Inflammatory bowel disease: Looking beyond the tract

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Abstract

Inflammatory bowel disease is a chronic inflammatory condition that encompasses Crohn’s disease and ulcerative colitis. Inflammatory bowel disease is not exclusive to the gastrointestinal system, as it has been identified to be associated with extraintestinal manifestations that encompass every other organ system in the human body. This review article will comprehensively review the current knowledge on extraintestinal manifestations of inflammatory bowel disease. In addition, it will discuss the recommendations for screening and surveillance for extraintestinal manifestations in these patients since early appropriate diagnosis is imperative in preventing morbidity and cancer development.

Keywords

Crohn’s disease, extraintestinal manifestations, inflammatory bowel disease, screening, treatment, ulcerative colitis

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Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract that includes two clinical entities, Crohn’s disease (CD) and ulcerative colitis (UC).¹ Recent research by the Centers for Disease Control and Prevention (CDC) using the 2015 National Health Interview Survey (NHIS) found that IBD is actually more prevalent than previously reported. Their analysis concluded that IBD affects 3.1 million or 1.3% of US adults, which is approximately three times more than previous estimates. Prevalence was found to be higher among adults aged 45 years or older, Hispanics, non-Hispanic Whites, and adults with less than a high school education, currently unemployed, living in poverty, and born in the United States. Contrary to earlier studies, IBD prevalence was not found to be associated with types of health insurance coverage, geographic region, or sex.²

Multiple factors have been found to contribute to the pathogenesis of the disease including environmental, genetic, microbial, and immune.³ IBD is frequently associated with the development of extraintestinal manifestations (EIMs). EIMs of IBD are so common that the disease should be regarded as a systemic disorder that is not limited to the gastrointestinal tract.⁴ EIMs may involve almost any organ system making them major contributors to the morbidity of patients with IBD.³

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EIMs
EIMs are estimated to affect approximately 6% to 47% of adult patients with IBD and around 25% to 29% of pediatric patients with IBD. They have been reported to occur more frequently in patients with CD compared with those with UC. A patient may be affected by several EIMs at the same time, given that the presence of one EIM increases the likelihood of developing another. A Swiss IBD cohort study showed that 25% of patients with IBD actually suffered from multiple, in some cases up to five different EIMs. EIMs may occur prior to the diagnosis of IBD, which happens in 25.8% of cases. Patients with IBD with smoking history, perianal CD, and colonic involvement are at an increased risk of developing EIMs.

The pathogenesis of EIMs of IBD is unclear; however, it is thought to include immune and genetic factors. It is believed that immune responses may be triggered at extraintestinal sites by diseased gastrointestinal mucosa due to shared epitopes at the different sites. Bacteria translocated across a leaky intestinal barrier triggers an adaptive immune response that eventually will not be able to discriminate between bacterial epitopes and epitopes of the joints and skin. In terms of genetic susceptibility, links have been demonstrated between EIMs and certain major histocompatibility complex loci. For example, EIMs in CD are found more frequently in patients with HLA-A2, HLA-DR1, and HLA-DQw5. EIMs in UC are associated with HLA-DR103. A higher risk of primary sclerosing cholangitis (PSC) in UC specifically has been associated with HLA-B8/DR3. Also, HLA-DRB10103, HLA-B27, and HLA-B58 have been found to be associated with EIMs in the joints, skin, and eyes, respectively.

In addition to EIMs, patients with IBD may also experience extraintestinal complications. This can be further divided into those caused by the disease itself, for example, consequences of loss of function of diseased or resected bowel including malabsorption, and those caused by treatments.

Musculoskeletal manifestations
The most common EIMs of IBD are musculoskeletal, which affects up to 40% of the patients. The use of corticosteroids, immunosuppressants, and anti-tumor necrosis factor (TNF) therapy in patients with IBD have been found to cause therapy-induced arthralgias in a number of patients requiring withdrawal of the offending agent when possible. Musculoskeletal manifestations are divided into peripheral arthropathies and axial arthropathies.

Peripheral arthropathies
Peripheral arthropathy in patients with IBD is typically a seronegative arthropathy, which affects 5%–10% of patients with UC and 10%–20% of patients with CD. Patients who are at increased risk for peripheral arthropathies include those with colonic involvement, perianal disease, erythema nodosum, stomatitis, uveitis, and pyoderma gangrenosum (PG). Peripheral arthropathies in patients with IBD are categorized into two types with the diagnosis being made clinically since imaging of the joints is usually normal.

Type I arthropathy is pauciarticular or oligoarticular, usually involving less than five large joints, acute, asymmetrical, and migratory. It is usually related to the pattern of intestinal activity of the IBD. It is self-limiting, typically lasting no longer than 10 weeks with no persistent joint damage. It has been found to be associated with HLA-B27, HLA-B35, and HLA-DR103. On the contrary, type II arthropathy is polyarticular, usually involving five or more small joints that are symmetrical. It most commonly involves the metacarpophalangeal joint. It is independent of the disease course and can persist for years. It is associated with an increased risk of uveitis and has been found to be associated with HLA-B44.

Axial arthropathies
Axial arthropathies in patients with IBD include ankylosing spondylitis (AS) and isolated sacroiliitis, which affect 5%–22% of patients with CD and 2%–6% of patients with UC. Similar to type II peripheral arthropathies, axial arthropathies do not follow the intestinal course of the underlying IBD. Back pain and morning stiffness are the most common presenting axial joint symptoms and often present prior to intestinal symptoms of IBD. A strong association has been suggested between AS and IBD. AS is found to occur in up to 10% of patients with IBD, and 6.5% of patients with AS go on to develop IBD. It has been suggested that part
of this association is due to a shared genetic relationship. First-degree relatives of patients with AS are three times more likely to develop IBD. HLA-B27 has been identified as the main culprit since individuals who are HLA-B27 positive have an increased risk of developing AS. Also, 25%–78% of patients who have both IBD and AS are HLA-B27 positive. Because of this strong association, physicians should remain alert to evidence of AS. Presenting symptoms include but are not limited to severe onset of back pain at a young age and morning stiffness or pain associated with long periods of rest. Physical exam findings include limitations in spine flexion and reduced chest expansion. Radiographic findings range from normal to minimal sclerosis. In advanced AS, squaring of vertebral bodies, marginal syndesmophytes, bone proliferation, and ankylosis may be evident.

Contrary to AS, sacroiliitis does not share this association with HLA-B27 with most patients being HLA-B27 negative. It is discovered radiographically in up to 25% of patients. Most patients do not progress to AS but are more likely to if there is radiographic evidence of bilateral sacroiliitis.

The diagnosis of axial arthropathies is made clinically and supported by imagining. Magnetic resonance imaging (MRI) is the current gold standard since it can detect acute and chronic changes before radiographs show any abnormalities, therefore, resulting in earlier disease detection.

**Treatment**

In type I arthropathy, the treatment of choice is therapy of the underlying bowel disease since it is related to the intestinal activity. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used but with caution due to reports of IBD exacerbation following their use. Selective cyclo-oxygenase-2 (COX-2) inhibitors may be a safer alternative in patients with IBD with peripheral arthropathies. Sulfasalazine is usually used if NSAIDs or COX-2 inhibitors fail to provide adequate symptom relief. Sulfasalazine has been found to have superior results in peripheral arthropathies compared with axial. If these drugs are not successful at relieving symptoms, patients with CD can undergo a trial of tumor necrosis factor alpha (TNF-α) inhibitor at the same doses used for rheumatoid arthritis, whereas patients with UC may be treated with a TNF-α inhibitor or a short course of intra-articular or oral steroids.

Patients with axial arthropathies should always be referred for physiotherapy. Like peripheral arthropathies, NSAIDs and COX-2 inhibitors can be used for symptom relief. If the patient does not improve or is intolerant to these therapies, early use of anti-TNF therapy is recommended. Infliximab and adalimumab have been found to be successful in improving both intestinal symptoms and axial arthropathies in several studies in patients with IBD. In severe cases of axial arthropathy, specifically in AS, the disease-modifying anti-rheumatic drug (DMARD) methotrexate proves to be effective in maintaining remission in IBD. However, it is not recommended as first line therapy due to the lack of evidence regarding its effect on AS.

**Screening recommendations**

Patients with IBD more commonly develop reduced bone mineral density (BMD) and bony fractures. Studies have estimated the incidence of osteoporosis in IBD to range from 10% to 15%. The cause of low BMD in IBD is thought to be multifactorial. In addition to risk factors affecting the general population, risk factors specific to IBD include corticosteroid use, low physical activity, vitamin D deficiency, poor calcium intake likely related to lactose intolerance, calcium and magnesium dietary malabsorption, and inflammatory-mediated bone resorption. The American Gastroenterology Association (AGA) guidelines identified age and glucocorticoid use as the strongest risk factors highlighting the fact that all efforts should be made to limit prolonged exposure to corticosteroids. This notion is supported by two European studies that found that the risk of IBD leading to major osteoporotic fractures decreased when there was adequate control of glucocorticoid use. Because the absolute risk of bone fractures is low, a more conservative, cost-effective approach to screening IBD patients for osteoporosis follows guidelines established for the general population. This means screening all patients with a preexisting fragility fractures, women aged 65 and older, men aged 70 and older, and those with risk factors that increase the likelihood of low bone mass using dual-energy X-ray absorptiometry (DEXA) scanning for BMD measurement. Regarding corticosteroid use, all patients who have used oral corticosteroids for more than 3 consecutive months at a dose of 7.5 mg/day should have a DEXA scan.
For patients who have a T-score above −1 on DEXA, recommendations are preventive including smoking cessation, calcium and vitamin D supplementation, exercise, limiting alcohol intake, and minimizing the use of corticosteroids. Osteopenia is reflected by a T-score of −1 to −2.5 on DEXA and it is recommended that these patients implement the same preventive measures and consider a repeat DEXA in 2 years. Bisphosphonates are recommended for osteoporotic patients (T-score less than −2.5) and patients with a history of atraumatic fracture or failure to withdraw from corticosteroids therapy after 3 months.25 Further workup should be completed for patients who are found to be osteoporotic or who sustain a low-trauma fracture to screen for secondary causes of low BMD including celiac disease, hypogonadism, and vitamin D deficiency.21

Mucocutaneous manifestations

Cutaneous disorders occur in up to 15% of patients with IBD, whereas mucosal disorders are less frequent and occur in up to 10% of the cases.4,7 In addition, skin lesions may occur as complications of IBD secondary to malabsorption or to specific treatments. Immunosuppressants and anti-TNF therapies commonly used in IBD are associated with the development of cutaneous infections and cutaneous lesions, including injection-site reactions. The use of these therapies may also lead to immune-mediated complications including psoriasis, eczematous eruptions, lupus-like syndrome, and rarely skin cancers.7 The most common cutaneous manifestations observed in IBD are erythema nodosum and PG. Less common mucocutaneous manifestations include psoriasis, Sweet syndrome, and oral aphthous stomatitis.16 Erythema nodosum, PG, and psoriasis were found to be associated with TRAF3IP2 gene in IBD patients based on a case-control cohort study carried out by Ciccacci et al.26

Erythema nodosum

Erythema nodosum (EN) (Figure 1) is more common in patients with CD, affecting 15% compared with 10% of patients with UC.4 It has been suggested that EN is more common in females.7 EN involves inflammation of the subcutaneous fat usually presenting as raised, red or violet, tender nodules with a diameter of 1–5 cm. It is most commonly found on the anterior surface of the lower extremities and less frequently can involve the face, neck, trunk, and arms. EN is usually diagnosed clinically, rarely requiring a skin biopsy.4

PG

PG (Figure 2) is generally more severe and less common than EN occurring in 0.1%–1.2% of patients with CD and 1%–5% of patients with UC.7 Up to 50% of patients with PG have underlying IBD. It is more common in females.4 A characteristic feature of PG is a phenomenon known as pathergy, defined as an exaggerated physiologic response to a minor trauma such as a venous puncture or biopsy.7 PG usually begins as an erythematous pustule or nodule that spreads and develops a burrowing ulcer with irregular
violaceous edges. These ulcers are usually purulent and found to be sterile when cultured. These lesions are variable and can be unilateral or bilateral, solitary or multiple, and cover several centimeters or an entire limb. The legs are most commonly affected but PG can occur anywhere on the body, including the abdominal wall adjacent to a postsurgical stoma. PG ulcers can leave behind scars after they heal. Like EN, PG is usually a clinical diagnosis but requires a biopsy in rare cases to rule out other possible causes including infection, malignancy, or vascular disease. Also, up to 50% of patients with PG have IBD.

Psoriasis

Studies suggest that psoriasis (Figure 3) is more prevalent among patients with CD compared with the general population. An immunologic relation is suggested due to the high concentrations of TNF-α found in both psoriatic lesions and similar lesions found in patients with CD.

Sweet syndrome

Sweet syndrome (Figure 4) is an acute febrile neutrophilic dermatosis. It is a rare disease that is associated with IBD and other systemic diseases including malignancy. Sweet syndrome presents as papulosquamous exanthema or nodules occurring on the arms, legs, hands, trunk, or face. Associated findings on presentation include arthritis, fever, ocular symptoms including conjunctivitis, and leukocytosis. It usually follows the course of intestinal disease activity but may precede the diagnosis of IBD. The use of azathioprine may be associated with the development of Sweet syndrome.

Oral lesions

Oral lesions affect up to 10% of patients with IBD and they include periodontitis, aphthous stomatitis, and pyostomatitis vegetans. Oral lesions usually follow the course of the underlying intestinal disease. Aphthous stomatitis lesions (Figure 5) are usually painful and occur on the buccal and labial mucosa, the tongue, and the oropharynx. Diagnosis is usually clinical, and biopsy is rarely required but if done, histology usually reveals noncaseating granulomas in CD similar to those found in the colon. Pyostomatitis vegetans presents as multiple ulcerations and hemorrhagic erosions anywhere on the oral mucosa usually with a cobblestone pattern.
**Treatment**

Erythema nodosum follows the course of intestinal disease activity and is self-limiting with treatment usually aimed at the underlying bowel disease. Supportive therapy includes leg elevation, compression stockings, and analgesics. Occasionally, EN may precede bowel exacerbations and require treatment with oral corticosteroids. In cases that are severe or resistant to therapy, alternative causes of EN should be considered including infections with streptococcus, tuberculosis (TB), sarcoidosis, coccidiodomycosis, histoplasmosis, blastomycosis, Yersinia pseudotuberculosis, Yersinia enterocolitica, syphilis and Behçet disease, or use of certain medications including sulfonamides, iodides, bromides, and estrogens. After excluding alternative causes, severe cases may require systemic corticosteroids, immunosuppressive therapy, or TNF antibodies. Prevalence of recurrent disease is thought to be nearly 20%. PG, unlike EN, is not associated with underlying intestinal disease activity; however, it may resolve with treatment of the IBD. Mild, localized disease usually responds to local and topical therapy including moist treatment with hydroactive dressings, topical or intralesional corticosteroid injections, and topical sodium cromoglycate. Widespread PG requires systemic therapy including oral sulfasalazine, dapsone, corticosteroids, and immunomodulators such as azathioprine, cyclophosphamide, cyclosporine, methotrexate, tacrolimus, and mycophenolate mofetil. Adalimumab and infliximab are effective treatments for severe or therapy-resistant cases of PG. Surgical intervention typically worsens PG and should be avoided.

When discussing psoriasis treatment options in IBD patients, one has to be cautious as some psoriasis treatment options may worsen IBD. A recent systematic review carried out by Whitlock et al. analyzed Food and Drug Administration (FDA)–approved biologic medications and FDA-approved nonbiological systemic medications for psoriasis and evaluated the evidence of their use in CD and UC. Among the FDA-approved biologic medications for psoriasis, infliximab and adalimumab are also FDA-approved for CD and UC; ustekinumab is also FDA-approved for CD but not yet studied for UC; etanercept, secukinumab, and ixekizumab have the potential risk of exacerbation of both CD and UC; brodalumab is contraindicated for CD and not yet studied for UC; and guselkumab is not yet studied for CD and UC. Among the FDA-approved nonbiologic systemic medications for psoriasis, cyclosporine has moderate efficacy in UC and modest efficacy in CD; methotrexate has strong efficacy in CD and modest efficacy in UC; and acitretin and apremilast are not yet studied for CD and UC.

Most cases of Sweet syndrome respond rapidly to topical or systemic corticosteroid therapy and subsequently heal without scarring.

Therapy for oral lesions includes antiseptic mouthwashes, topical steroids, and treatment of the underlying disease.

**Screening recommendations**

Studies have found that individuals with IBD, both CD and UC, have a 37% higher risk of developing melanoma compared with the general population. On the contrary, there is no suggestion that IBD itself increases the risk of non-melanoma squamous cell cancer (NMSC). In general, patients with IBD likely have the same risk factors as the general population, but additionally have risks specific to their treatment. A study by Long et al. found that the use of anti-TNF therapy increases the risk of developing melanoma. Also, individuals with prior or current use of antimetabolite therapy, including azathioprine or 6-mercaptopurine, have an increased risk of developing NMSC, including squamous cell carcinomas (SCC) and, to a lesser degree, basal cell carcinomas (BCC).

The United States Preventive Services Task Force (USPSTF) reported insufficient evidence to recommend universal skin cancer screening by whole-body skin examination by a primary care clinician or patient self-examination. There are no clear guidelines available for patients with IBD regarding annual skin examinations for the secondary prevention of skin cancer; however, many argue that this is warranted in patients with IBD on chronic immunosuppressive therapy due to the increased risk. The American College of Gastroenterology (ACG) recommends patients with IBD to undergo screening for melanoma independent of the use of biologic therapy and for those on immunomodulators to undergo screening for NMSC, especially when above the age of 50, with periodic skin examination.
Even though exact recommendations are unclear, there is general agreement that all patients with IBD should definitely be educated about the risk of skin cancer and have discussions with their primary care physicians or gastroenterologists about the importance of prevention and early treatment. It is highly recommended that all individuals should take proper precautions including the use of sunscreen and sun protective clothing, especially those initiating immunosuppressive therapy.

**Ocular manifestations**

Approximately 2%–5% of IBD patients experience ocular manifestations. They occur more frequently in patients with CD (3.5%–6%) compared with patients with UC (1.6%–4.6%). Ocular manifestations often occur concurrently with other EIMs, most commonly musculoskeletal manifestations. It is important to note that conjunctivitis is the most common cause of red and itchy eyes in the general population, which holds true for patients with IBD. Therefore, physicians should keep this in mind, especially since conjunctivitis can easily mimic more serious ocular conditions. In addition to ocular manifestations, ocular complications secondary to IBD treatments can be seen. Steroids can cause cataracts and open-angle glaucoma, whereas cyclosporine can lead to optic neuropathy, ophthalmoplegia, and nystagmus. The most common ocular manifestation found in patients with IBD is episcleritis. Less common manifestations include scleritis and uveitis.

**Episcleritis**

Episcleritis (Figure 6) is defined as inflammation of the blood-rich episclera. It is more common in patients with CD compared with UC. It usually presents with acute hyperemia, burning, and irritation in one or both eyes. Patients often have tenderness to palpation but no changes in vision.

**Scleritis**

If deeper layers of the eye are affected, a diagnosis of scleritis should be considered. Scleritis is more severe than episcleritis and has the potential to cause visual impairment if not diagnosed early. Patients usually present with severe pain and tenderness to palpation. Recurrent scleritis can lead to retinal detachment, swelling of the optic nerve, or scleromalacia.

**Uveitis**

Uveitis (Figure 7) is defined as inflammation of the eye’s middle chamber. It is less common than episcleritis, occurring in 0.5%–3% of IBD patients, and is four times more common in women. Patients usually present with pain, photophobia, headaches, and blurring of vision. Diagnosis is confirmed by slit-lamp examination, which reveals perilimbic edema in addition to an inflammatory flare in the anterior chamber. Characteristically, the eye will show a ciliary flush with the redness showing most intensely in the middle and fading as it radiates outward. Examination findings also include conjunctival injection and corneal clouding.

**Treatment**

Episcleritis often parallels intestinal activity and resolves with treatment of the underlying bowel disease. Patients occasionally require cool compresses or topical steroids for relief of symptoms. Scleritis, being more severe than episcleritis, requires more aggressive treatment with systemic...
corticosteroids or immunosuppressants, adequate control of the underlying intestinal disease, and prompt referral to an ophthalmologist to avoid loss of vision.\textsuperscript{16}

Uveitis occurs independently of disease activity. Prompt treatment with topical and systemic steroids is essential to prevent progression to permanent visual loss. In patients with disease refractory to steroids, cyclosporine A and infliximab can be used.\textsuperscript{7}

**Screening recommendations**

It is recommended that patients with IBD, especially those on immunosuppressive therapy, undergo regular, annual ophthalmologic evaluation and be encouraged to present to their physician’s office to discuss any eye or vision changes.\textsuperscript{38}

**Hepatobiliary manifestations**

Up to 50\% of patients with IBD experience hepatobiliary manifestations at some point during their disease.\textsuperscript{7} These manifestations include PSC, small-duct PSC, fatty liver disease, granulomatous hepatitis, autoimmune hepatitis, and hepatic steatosis. In addition, extraintestinal complications include cholelithiasis, hepatic abscess, drug-induced hepatotoxicity, and hepatosplenic T-cell lymphoma (HSTCL).\textsuperscript{4,7,16}

**PSC**

PSC is the most common biliary manifestation in IBD. It is more prevalent in patients with UC compared with CD with approximately 2.4\%–7.5\% of patients affected. However, 75\% of patients with PSC suffer from IBD, more commonly UC.\textsuperscript{4} Therefore, patients found to have PSC should have a colonoscopy to evaluate for the possibility of concomitant IBD.\textsuperscript{7} PSC is a chronic cholestatic disease with progressive inflammation, stricturing, and fibrosis of the intrahepatic and extrahepatic bile ducts.\textsuperscript{4} Patients with PSC can experience bouts of acute cholangitis and eventually advance to cirrhosis, portal hypertension, and acute decompensation.\textsuperscript{39} It is not associated with underlying intestinal disease activity, is more common among patients 30–59 years of age, and is twice as common in males than females. Patients with UC with more extensive involvement of the colon are more likely to develop PSC than patients with involvement of the left colon only.\textsuperscript{16} Studies suggest genetic susceptibility, with HLA-B8 found to be positive in up to 70\% of patients with PSC\textsuperscript{7} in addition to the most recently identified gene UBASH3A that is non-HLA based.\textsuperscript{40}

Patients with IBD who develop signs of cholestasis should be evaluated for PSC.\textsuperscript{16} Patients may present with unspecific findings at first including fatigue, abdominal pain, and weight loss and later pruritis and intermittent jaundice.\textsuperscript{18} Laboratory findings show elevated alkaline phosphatase and bilirubin levels whereas aspartate aminotransferase and alanine aminotransferase typically remain normal. Albumin levels and prothrombin time typically remain normal until disease progresses to cirrhosis.\textsuperscript{16} Serological workup may reveal positive autoantibodies in approximately 65\%–88\% of patients including antinuclear, anti-smooth muscle, and/or anti-perinuclear cytoplasmic antibodies.\textsuperscript{41}

The diagnostic test of choice is magnetic resonance cholangiopancreatography (MRCP) since visualization of the biliary tree is required for diagnosis. The classic finding is the “bead on a string” appearance, which describes the presence of irregular bile ducts with multifocal strictures and segmental dilation. Endoscopic retrograde cholangiopancreatography (ERCP) (Figure 8) is reserved for patients requiring interventions including stenting of high-grade strictures because of its associated risk of causing cholangitis due to inadequate biliary drainage.\textsuperscript{16}

It is interesting to note that PSC appears to influence the course of IBD; patients who have both PSC and UC demonstrate a milder course of their colitis with less inflammation of the colon on histology compared with patients with IBD without PSC.\textsuperscript{42} However, PSC is thought to be an independent risk factor for the development of colorectal cancer (CRC) in patients with IBD.\textsuperscript{7} PSC is also the greatest risk factor for developing cholangiocarcinoma.\textsuperscript{16}

**Hepatobiliary complications**

Up to 30\% of patients with IBD develop cholelithiasis, especially in patients with CD with ileal involvement or after ileal resection.\textsuperscript{43} Some of the factors contributing to this high risk include increased enterohepatic circulation of bile, impaired bile salt absorption, and reduced gallbladder motility. Hepatic abscess is a possible complication of IBD that can potentially be
life-threatening. The patient may present with fever and abdominal pain and be found to have leukocytosis, which is a similar clinical presentation to an IBD flare. Fluid drained from the abscess may culture oral or intestinal flora or be sterile and predominantly composed of neutrophils. Both usually respond to drainage and antibiotics, with sterile abscesses also responding to corticosteroids.\(^5\)

In general, medications that have been found to be associated with hepatotoxicity comprise of thiopurines, methotrexate, sulfasalazine, cyclosporine, and biologic agents.\(^4^3\) Specific drugs that might play a role in the development of non-alcoholic fatty liver disease (NAFLD), which, along with non-alcoholic steatohepatitis (NASH), affect approximately 9.4% of patients with UC and 19.3% of patients with CD, include corticosteroids, methotrexate, and azathioprine. Also, several cases have been reported of patients with IBD who went on to develop HSTCL after being treated with a combination of anti-TNF therapy, corticosteroids, and thiopurines.\(^7\)

**Treatment**

Unfortunately, no medical therapy has been found to prevent the progression of PSC as bile duct damage is irreversible and does not seem to respond to medication. Ursodeoxycholic acid (UDCA) has been found to improve liver enzymes without having any real effect on the disease course.\(^7\) In addition, one study on the long-term use of UDCA in high doses reported an increased risk of CRC in patients with PSC and UC.\(^4^4\) ERCP can be used to dilate dominant strictures in some patients. Nevertheless, the majority of patients with PSC will ultimately require a liver transplantation.\(^4\)

**Screening recommendations**

Patients who have PSC and IBD have a 10%–15% lifetime risk of developing cholangiocarcinoma. Consequently, some centers recommend annual screening using ultrasound or MRCP and measurement of tumor marker cancer antigen 19-9 (CA 19-9) in these patients.\(^5\) PSC is also an independent risk factor for the development of CRC in patients with IBD. Therefore, it is recommended that these patients undergo annual surveillance colonoscopies.\(^4\)

In addition, it is always crucial to screen patients for hepatitis B, hepatitis C, and TB infection prior to initiating biologic therapy since these agents could potentially promote hepatic viral reactivation.\(^1^6\)

**Pancreatic manifestations**

Pancreatic manifestations found in patients with IBD include acute pancreatitis, autoimmune pancreatitis, and exocrine and endocrine pancreatic insufficiency, whereas the main pancreatic complication seen is acute drug-induced pancreatitis.

**Acute pancreatitis**

Patients with IBD develop acute pancreatitis with a prevalence of 1%–1.5% independent of medical therapy.\(^7\) This increased risk is thought to be secondary to gallstones, CD of the duodenum, or CD-associated granulomatous inflammation of the pancreas.\(^1^6\) Drug-induced pancreatitis has been linked to azathioprine, 5-aminosalicylic acid, 6-mercaptopurine, metronidazole, and, less commonly, corticosteroids. Based on a genome wide association study, it was found that patients with the HLA-DQA1-HLA-DRB1 haplotype have a genetic susceptibility to pancreatitis after administration of thiopurine immunosuppressants.\(^4^5\) Heterozygous patients have a 9% risk of developing pancreatitis induced by thiopurine, while homozygous patients have a 17% risk.\(^4^5\) Patients usually present with abdominal pain associated with nausea and vomiting starting shortly after beginning therapy and usually resolving quickly following discontinuation of the offending agent.\(^7,^1^6\)
Autoimmune pancreatitis

IBD-associated autoimmune pancreatitis (AIP) carries a worse prognosis due to the greater degree of severity, with an increased incidence in UC.\textsuperscript{46} IBD has a stronger association with type 2 AIP, which has normal IgG4 levels, in contrast to type 1 AIP which has elevated IgG4 levels.\textsuperscript{46}

Treatment

Treatment of acute pancreatitis in IBD is the same as for the general population including early adequate aggressive intravenous fluid resuscitation, electrolyte replacement, bowel rest, analgesia, and treatment of underlying cause of acute pancreatitis.

Treatment of AIP in IBD is similar to the standard therapy of type 2 AIP which is oral steroids with similar recurrence rate of 9\%.\textsuperscript{46}

Screening recommendations

To date, there are no established guidelines on screening recommendations aimed at pancreatic manifestations in patients with IBD; especially that autoimmune pancreatitis is a relatively newly recognized disease with only several cases reporting the diagnosis of AIP in association with IBD.

Pulmonary manifestations

Pulmonary manifestations in patients with IBD are rare. However, lung involvement is probably more common than reported since many patients remain asymptomatic and imaging may be normal even when pulmonary function tests are not.\textsuperscript{5} Patients with UC are more likely to develop pulmonary EIMs than patients with CD. Pulmonary manifestations include large and small airway, upper airway, and parenchymal disease. Complications include drug-induced pulmonary disease.

Bronchiectasis, a manifestation of the large airways, is the most common pulmonary disease found in patients with IBD followed by chronic bronchitis.\textsuperscript{47} Diagnosis is made with a high-resolution computed tomography (CT) that shows dilated airways and bronchial wall thickening.\textsuperscript{48} On the contrary, upper airway manifestations are very rare and include subglottic stenosis diffuse tracheitis. The most frequent parenchymal lung disease in patients with IBD is cryptogenic organizing pneumonia (COP). Clinical presentation involves fever, cough, and dyspnea, therefore, requiring exclusion of infectious causes. Chest X-ray reveals opacities that range from patchy to diffuse and CT scan demonstrates scattered foci of consolidations that are either unilateral or bilateral in addition to centrilobular nodules.\textsuperscript{7}

The use of methotrexate in patients with IBD has been linked to the pulmonary complications of hypersensitivity pneumonitis and pulmonary fibrosis.\textsuperscript{49} Also, sulfasalazine and mesalamine have been found, on rare occasions, to induce interstitial lung disease.\textsuperscript{16}

Screening recommendations

To date, there are no established guidelines on screening recommendations for pulmonary manifestations in IBD.

Renal and genitourinary manifestations

Approximately 4\%–23\% of patients with IBD are affected by renal manifestations or complications.\textsuperscript{50} Reported renal manifestations include glomerulonephritis, tubulointerstitial nephritis, and amyloidosis. Renal complications that impact patients with IBD include nephrolithiasis, enterovesicular fistula, perivesicular abscess, non-calculous obstructive uropathy, and drug-induced renal complications.\textsuperscript{7}

Both glomerulonephritis and tubulointerstitial nephritis have been found to follow the intestinal course of the underlying bowel disease.\textsuperscript{51} The most common glomerulopathy that was found to be reported in patients with IBD is IgA nephropathy with HLA-DR1 being the investigated associated gene.\textsuperscript{52} Tubulointerstitial nephritis may also be a drug-induced complication of IBD caused by the use of 5-aminosalicylic acid.\textsuperscript{7}

Amyloidosis is a rare but serious EIM that predominantly affects patients with CD with a 10-fold increased risk compared with patients with UC. It is also three times more common in males than...
females. Amyloidosis is characterized by extracellular deposition of serum amyloid A and can be diagnosed with liver, rectal, or renal biopsy. Patients may present with proteinuria and uremia, which may proceed, if left untreated, to nephrotic syndrome and renal failure with poor outcomes.

Renal and genitourinary complications

Nephrolithiasis is the most common renal complication affecting 5%–15% of patients with IBD, predominantly patients with CD with ileocolonic involvement. Calcium oxalate and uric acid renal stones are the most common. The increased risk of calcium oxalate stones in IBD is explained by the malabsorption of bile acids causing free fatty acids to reach the colon, bind to calcium, and increase the amount of oxalate that is free to be reabsorbed. Uric acid stones form due to decreased urine pH and decreased urine volumes that result from diarrhea.

An additional complication seen in patients with IBD includes non-calculous obstructive uropathy, which usually occurs due to retroperitoneal inflammation, fibrosis, and/or scarring in patients with CD and surgical complications in patients with UC.

The use of certain drugs has been found to induce renal complications. Cyclosporine and tacrolimus can lead to renal vasoconstriction causing acute renal dysfunction and interstitial fibrosis causing chronic renal impairment. Anti-TNF therapy has been found to be associated with several cases of severe glomerulonephritis.

There also exists a possible risk of cervical dysplasia and cancer in patients with IBD. A recent Danish cohort study found that women with UC had an increased risk of both low-grade and high-grade lesions when compared with healthy controls, whereas women with CD had an increased risk of low-grade and high-grade lesions in addition to cervical cancer. They also noted an 8% increased risk of dysplasia in women with a history of azathioprine use.

Treatment

Therapy for glomerulonephritis, tubulointerstitial nephritis, and amyloidosis focuses on controlling and treating the underlying inflammatory process in IBD.

Therapy for nephrolithiasis depends on the composition of the stone. For calcium oxalate stones, calcium supplementation is recommended in the amount of 1–2 g per day to help prevent oxalate stone formation. Therapy for uric acid stones includes fluid replacement, a purine-reduced diet, and alkalization of the urine.

Screening recommendations

Conflicting data exist regarding the risk of cervical dysplasia and cancer in patients with IBD; however, studies have consistently reported an increased risk in patients using immunosuppressants. Therefore, the American College of Obstetricians and Gynecologists (ACOG) and the CDC recommend annual screening for women with a history of chronic immunosuppression starting at the age of 21. Unfortunately, some studies show that women with IBD are screened even less frequently than recommended for healthy women, which is once every 3 years, particularly those on immunosuppressive therapy.

Even though there are no specific cervical screening guidelines, it is important, as the European Crohn’s and Colitis Organization (ECCO) states, for all women with IBD to strictly adhere to a screening program of cervical surveillance and undergo human papilloma virus (HPV) vaccination according to recommendations. Papanicolaou (Pap) smear is the standard screening test and the HPV vaccine is recommended for all men and women 9–26 years of age. It is crucial to note that the HPV vaccine does not include all high-risk types and therefore does not eliminate the continued need for regular screening.

Hematologic manifestations

Hematologic manifestations that have been found to occur in patients with IBD include venous and arterial thromboembolisms and anemia. Some studies have revealed an increased risk of venous thrombosis by 2 to 4-fold in patients with IBD, whereas the risk of arterial thrombosis increased to a lesser degree. Chronic inflammation plays a large role in activating coagulation and fibrinolysis. Both patients with active disease and those in remission have been found to experience thromboembolic events more frequently than seen in the general population. Studies have not been able to find increased rates of common genetic factors linked to hypercoagulability in patients with IBD including factor V Leiden and methylenetetrahydrofolate reductase (MTHFR) gene mutation. However,
increased levels of homocysteine in the blood have been reported in patients with IBD compared with controls, but it is unclear whether this contributes to the increased risk of thromboembolism. Anemia occurs in 19%–32% of patients with IBD. The different types of anemia encountered in IBD include anemia of chronic disease, iron deficiency anemia, and megaloblastic anemia from vitamin B12 or folate deficiency. Because vitamin B12 and folate are absorbed in the ileum, patients with CD are more likely to be affected than those with UC, especially patients with CD who have undergone bowel resection. Drug toxicity is another cause of anemia in patients with IBD using azathioprine, 6-mercaptopurine, and methotrexate due to myelosuppression. There is also an association between immunosuppressive agents, particularly thiopurines, and increased risk of lymphoproliferative disorders. This was studied in the French Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France (CESAME) cohort study, which found that patients who received thiopurines were five times more likely to develop lymphoproliferative disorders. Similar to previous studies, the incidence of lymphoma was found to be low and patients who discontinued thiopurine therapy went back to having a similar incidence of lymphoma as the general population. The CESAME study also revealed that it is possible for HSTCL to occur in patients exposed to thiopurine therapy alone or in combination with anti-TNF therapy.

**Treatment**

Given the increased risk of thromboembolism among patients with IBD, it is recommended that all patients with IBD who are hospitalized or immobilized be treated with low-dose heparin for prophylaxis. Supplementation of iron is recommended for patients who present with iron deficiency anemia by the intravenous route, especially in active disease. If patients do not respond to iron supplementation or are not found to have iron deficiency, anemia of chronic disease is likely and treatment with erythropoietin is required. Oral supplementation of folate of at least 1 mg per day and intramuscular vitamin B12 of 1000 μg per month should be administered if the patient is found to be deficient.

**Screening recommendations**

There is no current effective screening method available for the timely diagnosis of lymphoproliferative disorders in patients with IBD exposed to thiopurine therapy. Presenting symptoms that should alert physicians to investigate for lymphoproliferative disorders include headaches that are unexplained, fatigue, fever, hepatosplenomegaly, or lymphadenopathy not attributable to intestinal inflammation. Given the possible increased risk of HSTCL in patients on a combination of thiopurine and anti-TNF therapy, it is reasonable to avoid using this combination for greater than 2 years in men less than 35 years old. Physicians should provide clear information about the risks associated with certain therapies to their patients, especially since no specific screening recommendations are available.

**Neurologic and psychiatric manifestations**

Intracerebral focal white matter lesions have been found on MRI in up to 42% of patients with CD and 46% of patients with UC who are asymptomatic. Demyelinating diseases including multiple sclerosis and ischemic optic neuropathy have been found among patients with IBD. Recurrent facial nerve palsy associated with Melkersson–Rosenthal syndrome has been described in some patients with CD specifically. However, the most common neurological manifestations found in patients with IBD are peripheral neuropathies. These have not been found to follow intestinal activity of the underlying bowel disease and therefore do not respond to IBD-specific treatments.

A typical neurological complication encountered among patients with IBD, particularly patients with CD who have undergone ileocecal resection, is peripheral polyneuropathy due to vitamin B12 deficiency. Drug-induced neurotoxicity is also described for various therapies used in patients with IBD. Metronidazole, sulfasalazine, and calcineurin inhibitors may potentially induce peripheral neuropathy. Calcineurin inhibitors are also associated with tremor, psychosis, parasthesia, ataxia, and motor deficit in up to 25% of patients. Anti-TNF therapy has been found to be associated with Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy.
Depression is a common problem affecting up to 35% of patients with IBD. In a recent systemic review, anxiety was found to be present in 19% of patients with IBD compared with 9.6% in the control group, while depression was found in 21.2% of patients with IBD compared with 13.4% in non-IBD controls. Predisposing risk factors for the development of depression in patients with IBD include frequent relapses and use of specific medications including steroids.

Treatment

Therapy for each of the above mentioned neurologic and psychiatric manifestations will be similar to that of the general population.

Screening recommendations

The American College of Preventive Medicine (ACPM) has provided evidence that effective screening for depression can be accomplished with just two questions:

1. Over the past month, have you felt down, depressed, or hopeless?
2. Over the past month, have you felt little interest or pleasure in doing things?

A positive response to either of these questions should prompt further investigation into the symptoms. Appropriate patient counseling can be offered during the office visit and continued at coming visits for mild symptoms. However, moderate to severe symptoms should be treated with pharmacological intervention and/or referral to primary care or a mental health specialist. With the availability of this quick and efficient method, screening for depression and anxiety in patients with IBD should be accomplished at every office visit. Addressing this issue in patients with IBD may be crucial for disease management and enhancing the chance of good outcomes.

Rare EIMs

Myocarditis, which is an inflammation of cardiac myocytes, is a rare cardiac manifestation of IBD which occurs as either a result of exposure to autoantigens leading to an autoimmune response or as a result of drug toxicity of 5-aminosalicylic acid or its derivatives. Treatment is supportive with immunosuppressive therapy including immunoglobulins and corticosteroids for a duration ranging from 3 to 6 months. Chronic recurrent multifocal osteomyelitis, a rare disease characterized by aseptic inflammation of long bones, is a rare skeletal manifestation of IBD which is mainly seen among children and adolescents with less than 30 cases reported worldwide. Treatment is mainly with corticosteroids and if that fails, reports have shown success of with anti-TNF agents and bisphosphonates.

Additional general screening recommendations

CRC screening

Patients with IBD have a significantly increased risk of developing colorectal cancer (CRC). The precursor to CRC is colonic dysplasia and, therefore, it is crucial to promptly identify and treat all IBD associated dysplasia.

Risk factors for CRC that are unique to IBD include the extent, severity, and duration of inflammation as well as previous history of colonic dysplasia. Patients that have extensive colitis (>50% involvement) that has been diagnosed for more than 10 years have a 7-fold increased risk of developing CRC compared with those without long-standing extensive colitis. Additional independent risk factors for the development of CRC in patients with IBD include active inflammation, and endoscopic findings of strictures, inflammatory polyps, and foreshortened colons. Also, patients with concomitant UC and PSC were found in a meta-analysis to have a 4-fold increased risk of CRC compared with patients with UC without PSC.

Current guidelines in the United States recommend CRC surveillance every 1–2 years after disease has been present for 8–10 years. Exceptions involve certain conditions that warrant yearly surveillance starting at the time of diagnosis including patients with a family history of CRC in a first-degree relative, active inflammation, or PSC. European guidelines including the British Society of Gastroenterology (BSG) and the European ECCO similarly recommend initiation of surveillance 8–10 years after diagnosis. They go on to offer detailed surveillance guidance based on risk stratification. Annual surveillance is recommended for patients with moderate to severe active inflammation, family history of CRC in a first-degree relative less than 50 years of age, or history of stricture, dysplasia.
<table>
<thead>
<tr>
<th>EIM organ system</th>
<th>Extraintestinal manifestation</th>
<th>Associated genes</th>
<th>Treatment</th>
<th>Screening recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal</td>
<td>Peripheral arthropathy (type I and type II)</td>
<td>Type 1: HLA-B27, HLA-B35, and HLA-DRB103; Type 2: HLA-B44</td>
<td>Treat underlying bowel disease (type I), COX-2 inhibitors, sulfasalazine, intra-articular or oral steroids, anti-TNF therapy</td>
<td>Screen for osteoporosis based on established guidelines for the general population with bone mineral density testing</td>
</tr>
<tr>
<td></td>
<td>Axial arthropathy</td>
<td>HLA-B27 (Ankylosing spondylitis)</td>
<td>Physiotherapy, COX-2 inhibitors, anti-TNF therapy, methotrexate</td>
<td>Screen for melanoma independent of the use of biologic therapy and screen for NMSC if on immunomodulators, especially when above the age of 50, with periodic skin examinations as per ACG recommendations</td>
</tr>
<tr>
<td>Muocutaneous</td>
<td>Erythema nodosum</td>
<td>TRAF3P2</td>
<td>Treat underlying bowel disease. Refractory: systemic steroids, immunosuppressive or anti-TNF therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyoderma gangrenosum</td>
<td>TRAF3P2</td>
<td>Local: moist treatment with hydroactive dressings, topical or intralesional steroid injections, and topical sodium cromoglycate. Widespread: oral sulfasalazine, dapsone, steroids, and immunomodulators</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psoriasis</td>
<td>TRAF3P2</td>
<td>Infliximab and adalimumab</td>
<td></td>
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<tr>
<td></td>
<td>Sweet syndrome</td>
<td>–</td>
<td>Topical or systemic steroids</td>
<td></td>
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<tr>
<td></td>
<td>Oral lesions</td>
<td>–</td>
<td>Treat underlying bowel disease. Antiseptic mouthwashes and topical steroids</td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td>Episcleritis</td>
<td>–</td>
<td>Treat underlying bowel disease. Cool compresses or topical steroids</td>
<td>Annual ophthalmologic evaluation, especially patients on immunosuppressive therapy</td>
</tr>
<tr>
<td></td>
<td>Uveitis</td>
<td>–</td>
<td>Systemic steroids, glaucoma management</td>
<td></td>
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<tr>
<td></td>
<td>–</td>
<td>–</td>
<td>Refractory: cyclosporine A and infliximab</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>Primary sclerosing cholangitis (PSC)</td>
<td>HLA-B8 and UBASH3A</td>
<td>No effective medical therapy (UDCA is optional. Avoid high doses). ERCP can be used in some to dilate dominant strictures. Majority will require liver transplantation</td>
<td>Some recommend annual screening using ultrason or MRCP and measurement of CA19-9 for cholangiocarcinoma and annual surveillance colonoscopies for colorectal carcinoma in patients with IBD and PSC</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Acute pancreatitis</td>
<td>HLA-DQA1-HLA-DRB1 (thiopurine induced)</td>
<td>Symptomatic therapy</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Autoimmune pancreatitis</td>
<td>–</td>
<td>Steroid therapy</td>
<td>None</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Large and small airway, upper airway and parenchymal disease</td>
<td>–</td>
<td>Inhaled or, in more severe cases, oral or intravenous steroids</td>
<td>ACOG recommend annual cervical screening for women with a history of chronic immunosuppression starting at 21. All women with IBD should strictly adhere to a screening program of cervical surveillance and undergo HPV vaccination at 9–26 years of age</td>
</tr>
<tr>
<td>Renal and Genitourinary</td>
<td>IgA Nephropathy</td>
<td>HLA-DRB1</td>
<td>Treat underlying inflammatory disease to prevent progression</td>
<td></td>
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<tr>
<td></td>
<td>Amyloidosis</td>
<td>–</td>
<td></td>
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<tr>
<td>Hematologic</td>
<td>Venous and arterial thromboembolisms</td>
<td>–</td>
<td>Prophylaxis with low-dose heparin for hospitalized or immobilized patients</td>
<td>No current screening recommendations for lymphoproliferative disorders in patients exposed to thiopurine therapy or thiopurine and anti-TNF combination therapy. Physicians should provide clear information about the risks associated with these therapies to their patients</td>
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<tr>
<td></td>
<td>Anemia of chronic disease</td>
<td>–</td>
<td>Erythropoietin</td>
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<td></td>
<td>Iron deficiency anemia</td>
<td>–</td>
<td>IV iron supplementation</td>
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<tr>
<td></td>
<td>Megaloblastic anemia</td>
<td>–</td>
<td>Oral supplementation of folate (1 mg per day) or intramuscular vitamin B12 (1000 μg per month)</td>
<td></td>
</tr>
<tr>
<td>Neurologic and Psychiatric</td>
<td>Peripheral neuropathies and central nervous system manifestations</td>
<td>–</td>
<td>Treat underlying neurologic disease</td>
<td>Screen for depression and anxiety at every office visit</td>
</tr>
</tbody>
</table>

or PSC. Surveillance is recommended every 2–3 years in patients with mild active inflammation, family history of CRC in a relative who is not less than 50 years of age, or history of post-inflammatory polyps. Finally, surveillance every 5 years is recommended for patients with only left-sided colitis, Crohn’s colitis with involvement of less than 50% of the colon, or extensive colitis but no active endoscopic and histologic inflammation.67,68

Furthermore, Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in IBD Patients International Consensus (SCENIC) also proposed evidence-based recommendations for the surveillance and management of colorectal dysplasia in IBD patients. In summary, these recommendations included the routine use of chromoendoscopy for the detection of dysplasia, the endoscopic removal of visible dysplasia, and, for patients with endoscopically invisible dysplasia that is confirmed by a gastrointestinal pathologist, referral to an endoscopist who is an expert in IBD surveillance using chromoendoscopy with high-definition colonoscopy.69 Chromoendoscopy with targeted biopsies has been found to have a higher sensitivity for detecting dysplasia and neoplasia than white light endoscopy with random biopsies.21

Smoking cessation

All patients with IBD should be encouraged to stop smoking.21 Smoking is associated with the development of CD.20 Also, patients with CD who are smokers have more disease progression, more frequent flares, higher rates of surgery, poorer medical and surgical outcomes, and an increased need for steroids and immunomodulators.20,21,38 These negative effects have been found to be dose dependent with higher tobacco load shown to be an independent predictor of stenosing phenotype.20 Therefore, any reduction in cigarette smoking is beneficial in improving disease course.21 Smoking cessation has been shown to decrease all of these risks stressing the importance of inquiring about tobacco use and discussing smoking cessation with IBD patients who are active smokers at every visit.38

Conclusion

IBD should be considered a systemic disease due to the high prevalence of EIMs and complications. Almost any organ system in the body may be affected, including those beyond the gastrointestinal tract, and in some cases, EIMs may be even more debilitating than the intestinal disease itself. Therefore, it is imperative that all measures be taken to quickly identify and adequately treat EIMs to minimize morbidity and mortality in affected patients. A thorough understanding of the current recommendations for screening and surveillance of EIMs in these patients is crucial and has the potential to greatly improve quality of life. Table I summarizes the EIMs in IBD, associated genes, treatment, and screening recommendations.

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