

Supplement Article

Crohn's and Colitis Canada's 2021 Impact of COVID-19 and Inflammatory Bowel Disease in Canada: Risk Factors and Medications

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ABSTRACT

Inflammatory bowel disease (IBD) is a disease that results from dysregulation of the immune system and frequently requires medications that can affect the immune response to infections; therefore, it was imperative to quickly understand the risk of coronavirus disease 2019 (COVID-19) infection on persons living with IBD and how that risk may be increased by commonly used IBD medications. The IBD research community in Canada and beyond quickly established collaborative efforts to better understand the specific risk posed by COVID-19 on persons with IBD. We learned that IBD itself was not a risk factor for death or serious complications of COVID-19, and that most commonly used drug classes (with the notable exception of corticosteroids) do not increase the risk of COVID-19-related adverse outcomes. The risk factors for serious complications and death from COVID-19 appear to be similar to those identified in the wider population; those being advanced age, having pre-existing heart or lung disease, and smoking. We recommend that persons with IBD do not alter their course of therapy to avoid complications of COVID-19, though the indiscriminate use of corticosteroids should be avoided. Persons with IBD should follow the same public health recommendations as the general population to reduce their personal risk of acquiring COVID-19.

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Key Messages

- Most people with IBD are not at increased risk of severe COVID-19 or death from COVID-19 as compared to the general population.
- No biologic medication has been shown to increase the risk of severe COVID-19 or death from COVID-19.
- Persons with IBD who are flaring and require a high dose of corticosteroids are at higher risk of acquiring or experiencing severe complications to COVID-19.
- Persons with IBD should stay on therapy to maintain remission as discontinuation of treatment due to fear of COVID-19 may lead to a flare requiring corticosteroids, which elevates the risk of worse outcome for COVID-19.

Keywords: *Biologics; COVID-19; Inflammatory bowel disease; Risk factors*

Introduction

At the outset of the pandemic, it was paramount to identify factors associated with an increased risk of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and, more importantly, which factors were associated with poor outcomes such as the need for hospitalization, ICU admission, mechanical ventilation or death. This concern was particularly acute among persons living with chronic immune-mediated diseases like inflammatory bowel disease (IBD), who not only suffer from immune dysfunction but are often on therapies that may affect their systemic immune system (1). At the beginning of the pandemic, it was unknown if persons with IBD would be more susceptible to infection and, if infected, at increased risk of poor outcomes.

Persons with IBD are more likely to suffer from infectious diseases than the general population (2). Prior to the emergence of coronavirus disease 2019 (COVID-19), several factors had already been identified that were associated with an increased risk of infections in people with IBD, including underlying disease activity, malnutrition, advanced age and certain therapies used to treat IBD. Many of these medications, in particular corticosteroids, purine anti-metabolites and anti-tumour necrosis factor (anti-TNF) biologics, have been associated with an increased risk of serious and opportunistic infections (3–7). Hence, there was concern that these may also be risk factors for contracting SARS-CoV-2 and developing severe complications of COVID-19. The most important questions to answer for persons living with IBD were:

1. Which individuals with IBD are at increased risk of poor outcomes of COVID-19?
2. Which medications commonly used by people with IBD increase the risk of poor outcomes from COVID-19?
3. What are the steps that individuals living with IBD who are at higher risk for serious complications of COVID-19 can take to reduce their personal risk?

Over the past year, there has been a significant expansion in our knowledge and many key learnings, including in the field of IBD. During this time, recommendations were updated in response to updated knowledge, especially about the behaviour

of the virus and strategies that were most effective in limiting its spread and its impact. In this article, we summarize our understanding about the risk of serious COVID-19 faced by persons with IBD, recommendations made by the Crohn's and Colitis Canada COVID-19 and IBD Taskforce to Canadians living with IBD and their health care providers regarding COVID-19 risk management, and what questions still remain unanswered.

GATHERING INFORMATION

The first article to specifically address how the novel coronavirus infection might impact persons with IBD reported that, among the 20,000 persons with IBD followed at China's seven largest IBD centres, none had yet been diagnosed with COVID-19 (8); this was the same as the early reports emerging out of Italy (9). By this time, advanced age, chronic cardiorespiratory disease, malignancy and obesity were being recognized as major contributors to COVID-19-related morbidity and mortality (10). Moreover, there did not appear to be an obvious signal of more severe outcomes in persons who either have diseases that suppress the immune system, or who are treated with immunosuppressive medications. However, as the risk of serious infection with COVID-19 had not yet been well characterized in persons with IBD, it was unclear whether persons with IBD should practise greater physical distancing and other preventative measures than persons who were otherwise healthy.

To understand the true impact of COVID-19 on the IBD community would require a large and comprehensive database of individuals with IBD who were diagnosed with COVID-19. The IBD research community was quick to mobilize to gather data on the IBD-specific risk of COVID-19 and established the Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) registry (11). This initiative sought physicians to register confirmed cases of COVID-19 among persons with IBD from all over the world. Within 1 month, there were sufficient data to draw some preliminary impressions about which individual and disease-related characteristics were potentially associated with an increased risk of serious COVID-19, defined as infections requiring hospitalization, ICU admission and/or mechanical ventilation, or those resulting in death. As

Table 1. Risk factors for worsened COVID-19 outcomes based on IBD medication

Drug class	Direction of increased risk
5-ASAs	0
Corticosteroids	
Over 20 mg/day in prednisone equivalents	++
Less than 20 mg/day in prednisone equivalents	?
Budesonide	0
Immunomodulators	+
Thiopurines (azathioprine/6-MP)	+
Methotrexate	+
Anti-TNFs	0
As monotherapy	0
In combination with thiopurines/methotrexate	+
Vedolizumab	0
Ustekinumab	0
Tofacitinib	0

0: no increased risk or no evidence of increased risk; ?: uncertain risk; ++: possible increased risk or probable small increased risk (use with caution in settings where risk of COVID-19 acquisition is appreciable); +++: definite increased risk (avoid unless no alternatives in settings where risk of COVID-19 acquisition is appreciable). ASA, Aminosalicylate acid; IBD, Inflammatory bowel disease; TNF, Tumour necrosis factor; 6-MP, 6-mercaptopurine.

more cases were reported to this registry, our understanding of the risk of a severe COVID-19 became more apparent. Despite, the uncertainty of the representativeness of the cases included in the SECURE-IBD registry, these data provide further reassurance as to the mild course of COVID-19 in the vast majority of people with IBD without additional non-IBD-related risk factors (12). Studies on risk factors for severe COVID-19 in those with IBD have also been corroborated in other study populations outside of the SECURE-IBD registry (13).

As of the end of April 2021, the SECURE-IBD database has nearly 6000 cases, of whom 15% were hospitalized for severe COVID-19 (14). The overall rate of requiring ICU admission or dying from COVID-19 was 4%. The strongest predictors of more serious COVID-19 or dying was advanced age (12% if aged 60 to 69 years, 18% if aged 70 to 79 and 25% if aged over 80 years), and having multiple other chronic medical conditions (33% rate of ICU admission or death in those with three or more chronic medical conditions, including IBD). For people under the age of 50, the risk of ICU admission or dying was around 1%. However, individuals under 50 with more severe disease activity were more likely to require hospitalization and have severe COVID-19 outcomes compared to those with mild disease or those in remission (15). Aside from corticosteroid use (13% risk of ICU admission or death), the risk of these more serious outcomes was low, ranging from 1% for persons using anti-TNF

monotherapy to 7% for persons using azathioprine or methotrexate. These results were not adjusted for age, so once again it could be that the higher rates of serious disease in persons using these drugs may be related to other factors, like the age and overall non-IBD health of those persons.

A research team at the University of Calgary developed an [interactive online dashboard](#) to visualize data from the SECURE-IBD registry such as depicting the IBD cases with COVID-19 by time, country, age, sex, disease type, disease activity and medication usage (Figure 1), which serves as a useful resource to the IBD community for accessing up-to-the-moment knowledge on COVID-19 risk factors for IBD (16). Additionally, the SECURE-IBD consortium has also developed an interactive tool to allow users to [calculate their risk](#) of developing severe COVID-19, based on the demographic and disease-related risk factors, which can be used to guide decisions about risk avoidance. The association between severe COVID-19 and the medications used to treat IBD are outlined below with recommendations in a subsequent section.

MEDICATIONS, DISEASE ACTIVITY AND OTHER RISK FACTORS

A summary of the association of commonly used IBD drugs and the risk of COVID is shown in Table 1.

Steroids

The use of corticosteroids, particularly at doses above 20 mg daily, was more frequently seen among persons who developed severe COVID-19. This may reflect the high levels of systemic immunosuppression resulting from high-dose steroid use and/or the severity of active disease.

Anti-TNF Therapy

In the initial release of data, there was no definite signal that anti-TNF use was associated with a higher risk of severe COVID-19.

5-Aminosalicylate Acid

Although the initial analysis found an association between 5-aminosalicylate acid (5-ASA) use and a higher rate of adverse outcomes, this was not believed by most to be plausible, given that 5-ASAs are not known to have a systemic immunosuppressive effect. In subsequent analyses on a larger number of individuals, the association between 5-ASAs and adverse events was no longer detected.

Immunomodulators

The most recent publication from SECURE-IBD in October 2020 detailed COVID-19 infections in 1439 persons with IBD in 47 countries. The main finding regarding medications was that the use of thiopurines, with or without anti-TNF therapy, was associated with a fourfold higher risk of developing severe

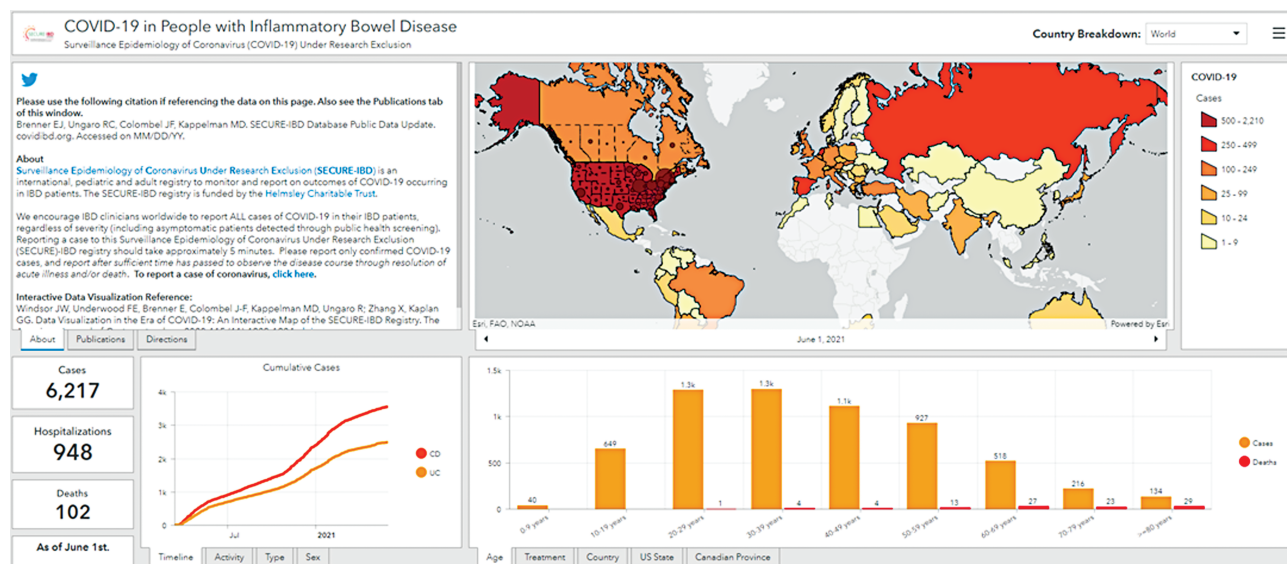


Figure 1. Interactive online dashboard and map of COVID-19 cases in those with inflammatory bowel disease (IBD) derived from the Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) database on June 1, 2021: Link to online interactive map: <https://kaplan-secure-ibd-ucalgary.hub.arcgis.com/>. Persons at the highest risk were those who were of 65 years of age or older, those with serious non-IBD-related medical comorbidities like advanced cardiovascular and pulmonary disease, those using over 20 mg of prednisone daily, those with moderate-to-severe inflammation or malnutrition and those on total parenteral nutrition. Persons at moderate risk were those under the age of 65 who were using immunomodulatory or biologic. All other persons with IBD were classified as being at average risk (i.e., the same as the general population).

COVID-19 outcome (hospitalization and/or death) than using anti-TNF therapy alone (14).

Newer Biologics: Vedolizumab and Ustekinumab

Persons who were using vedolizumab were not found to be at higher risk of severe COVID-19 outcomes when compared to people using anti-TNFs (17). There are no definitive data on the risk associated with ustekinumab, though this agent, like vedolizumab, has not been associated with an increased risk of infection in general (18). Furthermore, ustekinumab use has not been shown to increase the risk of COVID-19 in persons with psoriasis, another autoimmune condition where ustekinumab is commonly used (19).

Small Molecules: Tofacitinib

By December 2020, the SECURE-IBD group also reported that users of tofacitinib were not at increased risk of severe COVID-19 when compared to users of biologic medications (20).

Disease Activity

Early publications from the SECURE-IBD registry described a higher risk of severe COVID-19 among individuals with severely active IBD. Further analyses of this association indicated that moderately and severely active IBD (as defined by the Physician's Global Assessment) is associated with hospitalization; severely active IBD was associated with ICU admission, mechanical ventilation or death only in people ≤50 years of age, after adjusting for corticosteroid use (15).

Other Risk Factors

Throughout the publications from the SECURE-IBD registry, rates of severe COVID-19 were highest in persons with advanced age, and those with multiple concomitant medical comorbidities; this is similar to the general population.

Importantly, data from population-based European health care registries have also suggested that having IBD on its own likely did not increase the risk of COVID-19 (21–23). Therefore, independent of medication use, the risk of more serious COVID-19 in persons with IBD was due mostly from the same types of risk factors that are seen in the general population, including advancing age, chronic lung and heart disease, obesity and smoking. At this time, there is no definite evidence that having previously undergone intestinal surgery increases the risk of developing more serious COVID-19. However, inflammation and a history of intestinal resections can increase the risk of malnutrition, and malnutrition may be a risk factor for more severe COVID-19. Therefore, the risk of more severe outcomes for people with more active IBD must still be considered.

TASKFORCE RECOMMENDATIONS

Based on the initial data from SECURE-IBD as well as applying what is known generally about the risk factors for infection in IBD, the Crohn's and Colitis Canada COVID-19 and IBD Taskforce developed its first set of [risk-based recommendations](#) on how to limit the acquisition of SARS-CoV-2 and the development

of COVID-19. These recommendations are updated regularly as new information became available about the impact of IBD therapies on the risk of severe COVID-19. Persons with IBD were separated into **three risk categories**, with different levels of physical distancing and shielding recommended based on the degree of risk. These recommendations were based both on data from SECURE-IBD and extrapolated from factors known to increase the risk of infection-related morbidity in the general population.

The Taskforce also stressed the importance of not abruptly discontinuing effective medications without a discussion of the risks and benefits with their IBD specialists and/or primary care providers. Also, although newer biologic agents such as vedolizumab and ustekinumab are thought to have a lower risk of infections, it is unknown about their impact in the setting of COVID-19. In addition, there were some data that even suggested that persons using anti-TNF agents may be at lower risk than non-users for developing severe COVID-19. However, it is premature to consider anti-TNF users to be at lower risk than other persons with IBD. The Taskforce also advised physicians to avoid prescribing corticosteroids unless there were no other reasonable alternatives, given the higher rate of COVID-19 seen in the preliminary SECURE-IBD data along with the known risks posed by corticosteroid use for infection.

Overall, while the emergence of COVID-19 has increased the level of concern among persons with IBD and the people involved in their care, the overall impact of IBD on COVID-19-related adverse outcomes would appear to be fairly small. The risk of severe COVID-19 outcomes is primarily driven by non-IBD-related factors, like heart and lung health, age and being excessively over or underweight. Corticosteroid use appears to significantly increase the risk of severe COVID-19, and the indiscriminate use of corticosteroids should be discouraged. As for other medications, their impact on COVID-19 risk is likely small. The Taskforce recommends that any decisions made about medications in persons with COVID-19 should be made under the close monitoring of a gastroenterologist.

We also recommend that persons with IBD continue to follow public health advice on physical distancing, mask wearing, being promptly tested for symptoms suggestive of COVID-19 or if exposed to a known case of COVID-19 and be vaccinated at the first available opportunity. It is hoped that over the coming year, with greater rates of vaccination, that the risk of acquiring COVID-19 will be significantly reduced, and with it, the concern about the impact it has on IBD.

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CONFLICT OF INTEREST

E.I.B. has acted as a legal consultant for Hoffman La-Roche Limited and Peabody & Arnold LLP for matters unrelated to medications used to treat inflammatory bowel disease and has received honoraria from McKesson Canada. He is Chair of the Scientific and Medical Advisory Council of Crohn's and Colitis Canada. C.N.B. is supported in part by the Bingham Chair in Gastroenterology. He is on Advisory Boards for AbbVie Canada, Amgen Canada, Bristol-Myers Squibb, Janssen Canada, Pfizer Canada, Roche Canada, Sandoz Canada and Takeda Canada. He is a Consultant for Mylan Pharmaceuticals and Takeda. He has received educational grants from AbbVie Canada, Pfizer Canada, Takeda Canada and Janssen Canada. He is on the speaker's panel for AbbVie Canada, Janssen Canada, Pfizer Canada, Takeda Canada and Medtronic Canada and received research funding from AbbVie Canada, Pfizer Canada and Sandoz Canada. A.B. has participated in advisory boards with AbbVie, Janssen, Pfizer, Takeda, Hoffman-LaRoche and Amgen. He has received research support from AbbVie. He has received educational support from Fresenius Kabi and Takeda. G.G.K. has received honoraria for speaking or consultancy from AbbVie, Janssen, Pfizer and Takeda. He has received research support from Ferring, Janssen, AbbVie, GlaxoSmith Kline, Merck and Shire. He has been a consultant for Gilead. He shares ownership of a patent: Treatment of Inflammatory Disorders, Autoimmune Disease, and PBC. UTI Limited Partnership, assignee. Patent WO2019046959A1. PCT/CA2018/051098. 7 September 2018. P.L.L. has been a speaker and/or advisory board member for AbbVie, Amgen, Arena Pharmaceuticals, Fresenius Kabi, Genentech, Gilead, Janssen, Merck, Mylan, Pharmacosmos, Pfizer, Roche, Takeda, Tillotts and Viartis and has received unrestricted research grant from AbbVie, Takeda and Pfizer. R.P. reports consultant work for AbbVie, AGI Therapeutics, Alba Therapeutics, Amgen, Astellas, Athersys, Atlantic Healthcare, BioBalance, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eisai Medical Research, Elan, EnGene, Eli Lilly, Enteromedics, Ferring, Flexion Therapeutics, Genentech, Genzyme, Gilead, Given Imaging, GlaxoSmithKline, Human Genome Sciences, Ironwood, Janssen, Merck & Co., Merck Research Laboratories, Merck Serono, Nisshin Kyorin, Novo Nordisk, NPS Pharmaceuticals, Optimer, Orexigen, PDL Biopharma, Pfizer, Procter and Gamble, Santarus, Shire Pharmaceuticals, Sigmoid Pharma, Sirtris (a GSK company), Sandoz, S.L.A. Pharma (UK), Targacept, Teva, Therakos, Tillotts, TxCell SA, Speaker's fees for AbbVie, Amgen, Celgene, Ferring, Janssen, Merck, Novartis, Pfizer, Prometheus, Sandoz, Shire, Takeda Advisory board attendance for AbbVie, Abbott, Allergan, Amgen, Biogen Idec, Eisai, Ferring, Genentech, Janssen, Merck, Shire, Elan, GlaxoSmithKline, Hospira, Pfizer, Bristol-Myers Squibb, Takeda, Cubist, Celgene, Salix and Roche and research/educational support from AbbVie, Ferring, Janssen, Shire Takeda. L.E.T. has received research funding from AbbVie Canada, Takeda Canada,

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