

Supplement Article

The Impact of Inflammatory Bowel Disease in Canada 2018: Extra-intestinal Diseases in IBD

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Abstract

The burden of extra-intestinal disease is high in patients with IBD, some of whom respond to or are prevented by treating the bowel inflammation, whereas others require specific treatment because they are independent of the underlying bowel inflammation. Among the most common extra-intestinal manifestations are other chronic immune-mediated diseases such as erythema nodosum, ankylosing spondylitis and primary sclerosing cholangitis. Patients with IBD are at higher risk of complications in other organ systems such as osteoporosis, venous thromboembolism and cardiovascular disease. In addition, patients with IBD have a higher risk of cancer, including colon cancer. Mental health comorbidity is important and common in IBD though not always recognized and managed. Consequently, patients and care providers need to be vigilant in the surveillance of extra-intestinal manifestations and complications of IBD.

Highlights

1. The burden of extra-intestinal disease is high in patients with IBD.
2. Immune-mediated inflammatory diseases (IMIDs) commonly coexist with patients with IBD and the activity of IMIDs can be either dependent or independent of bowel inflammation.
3. Patients with IBD can be diagnosed with coexisting diseases that affect every organ, including bones, blood, heart, liver, and others.
4. Patients with IBD are at increased risk of cancer, including colon cancer, caused by their bowel inflammation, cholangiocarcinoma due to primary sclerosing cholangitis, and rarely lymphoma related to immunosuppressive medications.
5. The best way to prevent or reduce the burden of many of the extra-intestinal disease is to treat the inflammation of IBD, however some extra-intestinal inflammatory diseases run courses that are independent of the intestinal disease activity.

Key Summary Points

1. Patients with IBD are often burdened with extra-intestinal manifestations, some of which respond to or are prevented by treating the bowel inflammation whereas others require specific treatment because they are independent of the underlying bowel inflammation.
2. Other immune-mediated inflammatory diseases (IMIDs) can coexist with IBD.
3. Some IMIDs run an independent course from the bowel inflammation of IBD, such as ankylosing spondylitis, iritis, and primary sclerosing cholangitis.
4. Immune-mediated inflammatory diseases that often have courses that match the bowel inflammation of IBD include erythema nodosum and peripheral arthritis.
5. Immune-mediated inflammatory diseases such as multiple sclerosis and psoriasis have been associated with IBD. However, these conditions may also emerge as complications of therapy for IBD.
6. Patients with IBD are at risk for venous thromboembolic disease, which occurs at a rate of one per 200 person-years.
7. Venous thromboembolic disease can be reduced by treating patients admitted to hospital with an IBD diagnosis with venous thromboembolism prophylaxis.
8. Arterial vascular disease is also increased in IBD patients, including both coronary artery disease and cerebrovascular disease.
9. Osteoporosis is more prevalent in IBD patients and translates to a 40% increased risk of fracture. While corticosteroids increase the risk of osteoporosis, patients with IBD can also develop metabolic bone disease independent of corticosteroid use.
10. Persons with IBD are more likely to be infected with *Clostridium difficile* than community controls and often without prior antibiotic exposure.
11. Mental health comorbidity is important in IBD. Depression may antedate a diagnosis of IBD by several years and increase post-diagnosis. High stress can exacerbate symptoms in IBD but does not necessarily increase bowel inflammation.
12. Fatigue is a common symptom in IBD and is not always explained by depression, active inflammatory disease or other apparent factors.
13. The risk of colorectal cancer is increased twofold in Crohn's colitis and in ulcerative colitis and 10-fold in persons with primary sclerosing cholangitis with colitis.
14. Primary sclerosing cholangitis runs a course independent of IBD and can progress to cirrhosis, liver transplantation or death. Patients with IBD and primary sclerosing cholangitis are at higher risk of cholangiocarcinoma, which is often fatal.
15. The risk of lymphoma may be increased in older males with Crohn's disease and in patients using thiopurines or anti-TNF therapy.
16. The risk for intensive care unit admission is nearly twofold higher for patients with IBD and higher in Crohn's disease than in ulcerative colitis. Risk factors for intensive care unit admission from the year before admission included cumulative corticosteroid use and IBD-related surgery.

Gaps in Knowledge and Future Directions

1. Patients with IBD are often burdened with extra-intestinal disease. Future research should determine the collective frequency and added costs of living with extra-intestinal disease.
2. Immune-mediated inflammatory diseases are commonly codiagnosed with IBD. Future research should focus on the pathogenesis connecting coexisting IMIDs with IBD.
3. Care pathways that support the investigation and mitigation of extra-intestinal disease are needed. For example, when and how ambulatory patients with IBD should receive prophylaxis against venous thromboembolic disease is unknown.
4. With an aging IBD population, the burden of extra-intestinal disease should be studied in the context of comorbidities of advancing age.
5. Increasing mental health screening and access to mental health care should be a goal of IBD management.

Keywords: *Extraintestinal diseases; Chronic immune mediated inflammatory diseases; Venous thromboembolic diseases; Osteoporosis; Clostridium difficile; Cancer; Mental health; Critical illness.*

Inflammatory bowel disease is associated with a number of conditions that are extra-intestinal. Some of these conditions are also chronic immune diseases that impact other organ systems, while others are common diseases in other organs that occur with increased frequency in persons with IBD. Inflammatory bowel disease is associated with a number of extra-intestinal diseases, and this adds to the potential burden for the patient and to the health care system. This section of the report will characterize the impact of extra-intestinal diseases on patients with IBD. A complete overview of the objectives, working committees and methodology of creating the report can be found in the online supplemental file, Technical Document.

IMMUNE-MEDIATED INFLAMMATORY DISEASES CLASSICALLY ASSOCIATED WITH IBD

In a population-based study using the University of Manitoba IBD Epidemiology Database (UMIBDED), it was reported that 6.2% of persons with IBD had one of six major extra-intestinal IMIDs studied, and 0.3% had multiple extra-intestinal IMIDs (1). Iritis/uveitis, which is a chronic or recurrent inflammatory eye disease, was the most common of these extra-intestinal diseases of all assessed (2.2% of women and 1.1% of men). Iritis/uveitis was most common among women with ulcerative colitis (3.8%) (1).

Primary sclerosing cholangitis (PSC), which causes stricturing and dilations within the extrahepatic and intrahepatic biliary tree, was most common among men with ulcerative colitis in the UMIBDED study (3%) (1). In a retrospective Danish population-based study of 222 persons with IBD and PSC (2.7%), PSC-IBD patients primarily had ulcerative colitis (72%) and were diagnosed in young adulthood (median age at IBD diagnosis: 23 years) (2). Among patients with PSC and ulcerative colitis, 78% had pancolitis at diagnosis. Among patients with PSC and Crohn's disease, 91% had colonic involvement. The 25-year cumulative risk of liver transplantation was high (53%). In a General Practice Research Database population-based study of primary care in the UK between 1998 and 2014, there were 250 newly diagnosed PSC patients identified (3). Only 54% had a history of IBD. The mortality rate per 1000 person-years was threefold higher in PSC than population controls (49.5 versus 16.1; incidence rate ratio 3.1; 95% CI, 2.2–4.2) (3).

In the UMIBDED study, ankylosing spondylitis, which is an inflammatory disease of the spine and sacroiliac joints, was more common among men, with the highest rate among men with Crohn's disease (2.7%) (1). Ankylosing spondylitis in persons with IBD behaves similarly to sporadic ankylosing

spondylitis, the form of the disease occurring in the absence of concurrent IBD. After 20 years, 470 of the 599 living members from the original Inflammatory Bowel South-Eastern Norway (IBSEN) cohort (78.5%) were investigated for joint diseases (4). Ankylosing spondylitis was diagnosed in 21 patients (4.5%), and axial spondyloarthritis in 36 patients (7.7%). The higher rates in the IBSEN cohort may reflect the inclusion of some asymptomatic persons diagnosed based on investigations.

In a meta-analysis of 71 studies reporting on the prevalence of sacroiliitis, ankylosing spondylitis and arthritis, the pooled prevalence of sacroiliitis was 10%, ankylosing spondylitis was 3%, and arthritis was 13% (5). Geographical area, setting and use of different criteria contributed to the large heterogeneity. Further, the UMIBDED report determined that arthralgia may be evident in up to 25% of persons with IBD, while frank inflammatory arthritis is seen in much fewer than 25% in IBD.

Pyoderma gangrenosum, which is an ulcerating skin lesion often seen in the lower extremities but which can also occur around stomas and in other areas of the body, was more common in Crohn's disease (1.2%), with no sex predilection in the UMIBDED study (1).

Erythema nodosum is a form of panniculitis most commonly involving bilateral pretibial areas that typically manifests as raised, tender, red nodules. Unlike the other diseases discussed above, which may run a course independent of IBD and, in fact, may present before an IBD diagnosis (6), erythema nodosum quite commonly flares when luminal disease activity flares. In the UMIBDED report, it was similarly present in Crohn's disease and ulcerative colitis but was more common among women (1.9%) (1). In some cutaneous manifestations, granulomas may be present on biopsy histology, similar to the granulomas seen on intestinal biopsies. These may be evident in perianal Crohn's disease or in metastatic Crohn's disease, which can present with hidradenitis suppurativa-like features (7).

Arthritis, iritis, ankylosing spondylitis, pyoderma gangrenosum and erythema nodosum can all respond to corticosteroids and may all respond to antibodies to tumour necrosis factor (anti-TNF) (8). Therefore, management of either Crohn's disease or ulcerative colitis, in the setting of one of these IMIDs, may be best approached using anti-TNF therapy so that the IBD and other IMIDs can be treated simultaneously.

OTHER IMMUNE-MEDIATED INFLAMMATORY DISEASES AND IBD

In another study using the UMIBDED, other less commonly associated extra-intestinal diseases were reported in IBD patients (9). The prevalence of asthma was 7.9% in ulcerative

colitis and 7.1% in Crohn's disease, which translates into an increased prevalence ratio (PR) compared with the general population for both ulcerative colitis (PR = 1.66; 95% CI, 1.46–1.88) and Crohn's disease (PR = 1.43; 95% CI 1.26–1.62). The risk of asthma was corroborated in cohorts from Quebec and Alberta (10, 11). The next most common pulmonary disease in IBD may be drug-induced pulmonary disease (12).

Persons with IBD have an increased risk of psoriasis compared with the general population (9). The prevalence was 1.7% in both ulcerative colitis and Crohn's disease; the PR was 1.65 (95% CI, 1.27–2.15) in ulcerative colitis and 1.59 (95% CI, 1.24–2.05) in Crohn's disease. While the risk of psoriasis may be increased in persons with IBD and anti-TNF therapy may be very effective in the treatment of psoriasis, anti-TNF therapy for the treatment of IBD has also been associated with inducing psoriasis (13). Antibodies to interleukin12/interleukin23, such as ustekinumab, have been shown to be effective in treating both Crohn's disease and psoriasis and, therefore, may be the optimal choice for therapy when these diseases coexist.

The prevalence of multiple sclerosis, which is a T cell mediated IMID manifested by demyelination and neural debility, was increased in ulcerative colitis (prevalence = 0.54%; PR = 1.9; 95% CI, 1.19–3.03) but was not shown to be increased in Crohn's disease (9). While multiple sclerosis may be more commonly seen in persons with ulcerative colitis, demyelinating syndromes including multiple sclerosis may be rarely induced by anti-TNF drugs (14).

In the UMIBDED study, chronic renal disease was found to have an increased risk in persons with ulcerative colitis, with a prevalence of 0.39% and a PR of 2.46 (95% CI, 1.40–4.35), but not for those with Crohn's disease (9). Using administrative data, it is difficult to discern the type of chronic renal disease (i.e., if it was drug-induced or autoimmune). However, 5-aminosalicylates, one of the commonly used therapies especially in ulcerative colitis, has been reported only rarely to cause tubulointerstitial nephritis (15).

For patients with IBD compared with the general population, both males and females have increased prevalence ratios for asthma, psoriasis and chronic renal disease, while only males have an increased prevalence ratio of multiple sclerosis (9).

ARTERIAL VASCULAR DISEASE AND IBD

A study using the UMIBDED reported that the risk for coronary artery disease was increased with an incidence rate ratio (IRR) of 1.26 (95% CI, 1.11–1.44) in both males and females with both Crohn's disease and ulcerative colitis (16). Researchers at the University of Miami undertook a four-year longitudinal cohort study of 356 persons with IBD and matched controls (17). The unadjusted hazard ratio (HR) for developing coronary artery disease in the IBD group was 2.85 (95% CI,

1.82–4.46). Despite the increased risk, persons with IBD have significantly lower rates of selected traditional coronary artery disease risk factors (hypertension, diabetes, dyslipidemia and obesity; $P < 0.01$ for all). Adjusting for these factors, the HR for developing coronary artery disease between groups was 4.08 (95% CI, 2.49–6.70).

In a large Spanish cohort study of 991,546 participants, the risk of cardiovascular disease was increased in a number of IMIDs; and in IBD specifically, the hazard ratio was 1.18 (95% CI, 1.06 to 1.32), which is similar to that calculated as part of the UMIBDED study (18).

In Manitoba, only Crohn's disease was associated with increased risk of cerebrovascular disease (IRR, 1.32; 95% CI, 1.05–1.66) (16). Increased risk of vascular disease in Crohn's disease patients in part may be related to the fact that persons with Crohn's disease are more likely to be smokers. The rationale for an increased risk of coronary artery disease in ulcerative colitis patients is less obvious.

In a meta-analysis of eight studies, IBD was associated with a modest increase in the risk of cerebrovascular disease incidence (HR = 1.29; 95% CI, 1.16–1.43). Both Crohn's disease (HR = 1.32; 95% CI, 1.13–1.56) and ulcerative colitis (HR = 1.18; 95% CI, 1.06–1.31) were associated with increased risk of cerebrovascular disease (19). The risk was higher in women (HR = 1.49; 95% CI, 1.24–1.79) than in men (HR = 1.22; 95% CI, 1.12–1.32).

In a second meta-analysis of six studies, IBD was associated with a modest increase in the risk of coronary artery disease (odds ratio [OR], 1.19; 95% CI, 1.08–1.31), both in patients with Crohn's disease and ulcerative colitis (20). This risk increase was seen primarily in women (four studies; OR, 1.26; 95% CI, 1.18–1.35), with no significant risk increase for men (20). In a meta-analysis of five studies, there was a modest increased risk of cerebrovascular disease (OR, 1.18; 95% CI, 1.09–1.27), especially among women (OR, 1.28; 95% CI, 1.17–1.41) compared with men (OR, 1.11; 95% CI, 0.98–1.25) (20). The increase in risk was observed for patients with Crohn's disease and ulcerative colitis. As the overwhelming majority of the evidence points to increased risks for potentially life-threatening vascular disease in persons with IBD, this adds to the burden of the disease. Further, clinicians need to be vigilant with assessing conventional risk factors for vascular disease in persons with IBD so they can be mitigated.

VENOUS THROMBOEMBOLISM

The first population-based report on the incidence of venous thromboembolism (VTE) in IBD patients was from the UMIBDED (21). In Crohn's disease, the incidence rate of deep venous thromboembolism (DVT) was 31.4 per 10,000 person-years, and the incidence rate of pulmonary embolism

(PE) was 10.3 per 10,000 person-years. In ulcerative colitis, the incidence rates were 30.0 per 10,000 person-years for DVT and 19.8 per 10,000 person-years for PE. The IRR was 4.7 (95% CI, 3.5–6.3) for DVT, 2.9 (95% CI, 1.8–4.7) for PE in Crohn's disease, 2.8 (95% CI, 2.1–3.7) for DVT and 3.6 (95% CI, 2.5–5.2) for PE in ulcerative colitis. There were no sex differences for IRR. The highest rates of DVT and PE were seen among patients over 60 years old. However, the highest IRR for these events was among patients less than 40 years old, meaning that the younger adults with IBD carry an even greater increased risk for DVT and PE than their unaffected counterparts. These data translate to a rate of DVT or PE of 1 per 200 patient-years.

In a multicentred Austrian study of 116 IBD patients who had a history of first VTE, 86 incidents were unprovoked (22). The probability of recurrence five years after discontinuation of anticoagulation therapy was higher among patients with IBD than patients without IBD (33.4%; 95% CI, 21.8–45.0 versus 21.7%; 95% CI, 18.8–24.6; $P = 0.01$). After adjustment for potential confounders, IBD was found to be an independent risk factor of recurrence (HR = 2.5; 95% CI, 1.4–4.2). In a subsequent study from this Austrian group, the incidence rate of all VTE was 6.3 per 1000 person-years, which was not dissimilar from the rate reported in the earlier UMIBDED study (23). Patients with VTE did not differ with regards to sex, underlying IBD or disease duration. Most VTEs (77.1%) were unprovoked, most (77.7%) occurred in outpatients, and most (60.9%) occurred in patients with active disease.

In a four-centre Canadian retrospective study, patients admitted under surgeons were more likely than those admitted under gastroenterologists to receive VTE prophylaxis (84% versus 74%, $P = 0.016$) (24). Of note, the rate of VTE was the same for those who did and did not receive VTE prophylaxis (2.2 per 1000 hospital days) (24). Among the 14 VTE events, 79% had received prophylaxis, but only 36% were within 24 hours of admission (24).

The increased risk of VTE is known for hospitalized patients, and most centres currently institute VTE prophylaxis for hospitalized patients with IBD. Because many VTEs occur in ambulatory IBD patients, there is a need for guidance in instituting VTE prophylaxis when IBD patients have acutely or chronically active disease.

OSTEOPOROSIS AND OSTEOPOROSIS-RELATED FRACTURE IN IBD

Osteoporosis increases the risk of fractures that are associated with significant morbidity, particularly those of the proximal femur (hip), vertebra and wrist and even mortality (related to hip fractures) (25–27). A study using the UMIBDED reported that persons with IBD have a 40% higher risk of fracture than do

age- and sex-matched controls without IBD (estimated at 40.8 per 10,000 person-years for IBD patients under 40 and 107 per 10,000 person-years for IBD patients aged 40 to 59) (28). This translates to a risk of fracture at about one per 100 patient-years. The proportion of seniors with IBD is also expected to rise over the next decade. This is consistent with general trends in the population and the compounding prevalence effect (see section 3), which will increase further the rates of osteoporosis-related fractures among IBD patients (29, 30).

Failure to attain peak bone mass when young and accelerated bone loss in adulthood are associated with an increased risk of fracture later in life (31). Therefore, it is possible that young persons with IBD with a high burden of inflammation or significant exposure to corticosteroids may suffer from bone mineral loss that would leave them at increased risk of fracture as they age (32). More aggressive treatment of inflammation earlier in the disease course and the more widespread use of steroid-sparing medication have the potential to decrease the risk of bone disease in IBD (33, 34). However, corticosteroids are not the only risk factor for osteoporosis—and more importantly, fractures—in persons with IBD. Hence, anyone with IBD with chronically active inflammatory disease should have their bone mineral density tested (35).

CLOSTRIDIUM DIFFICILE INFECTION

In Alberta, the risk of *Clostridium difficile* infection within five years of diagnosis with ulcerative colitis was 3.4% (95% CI, 2.5–4.6%) (36). The risk of colectomy was higher among ulcerative colitis patients diagnosed with *C. difficile* (sub-hazard ratio [sHR] = 2.36; 95% CI, 1.47–3.80). *Clostridium difficile* increased the risk of postoperative complications (OR = 4.84; 95% CI, 1.28–18.35) and was associated with mortality (sHR = 2.56 times; 95% CI, 1.28–5.10). In a study comparing laboratory diagnoses of *C. difficile* to administrative database diagnoses of *C. difficile*, there was a lack of specificity of the administrative diagnoses. Linking the Manitoba provincial database of *C. difficile* infections with the UMIBDED, investigators reported that individuals with IBD have a nearly fivefold increase in risk of *C. difficile* infections compared with individuals without IBD (37). There was no difference found between persons with ulcerative colitis and persons with Crohn's disease. Among individuals with IBD, exposure to corticosteroids, infliximab or adalimumab, metronidazole, hospitalizations, higher ambulatory care visits, shorter duration of IBD, and higher comorbidities were associated with an increased risk of *C. difficile* infections. Although *C. difficile* infections increased mortality among individuals with and without IBD, there was a one-third lower mortality after *C. difficile* infections among individuals with IBD compared with those without IBD. This study did not report an increase in *C. difficile* infections over time.

In a study from the University of Pittsburgh, it was shown that during the year of a *C. difficile* infection, having a *C. difficile* infection was significantly associated with more corticosteroid and antibiotic exposure and increased disease activity, worse quality of life and increased health care utilization (all $P < 0.01$) (38). During the next year after a *C. difficile* infection, patients continued to have increased exposure to *C. difficile* infection-targeted antibiotics ($P < 0.001$) and other antibiotics ($P = 0.02$). They also continued to have more clinic visits ($P = 0.02$), telephone encounters ($P = 0.001$) and increased health care financial charges ($P = 0.001$).

In a multicentre retrospective cohort study of patients with IBD admitted from 2011 to 2013 to tertiary centres in Toronto, Montreal, Ottawa, and Vancouver, IBD patients admitted to surgeons were less likely to be tested for *C. difficile* (41% versus 88%, $P < 0.0001$) (24).

In a 2011 study assessing the Nationwide Inpatient Sample in the United States to identify patients more than 18 years of age with a discharge diagnosis of either Crohn's disease or ulcerative colitis, 4% had *C. difficile* infections (39). Venous thromboembolism was present in 6% of the group with *C. difficile* infections versus 3% in the group without *C. difficile* infections ($P < 0.001$). After a multivariate analysis after propensity-score matching was performed, *C. difficile* infection was significantly associated with VTE (adjusted OR, 1.7; 95% CI, 1.4–2.2; $P < 0.001$). The increased risk was similar for Crohn's disease and ulcerative colitis with concurrent *C. difficile* infection (39).

Even though the rates of *C. difficile* infection are not increasing, it remains an important infection to recognize. Clinicians need to be vigilant to assess for *C. difficile* infections in persons with IBD with a flare of diarrhea. It is not yet clear whether immunomodulatory therapy should be interrupted when *C. difficile* infection is diagnosed; currently, most clinicians maintain immunomodulatory therapy during *C. difficile* infections (personal observation).

MENTAL HEALTH

Depression and anxiety disorders are at least twice as common in persons with IBD as the general population (40–42). These disorders can antedate the onset of IBD by years (42, 43). Hence, the relationship between depression and anxiety disorders and IBD is not just a secondary response to having a chronic disease. However, Ontario women with IBD who became pregnant were more likely to experience mood-related disorders in the post-partum period compared with women without IBD (44). Notably, women with Crohn's disease were almost three times more likely to visit physicians for substance-related disorders in the post-partum period compared with women without IBD.

The biological underpinning of the relationship between psychiatric disorders and IBD is unknown and not well studied. Fatigue is one of the most common, but poorly understood, IBD symptoms and may also, in part, reflect brain abnormalities (45). Fatigue is also a manifestation of depression. Fatigue has impacts on employment, social functioning and quality of life.

In a population-based longitudinal cohort study in Manitoba with approximately 600 persons answering surveys every three months for one year, a high perception of stress was associated with a flare of symptomatic IBD (46). In a subsequent study by this group, 485 persons with IBD, answering surveys every three months for one year and submitting stool samples for fecal calprotectin, reported that a high perception of stress was associated with a flare of symptoms. However, there was only a modest association between symptoms and ulcerative colitis, and no association between symptoms and Crohn's disease (47).

Treatment of depression, anxiety and the management of stress are important for enhancing positive outcomes, reducing nonadherence to medications and increasing quality of life.

CANCER

Because colorectal cancer (CRC) is the second leading cause of cancer deaths in the general population (48) and because the colon is the predominant site of involvement of IBD, CRC has always garnered special attention in IBD. Pooled results from population-based studies suggest an attenuation in the magnitude of CRC risk in persons with IBD over time (49). Similarly, Soderlund et al. report a several-fold decrease in CRC mortality over time among three successive cohorts of individuals with IBD in Sweden from the 1960s through 2004 (50).

Population-based data from Manitoba demonstrate a twofold increase in CRC incidence (HR = 1.95; 95% CI, 1.65–2.30) and CRC-related mortality (HR = 2.15; 95% CI, 1.60–2.89) among individuals with IBD as compared with those without IBD between 1987 and 2012 (51). In a stratified analysis, there was no decrease in HR for CRC mortality in later time periods. Similarly, a recent study from Northern California reported stable CRC incidence rates among individuals with IBD, with a 1.6-fold higher incidence than in the general population (52). This group also reported a standardized mortality ratio (SMR) for CRC in Crohn's disease patients of 2.3 (95% CI, 1.6–3.0) and for CRC in ulcerative colitis patients of 2.0 (95% CI, 1.3–2.7) among individuals diagnosed with IBD between 1998 and 2008. However, a recent study from Denmark reported that IBD patients no longer have a higher incidence of CRC (53), although substantially higher rates of colectomy in IBD patients in Denmark as compared with other jurisdictions may have influenced their findings (54).

A meta-analysis of eight population-based studies reports no overall increased risk of extra-intestinal cancers among individuals with IBD (55). However, these data were from an era of infrequent use of immunomodulators and biological agents, which have more recently been reported to increase the risks of non-Hodgkin's lymphoma (azathioprine/6MP) and both non-melanoma (thiopurines and anti-TNF) and melanoma (anti-TNF) skin cancers among individuals with IBD (56, 57). There is a male predilection for lymphoma at all ages and especially in relation to lymphoma diagnosed in the setting of immunomodulatory and biological therapy. While the highest incidence rate for lymphoma in IBD is among older males, just as in the general population, the highest IRR is among younger male adults. A more recent study based on Danish health care databases reports a standardized incidence ratio (SIR) of 1.3 (95% CI, 1.2–1.4) for Crohn's disease and 1.1 (95% CI, 1.0–1.1) for ulcerative colitis with respect to extra-intestinal cancers (58).

CRITICAL ILLNESS

A study using the UMIBDED reported that the risk for intensive care unit (ICU) admission is higher for patients with IBD than population controls (HR = 1.79; 95% CI, 1.58–2.02) (59). The risk of ICU admission was higher for patients with Crohn's disease (HR = 2.31; 95% CI, 1.95–2.75) than ulcerative colitis patients (HR = 1.37; 95% CI, 1.13–1.65). From 2000 through 2010, age- and sex-standardized annual incidence rates for ICU admission in the prevalent IBD cohort ranged from 0.55% to 1.12%. Compared with controls admitted to ICUs one year after ICU admission, mortality was 32% higher among patients with IBD.

The investigators in that study assessed predictors of ICU admission and health care utilization (HCU) post-ICU admission (60). Risk factors for ICU admission from the year before admission included cumulative corticosteroid use (IRR, 1.006 per 100 mg of prednisone; 95% CI, 1.004–1.008) and IBD-related surgery (IRR, 2.79; 95% CI, 1.99–3.92). Neither use of immunomodulatory therapies within one year nor surgery for IBD beyond one year prior were associated with ICU admission. In those who used corticosteroids and immunomodulatory medications in the year before ICU admission, the use of immunomodulatory medications conferred a 30% risk reduction in ICU admission (IRR, 0.70; 95% CI, 0.50–0.97). Persons with IBD who survived ICU admission had higher health services utilization in the year after ICU discharge than controls. Hence, it was concluded that corticosteroid use and surgery within the year are associated with ICU admission in IBD, whereas immunomodulatory therapy is not.

CONCLUSION

The burden of extra-intestinal disease is high in patients with IBD. Extra-intestinal disease may arise in any organ system of the body. The most common and complicated extra-intestinal

manifestations are other chronic IMIDs. Some IMIDs occur when IBD is active; examples include erythema nodosum and peripheral joint arthritis. Alternatively, other IMIDs like ankylosing spondylitis and primary sclerosing cholangitis run a course that is independent of bowel disease activity (i.e., they may progress even in patients whose IBD is in remission). Recent studies have expanded the scope of IMIDs with associations being made between IBD and IMIDs such as asthma and multiple sclerosis. Moreover, patients with IBD are at higher risk of complications in other organ systems such as osteoporosis, venous thromboembolism and cardiovascular disease. In addition, patients with IBD have a higher risk of cancer, including colon cancer likely caused by their bowel inflammation. Other cancer risks include cholangiocarcinoma in the setting of primary sclerosing cholangitis and lymphoma in the setting of ongoing immunosuppressive treatment. Consequently, patients and care providers need to be vigilant in the surveillance of extra-intestinal manifestations and complications of IBD. Ultimately, the most effective means of preventing or reducing the burden of most extra-intestinal diseases is to treat the underlying inflammation of IBD.

Acknowledgements

The authors would like to thank Shabnaz Siddiq who acted as a coordinator for this work, and Joseph Windsor and Fox Underwood who edited the articles. This work was funded by Crohn's and Colitis Canada. EB and GN were supported by New Investigator Awards from CIHR, Crohn's and Colitis Canada, and the Canadian Association of Gastroenterology. EB was also supported by the Career Enhancement Program from the Canadian Child Health Clinician Scientist Program. CB was supported in part by the Bingham Chair in Gastroenterology. GN and GK were CIHR Embedded Clinician Research Chairs.

Supplement sponsorship. This article appears as part of the supplement "The Impact of Inflammatory Bowel Disease in Canada 2018," sponsored by AbbVie Corporation and co-sponsored by Crohn's and Colitis Canada.

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