and tissue healing.

Monitoring thiopurine therapy

Long-term thiopurines (i.e. azathioprine and 6-mercaptopurine) are increasingly used in IBD, and most patients tolerate them well. Nevertheless, continuous monitoring is required with CBC and Liver function tests (LFTs) every 3 months to monitor for myelosuppression and for abnormalities in liver chemistries [90,91]. However, despite awareness of the importance of such monitoring, there are variations in the frequency of CBC or liver chemistry monitoring [92].

An association with thiopurine use and non-melanoma skin cancer has been noted in two major studies, with odds ratios ranging from 5.0 to 5.9 [93,94]. Hence, lifelong, regular dermatologic screening is recommended [95]. Nonetheless, a recent survey found that at least half of IBD patients were not undergoing dermatological screening since <50% of gastroenterologists were aware of the association between non-melanoma skin cancer and immunosuppression [96]. Patients should be advised to avoid excessive sun exposure and use a high-strength sunscreen and sun protective measures.

Delayed effects of treatment or disease

Metabolic bone disease is a significant concern in IBD. In one study, 47% of CD patients were found to have osteopenia and 12% found to have osteoporosis, while in UC those numbers were 34% and 14%, respectively [97]. This could be related to active inflammation reducing bone mineral density or other factors such as prolonged steroid use or malnutrition, especially of calcium and vitamin D. One study found that combined treatment with immunomodulators and TNF-α inhibitors resulted in an increase of bone mineral density [98]. Patients with long disease duration and those suffering from stricture-forming CD with ileal or ileocolic locations and those with prior proctocolectomy are at higher risk of developing osteoporosis than other IBD patients [99]. Moreover, patients requiring hospitalization for IBD exhibit the highest risk of developing osteoporosis and pathological fractures [100].

Screening for osteoporosis is an important component of management of IBD patients in remission, particularly those with a prior history of fracture, those using glucocorticoids for >3 months or those on repeated courses as well as postmenopausal women and all men >50 years of age. The predominant recommended screening tool is the Dual Energy X-ray Absorptiometry (DEXA) scan [101]. However these recommendations do not include fracture risk measurement tools such as Fracture Risk Assessment Tool (FRAX), nor do they take into account the severity or duration of disease or persistent inflammation. Some authors suggest that DEXA be performed in all IBD male patients >30 years old and in all female patients at the time of diagnosis [102]. Another study suggested that adding body mass index <21 as a criterion for screening would help identify many patients with osteoporosis who do not meet other criteria for screening [103].

Prevention and management of osteoporosis in IBD begins with identifying risk factors. Calcium and vitamin D deficiencies must be identified and replacement begun wherever appropriate. A balanced diet with adequate nutrient intake may prevent bone loss [104]. Smoking and alcohol cessation and steroid sparing should be recommended. FRAX scores should be used more widely to identify patients at risk for fractures. Among the pharmacological treatments, data are strongest for bisphosphonates, which are effective and well tolerated in IBD patients and reduce the risk of vertebral fractures [105].

Surgical outcomes and sequelae

The prevalence and number of comorbidities affect postoperative outcomes after an IBD-related operation. Congestive heart failure, liver disease, thromboembolic disease and renal disease are associated with a significant increase in mortality rate, length of stay and hospital charges [106]. Familiarity with the structural alterations that may result from the various surgical interventions in IBD and their clinical, physiological and nutritional sequelae are pivotal for anyone involved in the care of postoperative patients in remission.

Nutrition

IBD patients are at risk of nutritional deficiencies, mostly because of poor intake due to abdominal symptoms or diet restrictions. In one study, IBD patients were found to consume significantly less iron- and protein-rich foods compared with the general population. Unfortunately, many of the foods are excluded from the diet due to personal preferences unrelated to IBD [107]. Another major cause for malnutrition in IBD is malabsorption and protein-losing enteropathy. While active inflammation is associated with metabolic abnormalities, they can persist while patients are in remission. Vitamin and micronutrient deficiencies such as vitamin D, niacin and thiamine are common in IBD patients, particularly those with CD, and are present in both active disease and remission [108]. Iron-deficiency anemia and anemia of chronic disease are common. Screening for anemia should be routine for all IBD patients, and treatment should be started when appropriate. Iron replacement could be done orally or intravenously, depending on patient tolerability. Rarely, treatment with erythropoietin or blood transfusions may be necessary. Newer therapies such as anti-hepcidin antibodies are under study [109].

Vitamin B12 and folate deficiencies are frequent in IBD, and these could lead to hyperhomocysteinemia, which could in turn cause increased risk of thromboembolic disease [110]. Early

identification and replacement are recommended. Some studies have also shown an association between disease activity and vitamin D deficiency; a higher vitamin D level correlates with improved quality of life, although more controlled trials are needed [111,112]. Targeting serum 25-hydroxy vitamin D [25(OH)D] levels between 30 and 50 ng/mL appears safe and may have benefits for IBD disease activity [113].

Aside from nutrient replacement, dietary management is a vital part of nutritional management in IBD. Identifying intake and food avoidance patterns in patients is a reasonable first step. In selected cases, a dietician's input may be considered. Enteral nutrition is an important aspect of treatment and has been shown to be superior to total parenteral nutrition. However, this is rarely required when the patient is in remission. When enteral nutrition is used as maintenance therapy, it carries a significant relapse-preventing effect for both patients with active disease or those in remission [114].

Gut microbiota

Many studies have shown that patients with IBD have altered gut microbial composition or dysbiosis. In fact some studies even indicate this could play a role in the pathogenesis of IBD, resulting from an abnormal immune response in relation to the intestinal microbiota in genetically predisposed individuals [115]. Although the hypothesis of causation is still under study, there have been several therapeutic approaches targeting dysbiosis in IBD, some of which have shown promise.

The benefits of probiotics in IBD may include reduction of pathogens by competition, immunomodulation, production of anti-inflammatory interleukins or production of short chain fatty acids [116–118]. The most satisfactory results with probiotics are in patients with pouchitis [119]. While antibiotics are the mainstay of treatment for acute pouchitis, probiotics, especially VSL#3, may benefit chronic pouchitis, maintenance of remission and lead to improved quality of life [120,121]. Probiotics have not been shown to be useful in patients with CD.

Fecal microbiota transplant (FMT) is under study, with varying results. In a recent randomized controlled trial, FMT induced remission in a significantly greater percentage of patients with active UC than placebo, with no differences in adverse events. Larger trials are awaited [122].

Ostomy issues

Postoperative stomal and peristomal complications may occur early—or many years following construction of a stoma—even with patients in remission. Parastomal hernia, prolapse and stenosis are the most common late complications [123] and are less likely with end-colostomy or end-ileostomy [124]. The most common problems of end- or loop-ileostomies are dehydration and peristomal skin irritation (usually due to high fluid output) and small bowel obstruction [125]. All of these complications may lead to pain, difficulties with odor and gas management compromising quality of life, and significant challenges with diet, body image, sexual activity and travel. The involvement of an ostomy nurse may improve outcomes and reduce complications [126].

Extra-intestinal manifestations

Several extra-intestinal manifestations of IBD may occur while patients are in remission, and they require early recognition and treatment. Pyoderma gangrenosum or deep purulent ulcerations (usually on the legs) require systemic steroids or TNF antagonists [127]. In a similar fashion, uveitis manifesting as eye pain and redness usually does not parallel the activity of IBD and requires prompt evaluation by an ophthalmologist and intervention using topical or systemic steroids [128]. Although PSC may present with fatigue and pruritus, it is often detected in the context of evaluating abnormal (predominantly cholestatic) liver tests in patients with UC and less often CD [129–130]. Patients with PSC require yearly screening for gallbladder and hepatobiliary and pancreatic cancer by ultrasound or magnetic resonance imaging. Those with PSC and UC require screening for colorectal cancer with yearly colonoscopy and random biopsies [131]. The axial arthropathies, such as ankylosing spondylitis and sacroiliitis, are usually independent of intestinal IBD activity, but they can impact work ability and cause an additional burden for patients with IBD in remission [128].

Conclusions

Caring for patients with IBD in remission can be challenging due to its multifaceted nature and practice variations. Nonetheless, several of its aspects could be amenable to quality improvement and coordination initiatives. It is important that gastroenterologists and other practitioners caring for IBD patients in remission beaware of them and consider implementing quality measures as needed.

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