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Impact of Inflammatory Bowel Disease in Canada

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Foreword

What is the burden of inflammatory bowel disease (IBD), how can it be quantified, and what is the value of measuring it? As an organization it's our goal to improve the quality of life of everyone affected by Crohn's disease and ulcerative colitis and to find the cures. This comprehensive report provides a valuable resource in understanding the impact on Canadians and areas of need.

First and foremost, the burden encompasses the personal impact on the lives and health of Canadians affected by IBD. We are becoming ever more aware that the impact is not just the significant health impact of IBD itself, but also the mental health toll, the lost time at school and work, as well as the impact on caregivers. The impact also encompasses the financial cost to healthcare systems across the country as well as the individual and family out-of-pocket expenses or private insurance plan costs.

In this report, we took on some topics that had not been studied in depth in the past, including questions surrounding mental health, cancer, and treatment options currently available.

The value of assessing the impact is that it provides all stakeholders across Canada with the best and most current information available. The findings are vital, whether used to guide research, treatments, and increasingly to address how best to provide care or address the unequal impact on various affected groups.

We are thankful to the 100+ experts and people affected by IBD who contributed to this report. We are especially grateful to Drs Gil Kaplan and Eric Benchimol, who led the report's development. They drew upon the nation's best scientific minds to amass a wealth of statistics, giving the report a clear Canadian focus that puts individuals at the heart of recommendations.

We hope that you find the information valuable in understanding these diseases, whether you yourself have a form of Crohn's or colitis, know someone who does, or are involved in any way in the IBD community across Canada.

Lori Radke

Lori Radke
President and CEO
Crohn's and Colitis Canada

ANECDOTALLY I KNEW THAT IBD WAS VERY PREVALENT IN CANADA BECAUSE ANYTIME SOMEONE FINDS OUT I HAVE CROHN'S DISEASE, THEY KNOW WHAT I AM TALKING ABOUT BECAUSE THEY KNOW SOMEONE ELSE IN THEIR LIFE WITH EITHER CROHN'S DISEASE OR ULCERATIVE COLITIS. THIS RESEARCH SHOWS JUST HOW MANY CANADIANS ARE IMPACTED BY IBD AND THE NUMBERS ARE STAGGERING.

THE IMPACT OF IBD IN CANADA REPORT IS SO IMPORTANT FOR CONTINUED AND UP-TO-DATE EDUCATION OF IBD FOR THOSE AFFECTED BY THESE DISEASES, GOVERNMENT AND POLICY-MAKERS, AND THE GENERAL PUBLIC.

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Glossary

5-AMINOSALICYLATE ACIDS (5-ASA):
An anti-inflammatory medication used to treat different parts of the lower gastrointestinal tract by reducing inflammation and allowing the intestines to heal. (Examples: Pentasa®, Salofalk®, Mezavant®.)

ABSCESS:
A collection of pus, frequently due to bacterial infection.

ABSENTEEISM:
Absence from paid work due to sick days/leave, unemployment, short-term and long-term disability, early retirement, premature death, and caregiver leave.

ACCELERATION IN INCIDENCE (STAGE 2):
The second stage of IBD evolution in which a dramatic rise in the number of new cases of IBD are seen each year, but where the total number of people living with IBD is still relatively low.

ADALIMUMAB:
A type of anti-TNF biologic medication marketed in Canada under brand names Hurmira®, Abrilada®, Simlandi®, Yuflyma®, Hyrimoz®, Idacio®, Amgevita®, Hulio®, and Hadlima®.

ADENOVIRUS-VECTOR:
A vaccine delivery system that uses a non-infectious virus to introduce genetic material from another virus into a person and train their immune system to fight off the harmful virus if they come in contact with it in the future.

ALBUMIN:
A protein that circulates in the blood and keeps blood vessels functioning properly. It can be tested to help determine organ (liver and kidney) health and the general health of an individual.

ALL-CAUSE MORTALITY:
Death recorded in health databases, regardless of the cause of death. Contrasted with IBD-specific mortality (for example), where the recorded cause of death is specifically linked to IBD (rare).

ALLIED HEALTHCARE:
This term encompasses other medical professionals or treatments outside of primary medical care, for example dietitians or mental health professionals.

AMBULATORY CARE:
Care provided in outpatient settings, i.e., without being admitted to hospital.

ANTIBODIES:
Proteins made by white blood cells in response to an antigen. Antibodies neutralize antigens.

ANTI-DRUG ANTIBODIES:
As above, but antibodies that neutralize a medicine, causing it to be ineffective. Individuals can create anti-drug antibodies to several medications used to treat IBD, especially biologic medications.

ANTIGEN:
A foreign/toxic substance that causes the body to mount an immune response.

ANTI-TNF (ANTI-TUMOR NECROSIS FACTOR ALPHA):
Drugs that help stop inflammation; used for inflammatory diseases like ulcerative colitis and Crohn's disease (e.g., Adalimumab or Infliximab).

AUTOIMMUNE DISEASE:
A disease that causes the body's immune system to attack itself, where the immune system attacks otherwise healthy tissue.

AVERAGE ANNUAL PERCENT CHANGE (AAPC):
The mean (average) value of all increases or decreases to a rate across a given time span, given as a percentage.

AZATHIOPRINE:
An immunosuppressive medication used to control the immune response in a variety of conditions, including IBD.

BA.1/BA.4/BA.5 SUBVARIANTS:
Members of the omicron family of the SARS-CoV-2 virus, which are descendant from the originator strain that began infecting humans in late 2019.

BARIUM ENEMA:
A contrast material inserted rectally to highlight the large bowel so it can be better imaged by x-ray.

BASAL CELL CARCINOMA (BCC):
A type of skin cancer that starts in the cells responsible for replacing old skin cells with new ones (basal cells).

BIOLOGICS:
Drugs made from living cells that have large, complex molecular structures. Some biologic medications are engineered to target specific activity in the immune system to treat inflammation.

BIOPSYCHOSOCIAL:
A term that covers three distinct areas that may all require treatment or help: biological, psychological, and social.

BIOSIMILAR:
A medication that has no clinically meaningful differences from the biologic medication it is based on, which has already been approved for treatment. Biosimilars are typically much less expensive than their biologic originator drugs.

BIVALENT VACCINE:
A vaccine that contains strains from two variants of a virus e.g., the originator SARS-CoV-2 virus and the Omicron SARS-CoV-2 strain.

BODY-MASS INDEX (BMI):
A score based on height and weight that helps determine if an individual is underweight, at a healthy weight, or overweight.

BREAKTHROUGH INFECTION:
A viral infection that occurs despite the individual being vaccinated against the virus. For example, people who have received a COVID-19 vaccine may still develop COVID-19, though often with reduced severity.

BURDEN
The collective impact of a disease on the individual, their caregivers, and society. Burden can be measured in terms of the number of people newly diagnosed each year, the total number of people with the disease, rates of healthcare utilization, and the associated costs of care, among other factors.

CANDIDIASIS:
A fungal (yeast) infection.

CARCINOGENIC:
A substance known to be a potential cause of cancer.

CEREBROVASCULAR DISEASE:
Disease affecting the blood vessels in the brain.

CHIMERIC:
Having parts from different origins, a result of a mutation or combination of separate proteins (e.g., white blood cells produce specific antibodies based on normal anatomy and the anatomy of an invading cell or virus).

CHROMOENDOSCOPY/ VIRTUAL CHROMOENDOSCOPY:
This is a type of endoscopy procedure that uses stains to locate cancers in the lining of the digestive tract. Virtual chromoendoscopy refers to the technology used to provide better contrast between the normal tissue and stains.

CLINICAL REMISSION:
Partial or total disappearance of clinical symptoms or biochemical markers of disease. For example, no visible inflammatory markers in bloodwork.

COGNITIVE BEHAVIOURAL THERAPY (CBT):
A type of psychotherapy that challenges negative perceptions to help treat mental health disorders such as anxiety or depression.

COLECTOMY:
Surgical resection of part or all of the colon.

COLONOSCOPY:
An imaging study where a camera is inserted into the colon to allow the physician to view or biopsy the large intestine.

COMBINATION THERAPY:
Using two or more drugs to manage a single disease. For example, simultaneous use of a thiopurine and an anti-TNF to control IBD.

COMORBIDITIES:
Two or more disorders or illnesses occurring in the same person.

COMPASSIONATE USE PROGRAM:
Emergency assistance programs whereby pharmaceutical companies cover the cost of medications for low-income individuals.

COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM):
Non-pharmaceutical therapies used to assist pharmaceutical therapies in treating an illness. For example, anti-inflammatory diets that may help reduce gut inflammation.

COMPOUNDING PREVALENCE (STAGE 3):
The third stage of IBD evolution in which the number of new cases of IBD seen each year stabilizes, but where the total number of people living with IBD increases exponentially.

CONCOMITANT IMMUNOMODULATORS:
Medications that suppress the immune system (e.g., azathioprine, 6-mercaptopurine, methotrexate) used together with biologics to improve the effectiveness of the biologics, reduce the rate of elimination of the biologics from a person's body, or decrease the formation of anti-TNF antibodies.

CONNOR-DAVIDSON RESILIENCE SCALE:
A validated psychological scale to rank resiliency in individuals and assess baselines and progress in resiliency during treatment.

CORTICOSTEROIDS:
A class of drug that suppresses the immune system and lowers inflammation in the body. Examples include prednisone, prednisolone, methylprednisolone, and hydrocortisone.

CROSS-SECTIONAL IMAGING:
Medical imaging that provides a series of images representing narrow portions of the body. For example, CT (computerized tomography), MRI (magnetic resonance imaging), or ultrasound.

CYTOKINES:
Small proteins important in cell signaling. Cytokines are part of the body's immune response to infection.

CYTOMEGALOVIRUS COLITIS:
A virus in the herpes family that may cause gastrointestinal symptoms similar to many symptoms of IBD.

DIRECT COSTS:
Healthcare expenditures for medically necessary services and treatments, paid for by public and private payers, including hospital-based care, outpatient physician consultations, prescription medications, diagnostic tests, diagnostic and therapeutic procedures, complex continuing care, and home care. Some direct costs are also borne by the individual; these are referred to as out-of-pocket costs.

DISABILITY:
Chronic limitations that hinder the ability to engage in usual daily activities. Disability may also refer to a government-paid assistance or tax credit resulting from chronic limitations on the individual.

DIVERTICULOSIS:
A condition where small bulges (called diverticula) occur in the digestive tract. Diverticulitis, perhaps a more commonly known term, is when the diverticula become inflamed or infected.

DYSBIOSIS:
An imbalance in the healthy gut microbiota.

DYSPLASIA:
The presence of abnormal cells within an organ, which may evolve into cancer.

EARLY-INDUSTRIALIZED COUNTRIES:
Regions that had their industrial revolution prior to World War II.

EHEALTH:
Virtual options for healthcare, including telemedicine, mobile applications, and video conferencing.

EMERGENCE (STAGE 1):
The first stage in the evolution of IBD in which sporadic cases of IBD begin to be diagnosed within a population. Both the annual rate of new diagnoses and the total population living with IBD are low.

ENDOMETRIOSIS:
A condition whereby tissue similar to the uterine lining (the endometrium) is located outside of the uterus causing chronic inflammation and possibly other adverse effects over time.

ENDOSCOPIC HEALING:
The absence of visual inflammation or ulceration during endoscopy.

ENDOSCOPY:
A procedure in which an instrument is introduced into the body to give a view of its internal parts.

EOSINOPHILS:
A type of white blood cell that is part of the immune response in combating infections.

EPIDEMIOLOGY:
The study and analysis of the distribution, patterns, and determinants of health and disease conditions in defined populations.

EPITHELIUM:
A thin layer of skin that lines all internal and external surfaces of the body, including the intestines.

EPSTEIN-BARR VIRUS:
A virus in the herpes family that can cause infections such as mononucleosis.

ESTROGEN:
A hormone that is associated with female reproductive health, though it is naturally found in both males and females, but in greater abundance in females.

ETIOLOGY:
The cause or causes of a particular condition or disease.

ETRASIMOD:
A sphingosine-1-phosphate (S1P) inhibitor. S1P is a mediator of cytokines and can be used to control or prevent inflammation. Etrasimod is not yet approved to treat IBD (specifically, ulcerative colitis) in Canada.

EXCLUSIVE ENTERAL NUTRITION (EEN):
A nutritional liquid provided orally or through a gastronomy/nasogastric feeding tube, temporarily replacing all food and drink.

EXTRA-INTESTINAL:
A manifestation of disease or associated disease outside of the intestinal tract. For example, Crohn's disease may present with red sores on the skin called erythema nodosum.

FECAL CALPROTECTIN:
A biochemical measurement of the protein calprotectin in the stool. Elevated fecal calprotectin occurs during intestinal inflammation, including inflammation caused by inflammatory bowel disease.

FECAL MICROBIAL TRANSPLANT:
A process whereby feces from a healthy donor are transplanted into the intestine of a person with intestinal disease in an attempt to restore the proper balance of healthy microbes in the gut (also called fecal microbiota transplant).

FIBROSTENOTIC DISEASE:
Crohn's disease in which the bowel wall has undergone scarring (fibrosis), resulting in narrowing and stiffening (stenosis) and eventually blockage (obstruction). It is thought to result from chronic, untreated inflammation.

FILGOTINIB:
A Janus kinase (JAK) inhibitor used to treat inflammatory diseases by limiting cytokine activity. Filgotinib is not yet approved in Canada for use in IBD.

FISTULA/FISTULAE:
A fistula (plural: fistulae) is a malformation where a tunnel forms inside the body between two organs; for example, connecting the rectum and the vagina or the rectum and the external skin surface.

FLARE:
A period of active inflammation where a person may experience worse symptoms of disease.

FRAILTY:
The condition of being weak and delicate typically indicated by unintentional weight loss (10 or more pounds within the past year), muscle loss and weakness, a feeling of fatigue, slow walking speed, and low levels of physical activity.

GENDER:
An individual's sense of self relating to how they portray themselves to the world (gender identity), potentially but not necessarily relating to sex. Gender may be masculine, feminine, non-binary, two spirit, or many other nuanced identifications of gender.

GENDER-NONCONFORMING:
Identifying as a gender distinct from the sex a person was born into.

GENOME/GENOMIC:
The complete set of genetic material present in an organism.

GEOMETRIC MEAN TITER:
An average of logarithmic test values (for example, antibody levels after a vaccine dose) converted to a real number in order to better understand or visualize data about concentrations of a substance within the blood.

GRANULOMA:
A small area of inflammation seen under a microscope.

GUSELKUMAB:
An IL-23 inhibitor used to treat inflammatory diseases by blocking the signaling pathways that trigger inflammation. Guselkumab is not yet approved in Canada for use in IBD.

HAZARD RATIO:
A ratio of hazard rates related to a condition being examined among those exposed versus those not exposed to the condition. For example, the ratio of contracting COVID-19 between those who are vaccinated and those who are not vaccinated over a given time period.

HEALTH SERVICES:
Medically necessary services used by persons with illness, encompassing hospital-based care, outpatient physician consultations, diagnostic tests, diagnostic and therapeutic procedures, complex continuing care, and home care.

HEALTH-RELATED QUALITY OF LIFE (HRQOL):
An individual's or group's perceived physical, mental, emotional, and social functioning over time.

HEMATOLOGIC MALIGNANCY:
Cancers of the blood.

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT):
Infusion of stem cells that can develop into different types of blood cells used for treating individuals with damaged or defective immune systems.

HEMOGLOBIN:
The part of the blood responsible for transporting oxygen.

HERPES ZOSTER VIRUS:
The virus that causes chicken pox and shingles.

HEPATOBILIARY:
Pertaining to the liver, bile ducts, and/or gallbladder.

HEPATOSPLENIC T-CELL LYMPHOMA (HSTCL):
A rare type of lymphoma (see definition below), which involves expansion of a subset of lymphocyte T-cells known as gamma delta T-cells, often seen in association with immunosuppression and especially azathioprine alone or in combination with biologics.

HEPATOTOXICITY:
Damage to the liver, most frequently by chemicals, drugs, toxins, or other substances from outside the body.

HORMONE REPLACEMENT THERAPY:
Medical supplementation of hormones, such as estrogen, to treat various disorders or for gender affirming procedures.

HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS):
A score commonly used by doctors to determine an individual's level of anxiety and depression.

HUMAN CAPITAL:
The intangible value that a person has due to their abilities, skills, and knowledge.

IBD COMMUNITY:
The IBD community is the total population of people who have or are affected in some way by IBD. Having IBD means different things to various members of this community. For some, it remains an invisible disease that others may not know an individual has. For others, they wear the scars, ostomy bags, or worry on their face from the various surgeries, medical treatments, or concern over coping with this disease. This community also includes the parent of a child with IBD, the partner of a person with IBD, or the children of adults/seniors with IBD. It is impossible to sum everything that being part of the IBD community can mean to the many individuals who are included.

ILEAL POUCH-ANAL ANASTOMOSIS:
A type of surgery where the large intestine is removed. More commonly called a J-pouch surgery.

ILEOCECAL:
A sphincter muscle located at the end of the small intestine (ileum) and beginning of the large intestine (cecum).

ILEOCOLONIC:
The portion of the bowel that includes the final part of the small intestine (ileum) and the beginning part of the colon or large intestine.

IMMUNE-MEDIATED INFLAMMATORY DISEASES (IMID):
Chronic diseases in any organ system that involve abnormal inflammation.

IMMUNOCOMPROMISED:
Having a deficient immune system, either related to disease or medication. For example, some medications used to treat IBD limit the immune response and therefore leave individuals on that medication immunocompromised.

IMMUNODEFICIENCY:
An inadequate immune system to fight off infection.

IMMUNE SYSTEM AGING (IMMUNOSENESCENCE):
The changes in the immune system associated with age.

IMMUNOGENICITY:
A measure of the type of immune responses a vaccine generates and magnitude over time.

IMMUNOMODULATORS:
Medications (e.g., azathioprine, 6-mercaptopurine, methotrexate) that modify the activity of the immune system and decrease inflammatory responses.

IMMUNOSUPPRESSANT:
A medication that suppresses the immune system, typically used to subdue immune dysregulation, such as in IBD.

INCIDENCE:
The number of new diagnoses of a given disease (e.g., IBD) made in a geographic region in a year.

INCIDENCE RATE RATIO:
A relative difference measure used to compare the incidence rates (rates of new events) occurring at any given point in time. It is the rate of one outcome over the rate of another outcome (for example, the rate of developing cancer among people with IBD over the rate of developing cancer in the general population).

INDIRECT COSTS:
Costs borne by individuals and society that are not covered by third party payers, such as lost productivity due to illness and disability, premature retirement, premature death, and lost productivity of caregivers.

INDUCTION THERAPY:
An introductory therapy used to put an individual's disease into remission (as opposed to maintenance therapy, used to keep an individual's disease in remission).

INFUSION:
The process of receiving medication intravenously.

INFLIXIMAB:
A type anti-TNF biologic medication marketed in Canada under brand names Remicade®, Renflexis®, Inflectra®, and Remsima®.

INPATIENT CARE
Medical care received as part of a hospital admission.

INSIGHTSCOPE:
A proprietary web application and technology platform used for systematic reviews.

INTANGIBLE COSTS:
Costs to the individual or society that are not directly tied to a monetary value—lost opportunity.

INTEGRATED MODEL OF CARE (IMC):
Multidisciplinary care where an individual has access to several needed healthcare practitioners within a single system or care team.

INTEGRIN INHIBITOR:
Integrins are proteins that play a role in the pathogenesis of IBD due to their role in immune cells. Integrin inhibitors regulate the immune system by decreasing immune cell trafficking.

INTERLEUKIN-1 (IL-1) RECEPTOR ANTAGONISTS:
A type of drug used in the management of IBD by preventing IL-1 signal pathways, which are responsible for some forms of inflammation.

INTERLEUKIN-12/23 (IL-12/23) INHIBITOR:
A type of drug used in the management of IBD by preventing IL-12 and IL-23 pathways, which are involved in adaptive immune responses.

INTESTINAL PERMEABILITY:
The ease with which substances (e.g., nutrients) pass through the intestinal wall.

IONIZING RADIATION:
A type of radiation that people are exposed to during imaging studies, such as x-ray or computerized tomography, but not magnetic resonance imaging.

ISCHEMIC COLITIS:
A condition resulting from interrupted blood flow to (part) of the large intestine.

JANUS KINASE (JAK) INHIBITOR:
A class of anti-inflammatory medication that works by modifying the immune system through inhibiting cytokine action.

J-POUCH:
See ileal pouch-anal anastomosis.

KNOWLEDGE TRANSLATION:
A term increasingly used in science that describes the process of transitioning generated knowledge from research to various stakeholders to inform decision-making and application to real-world problems.

LEFT-SIDED ULCERATIVE COLITIS:
Colitis affecting the descending colon and rectum—the portion of the large intestine on a person's left side.

LGBTQ2S+:
An initialism representing: lesbian, gay, bisexual, trans, queer and questioning, two spirit, and additional members of this community not specifically named in the initialism.

LYMPHOMA:
A type of cancer that begins from the immune system cells called lymphocytes, which are found mostly in the lymph nodes, spleen, thymus, and bone marrow. The two main types of lymphoma are non-Hodgkin and Hodgkin lymphoma, which involve different types of lymphocytes.

LYMPHOPROLIFERATIVE DISORDER:
A condition that causes uncontrolled production of lymphocytes—white blood cells—which may cause inflammation.

MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY:
An imaging study that uses an intravenous dye to visualize the pancreatic and biliary duct systems.

MAGNETIC RESONANCE ENTEROGRAPHY (MRE):
A type of magnetic resonance imaging that uses contrast to visualize the intestines.

MAINTENANCE THERAPY:
Treatment for IBD started once remission has been achieved; aimed at keeping an individual in remission and ensuring the bowel remains healed.

MALIGNANCY:
Another term for a cancerous tumour.

MEDICALLY REFRACTORY:
A disease or condition that does not respond to treatment.

MELANOMA:
A type of skin cancer that develops in melanocytes (skin cells that contain pigment called melanin).

MESALAMINE:
An anti-inflammatory medication used to treat IBD in the 5-ASA family.

MESENCHYMAL STEM CELL TREATMENT:
Infusion of stem cells that can develop into different types of connective and skeletal tissues.

MESENTERY:
The tissue that adheres the intestines to the abdominal wall.

MESSENGER RIBONUCLEIC ACID (MRNA):
A single-stranded molecule that carries genetic code from DNA in a cell's nucleus to ribosomes, the cell's protein-making machinery. MRNA is a method for delivering a part of a virus—in the case of SARS-CoV-2, the non-infectious spike protein only—into a person so that their immune system can recognise the virus and fight it off in the future if encountered again.

META-ANALYSIS:
A type of study that examines data from several pre-existing studies on a defined topic to look for trends that hold across the different studies (frequently amalgamating data from several world regions).

METABOLOMIC:
Relating to metabolism.

METHOTREXATE:
An anti-inflammatory medication that works by supressing the body's immune system.

MEVALONATE KINASE DEFICIENCY:
A metabolic condition that can lead to inflammation and various gastrointestinal symptoms, among other effects.

MICROBIOME:
A community of microorganisms including bacteria, fungi, and viruses, living in an environment such as the human intestine.

MICROSCOPIC COLITIS:
A type of colitis that is not visible to the naked eye during colonoscopy and must be identified using a microscope.

MIRIKIZUMAB:
An IL-23 inhibitor used to treat inflammatory diseases by blocking the signaling pathways that trigger inflammation. Mirikizumab is not yet approved in Canada for use in IBD.

MONOCLONAL ANTIBODY:
A type of medication that mimics the body's natural immune system in order to modify the immune response.

MONOGENIC:
Related to genetic disease and involving or controlled by a single gene.

MONOTHERAPY:
A single pharmaceutical therapy to manage disease.

MORBIDITY:
The proportion of a population who contracts a specific disease or state (e.g., COVID-19). Also, comorbid/comorbidity: having another disease or condition at the same time (e.g., comorbid IBD and rheumatoid arthritis).

MORTALITY:
Mortality is another term for death; in epidemiology, mortality rates are used to understand the burden of disease.

MUCOSA:
The inner lining of organs such as the intestine.

MUCOSAL HEALING:
The lack of ulceration or inflammation in the mucosa of the intestines.

MULTIDISCIPLINARY:
Involving specialists of various disciplines, such as gastroenterologists, rheumatologists, pulmonologists, general practitioners, IBD nurses, mental health specialists, and dietitians.

MYELOTOXICITY:
Bone marrow suppression leading to decrease in cell distribution, such as the cells responsible for immunity, among others.

NEOPLASTIC LESION:
An abnormal growth that may or may not be cancerous.

NETWORK META-ANALYSIS (NMA):
A type of meta-analysis that compares three or more factors through direct and indirect comparison.

NEUTRALIZING ANTIBODIES:
An antibody that defends a cell from a pathogen or infectious particle by neutralizing any effect it has biologically.

NEWLY INDUSTRIALIZED COUNTRIES:
Regions that have experienced economic advancement leading to a societal shift towards industrialization and urbanization since World War II.

NOCEBO EFFECT:
The opposite of a placebo effect where a medical therapy fails due to the belief that it will fail rather than ineffectiveness of the treatment.

NON-MEDICAL SWITCH POLICY:
A policy implemented by a governing organization (e.g., a provincial government) that mandates individuals receiving medical coverage through that organization (e.g., provincial healthcare) must switch from an originator biologic medication to a biosimilar medication for cost saving rather than medical reasons.

NON-REPLICATING VIRAL VECTOR:
A viral vector vaccine uses a harmless version of a different virus, called a vector, to deliver information into the cells to tell the cells to produce a protein that is encoded by that information. The vaccine teaches the body to make copies of the spike proteins so the body can recognize it, create antibodies, and fight off the real virus later.

NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID):
Drugs that treat inflammation without the use of steroids. Many of these medications are available over the counter, such as aspirin or ibuprofen.

NUCLEAR FACTOR-KAPPA B MODULATOR DEFICIENCY:
A condition that causes dysregulation of the immune system by affecting signaling pathways of cells.

ODDS RATIO, RISK RATIOS, AND CONFIDENCE INTERVALS:
An odds ratio is comparison of the odds of developing a given outcome for those exposed to a particular factor as compared to the odds of developing the outcome if unexposed to the factor being investigated. The risk ratio is the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group. The confidence interval (typically 95%) estimates the likelihood of a true value falling in that range if an experiment is repeated over and over—the more narrow the interval, the more accurate the statistic is likely to be. If both numbers in a confidence interval are negative, the result is a significant decrease/reduction. If both numbers in a confidence interval are positive, the result is a significant increase. If the two numbers in a confidence interval cross zero (0), the result is not statistically significant.

OMICRON:
The 15th letter of the Greek alphabet and the name given to the BA/XBB lineage of the SARS-CoV-2 virus, which were the predominant strains of the virus circulating in Canada since December 2021 (to the time of writing: April 2023).

OPPORTUNISTIC INFECTION:
An infection that occurs more frequently in people with weakened immune systems.

OSTEOPOROSIS:
A degenerative condition that weakens bones.

OSTOMY:
A surgical opening between the bowel and the body surface for fecal-waste collection after some bowel resection surgeries.

OUT-OF-POCKET COSTS:
Medical or other costs associated with receiving care that the individual is responsible for, i.e., not covered by healthcare or insurance.

OUTPATIENT VISIT:
See ambulatory care.

OZANIMOD:
Ozanimod is marketed under the label Zeposia®. It is a sphingosine-1-phosphate (S1P) inhibitor. S1P is a mediator of cytokines and can be used to control or prevent inflammation. Ozanimod was approved in 2022 to treat ulcerative colitis in Canada.

PANCOLITIS:
Ulcerative colitis affecting the entire large intestine.

PAPANICOLAOU TEST:
A test that collects cells from the cervix to test for cancer in females.

PARTIAL ENTERAL NUTRITION:
Similar to exclusive enteral nutrition except that only 30%–50% of the nutrition comes from a formula rather than regular food.

PATHOBIOLOGY:
The study of the pathogenesis (see below) of disease that focuses on biological aspects rather than medical aspects.

PATHOGENESIS:
The manner or mechanism of disease development.

PATIENT-CENTERED:
An approach to care that focuses on the needs and wants of the individual, while balancing what is medically necessary to improve quality of life and control the disease.

PAXLOVID:
An oral antiviral medication used to treat COVID-19.

PEDIATRIC-ONSET:
Disease beginning before adulthood, typically considered to be before age 18.

PENETRATING DISEASE:
Crohn's disease in which the inflammation has resulted in abnormal passageways (fistulae) between the bowel and areas outside the bowel, such as the intra-abdominal cavity, other organs, or the skin. These passageways can sometimes become blocked, resulting in pockets of infection (abscesses).

PERIANAL DISEASE:
Disease affecting the anus, the final section of the colon.

PERIPHERAL ARTHRITIS/ARTHRALGIA:
Arthritis that affects the large joints such as the elbows, wrists, knees, and/or ankles. Arthralgia is joint stiffness, but not necessarily arthritis (inflammation of the joints).

PERIPHERAL VASCULAR DISEASE:
A progressive disease that causes narrowing or blockage of blood vessels.

PERSON-YEARS
For each year a person spends in an at-risk population (for example, the total Canadian population who could develop IBD), they contribute one person-year to a study. In a study of incidence across five years, for example, each person at risk of developing IBD would contribute five person-years to the overall measure.

PHENOTYPE:
A set of characteristics that differentiates different types of disease. For example, Crohn's disease and ulcerative colitis are different phenotypes of IBD.

PHOTOSENSITIZER:
Molecules that can be activated by light to perform their specific functions.

PNEUMOCOCCAL VACCINE:
A vaccine (preventative medicine) against the pneumococcal virus—the virus that causes certain types of pneumonia.

POLYPHARMACY:
Use of multiple medications simultaneously, for multiple purposes (not simply multiple drugs to control IBD).

POPULATION-BASED STUDY:
A type of study that examines the entire population at risk (total population of a given area), or a representative sample of that population.

POST ACUTE COVID-19 SYNDROME:
Symptoms of COVID-19 that persist after the initial infection has passed.

POST HOC ANALYSIS:
A data analysis that takes place after data collection rather than something that was planned before data collection.

POST-MONONUCLEOSIS B-CELL LYMPHOMA:
A type of cancer associated with the Epstein-Barr virus.

POUCHITIS:
Inflammation that occurs in a pouch—an artificial pocket created after some surgeries to treat IBD such as colectomy.

PRECISION MEDICINE:
Healthcare or therapy designed for maximum benefit to the individual or a group of individuals.

PREDNISONE:
A type of steroid that supresses the immune system used to get an IBD flare under control—not typically used for maintenance therapy, but necessary for some individuals.

PRESENTEEISM:
Reduced productivity at work due to illness.

PREVALENCE:
The number of people living with IBD in a geographic region at a point in time.

PREVALENCE EQUILIBRIUM (STAGE 4):
A theoretical forth stage of IBD evolution where the total number of people with IBD remains stable year over year. No region has yet transitioned into stage 4.

PRIMARY SCLEROSING CHOLANGITIS (PSC):
A chronic inflammatory disease of the bile ducts.

PROBIOTIC:
A substance that stimulates growth of micro-organisms and promotes a healthy gut microbiome.

PROSPECTIVE COHORT STUDY:
A study that follows a group of people for a predetermined time. Contrasted with a retrospective cohort study, which selects a group of people and looks into their history.

PROTEOMIC:
Pertaining to proteins, organic compounds consisting of one or more amino acids.

PSEUDOPOLYPS:
Protrusions from the intestinal mucosa resulting from the healing of ulcerations.

PSORIASIS:
An autoimmune disease, causing inflammation of the skin.

PSORIATIC ARTHRITIS:
An autoimmune disease that causes inflammation of the joints and an overproduction of skin cells.

PSYCHOGASTROENTEROLOGY:
The field of study that focuses on the brain-gut axis and recognises the bidirectional link between mental health and gut health.

PSYCHOSOCIAL:
The area that overlaps between psychological and social factors.

PSYCHOSOMATIC:
A physical condition caused or exacerbated by a mental factor (e.g., anxiety or depression).

PSYCHOTHERAPY:
An umbrella term for therapy used to treat psychological concerns.

QUALITATIVE RESEARCH:
Research that relies on non-numerical data to understand themes or experiences. Contrast with quantitative research, which uses numerical data to analyze trends or outcomes.

QUALITY-ADJUSTED LIFE YEARS:
An analysis that estimates the quality and duration of life after medical intervention (e.g., medication or surgery).

QUALITY OF LIFE (QOL):
A broad, multidimensional concept that usually includes subjective evaluations of both positive and negative aspects of life.

RADIATION ENTERITIS:
Inflammation of the intestines following radiation therapy.

REACTIVE OXYGEN SPECIES:
An unstable molecule containing oxygen and reacting with other molecules in their environment.

REAL-WORLD EVIDENCE (RWE):
Data on healthcare observed and documented during routine clinical practice.

RESILIENCE:
The ability to adapt to difficult situations or recover from difficulties.

RANDOMIZED CONTROLLED TRIAL (RCT):
A scientific experiment that aims to reduce bias by randomly allocating subjects to two or more groups, treating them differently, and then comparing them with respect to a measured response (e.g., vaccinated versus placebo study groups against COVID-19).

RHEUMATOID ARTHRITIS:
An autoimmune disease that causes joints to become inflamed, usually many joints at the same time.

RIZANKIZUMAB:
An IL-23 inhibitor marketed under the name Skyrizi® approved in Canada to treat Crohn's disease as of 2022.

SELECTIVE NORADRENALINE RECEPTOR INHIBITOR:
A type of drug used to treat mental health disorders such as depression.

SELECTIVE SEROTONIN RECEPTOR INHIBITOR (SSRI):
A type of drug used to treat mental health disorders such as depression, particularly severe cases.

SELF-EFFICACY:
A person's confidence in their own ability to achieve a goal.

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 (SARS-COV-2) AND CORONAVIRUS DISEASE, DISCOVERED 2019 (COVID-19):
SARS-CoV-2 is the virus that causes COVID-19 in people who are infected; COVID-19 is the disease that results from infection with the SARS-CoV-2 virus.

SEROCONVERSION:
Becoming antibody positive based on blood test.

SEROCONVERSION RATE:
The rate of people who mount an immune response to an infection or foreign substance (e.g., the COVID-19 spike protein after infection or vaccination), detectable as antibodies in the bloodstream.

SEROLOGY:
Blood testing.

SERO-NEGATIVE:
A negative value on a serology test. For example, someone may be sero-negative for anti-nucleocapsid antibodies to SARS-CoV-2, indicating that they never had COVID-19. Contrastively, the same person may be sero-positive for anti-spike antibodies to SARS-CoV-2 due to receiving a vaccine that targets the spike protein of that virus.

SEX:
Separate from gender, sex identifies the biological characteristics of an individual based on their chromosomes.

SHIELDING:
With respect to public health emergencies, the act of protecting an individual or population from the effects of the emergency (e.g., protective measures taken during the COVID-19 pandemic).

SMALL MOLECULE:
A class of drugs that easily enter cells due to low molecular weight. In IBD, small molecule drugs can be JAK inhibitors or S1P inhibitors.

SOCIODEMOGRAPHIC:
Sociodemographic variables are factors that situate an individual or group within the broader society, such as age, sex, education level, or household income.

SOCIOECONOMIC:
Socioeconomic status situates an individual or group within brackets of household income. Socioeconomic factors can influence lifestyle behaviours, including access to nutrition, allied healthcare, or access to specialist care, among other things.

SOMATIZATION:
The physical realization of symptoms without an observable cause, such as the link between mental health and IBD activity.

SONOGRAPHIC:
Visualization of sound waves, such as is used in ultrasound.

SPIKE PROTEIN:
A protein which protrudes from the outside of a coronavirus, enabling the virus particle to enter a host cell by binding to a receptor on the host cell's surface. This is the portion of the virus used in currently approved vaccines against COVID-19.

SPHINGOSINE-1-PHOSPHATE (S1P) INHIBITOR:
S1P inhibitors are a class of small molecule drugs that regulate lymphocytes and lymph nodes (cells that are part of the immune response) entering circulation.

SPONDYLOARTHRITIS:
A type of arthritis that predominately affects the spine.

SQUAMOUS CELL CARCINOMA (SCC):
A type of skin cancer that develops in a particular type of skin cell called squamous cells.

SQUAMOUS INTRAEPITHELIAL LESION (SIL):
A concentration of abnormal cells that may become cancerous.

STANDARD DEVIATION
A standard deviation provides information about how spread-out data are from an average value. A small standard deviation indicates that most of the data are clustered together around the average value, while a large standard deviation indicates that there is more variability among data in the sample.

STANDARDIZED INCIDENCE RATIO (SIR):
An estimation of the number of cases of a given disease expected within a population based on the number of cases observed in a larger population. A higher SIR indicates that the population is at greater risk of a disease than the larger population it is being compared to.

STEP-UP THERAPY:
This term refers to an approach to treatment where individuals start with an introduction therapy and are then upgraded as needed to manage the disease specific to the individual.

STOMA:
An artificial (i.e., surgical) opening leading to a hollow organ, such as from the surface of the skin to the intestines.

STRICTURING DISEASE:
A complication of IBD that causes a narrowing of the intestines due to scar tissue that develops from repeated cycles of uncontrolled inflammation.

SUBMUCOSA:
The tissue below the mucosal layer of an organ.

SUBMUCOSAL FIBROSIS:
Thickening or scarring of submucosal tissue, frequently due to repeated or uncontrolled inflammation.

SURVEILLANCE EPIDEMIOLOGY OF CORONAVIRUS UNDER RESEARCH EXCLUSION (SECURE-IBD):
An international database to monitor and report on outcomes of COVID-19 occurring in people with IBD.

TELEMEDICINE:
The remote diagnosis and treatment of individuals by means of telecommunications technology (including telephone, video, email, smartphone apps, and wearable devices).

THIOPURINES:
A class of immunosuppressive medication used for the treatment of IBD (e.g. azathioprine, 6-mercaptopurine).

TOFACITINIB:
A type of medication marketed under the brand name Xeljanz® that acts to inhibit certain enzymes (called JAK 1 and JAK 3) and maintain remission. Xeljanz® is approved in Canada to treat ulcerative colitis.

TOXIC MEGACOLON:
A rare and potentially life-threatening condition that presents with extreme inflammation of the colon.

TUMOR NECROSIS FACTOR ALPHA (TNF-A):
A protein in your body produced during acute inflammation, responsible for a range of cell signalling events and important for the body's ability to resist infection. Anti-TNF biologics are antibodies that destroy this protein.

TRANSMISSIBILITY:
The probability of an infection, given contact between an infected individual and non-infected individual.

TRANSMURAL HEALING:
Restoration of normal bowel wall thickness, indicating the absence of inflammation in any layer of the intestinal tissue.

TROUGH CONCENTRATION:
The amount of a medication present in the body immediately before receiving another dose.

UPADACITINIB:
A JAK inhibitor marketed under the name Rinvoq®. Upadacitinib is yet to be approved in Canada to treat IBD.

URBANIZATION:
The process of a society becoming more urban, i.e., becoming more city-like.

USTEKINUMAB:
A type of biologic drug marketed under the brand name Stelara® that acts to suppress certain cytokines (IL-12 and IL-23) from triggering an inflammatory response.

UVEITIS/IRITIS:
Chronic or recurrent inflammatory disease of the eye.

VARIANT:
In the context of this report, variant specifically describes viral variants: Mutations from an originator virus. Variants may change how infectious a virus is, or the symptoms or severity of a virus. A sub-variant is a further mutation of a variant. For example, Omicron is a variant of the SARS-CoV-2 virus, and XBB is a sub-variant of Omicron.

VEDOLIZUMAB:
A type of biologic drug marketed under brand name Entyvio® that acts to reduce the ability of white blood cells in the gut from entering the tissue to cause inflammation.

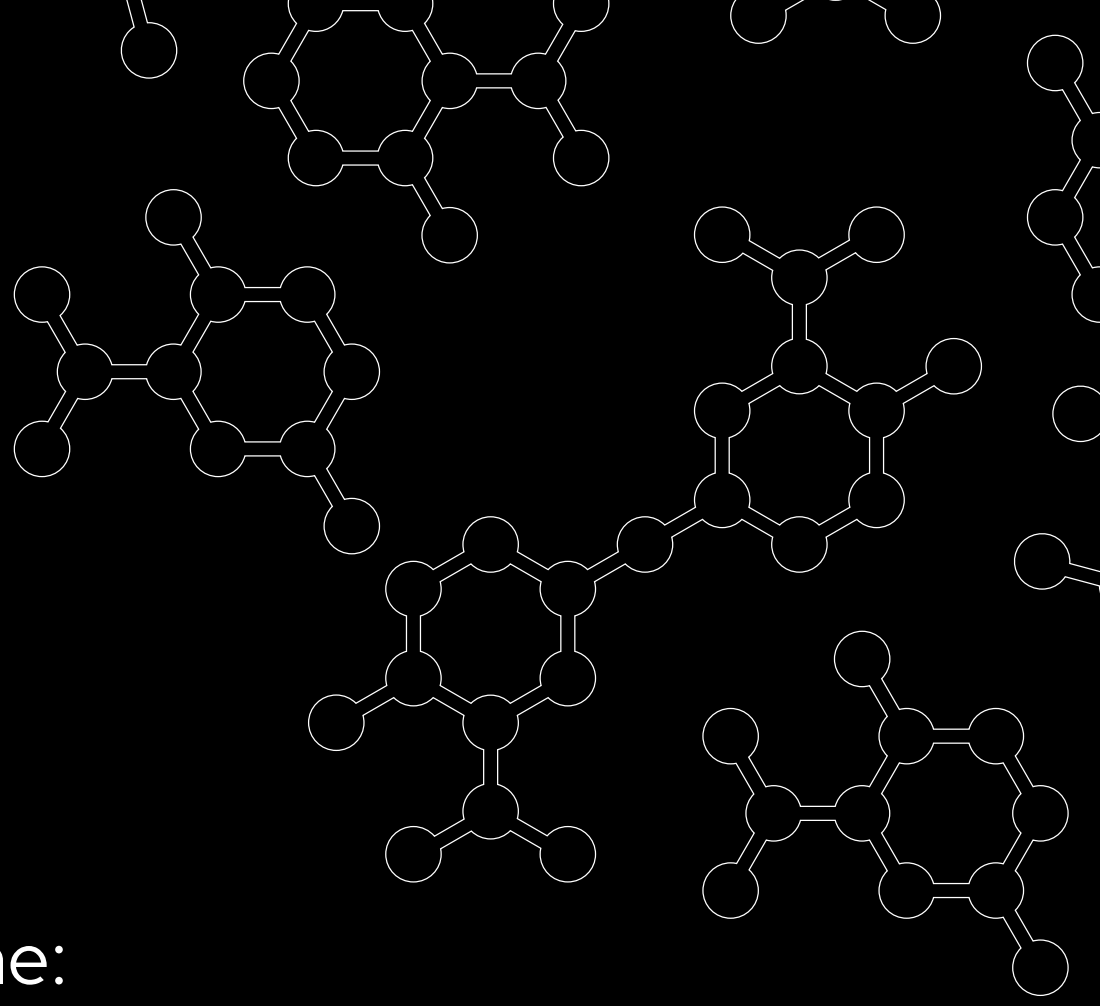
VENOUS THROMBOEMBOLISM:
A blood clot in a large vein most typically occurring in the deep veins of the leg, pelvis, or lungs.

VERY-EARLY-ONSET IBD (VEOIBD):
Onset of IBD before age six.

VIRTUAL HEALTHCARE:
Remote healthcare making use of telemedicine, digital applications, and/or videoconferencing.

WESTERNIZATION:
The process of a society adopting some cultural, dietary, and lifestyle aspects of the Western world.

WHOLE EXOME SEQUENCING:
A type of genetic sequencing used to understand the determinants of disease.



Section One:

Executive Summary

Executive Summary

Abstract

The burden of inflammatory bowel disease (IBD) (i.e., associated direct and indirect costs, the number of people living with the disease, and the personal impact to individuals and caregivers) continues to increase in Canada. The prevalence (the total number of people living with the disease) of IBD has increased since Crohn's and Colitis Canada's 2018 Impact of Inflammatory Bowel Disease in Canada report from an estimated 270,000 Canadians living with IBD in 2018 to an estimated 322,600 Canadians living with IBD today in 2023. Consequently, associated costs of IBD have also dramatically increased from an estimated $2.57 billion in 2018 to an estimated $5.38 billion in 2023; this increase is due to multiple factors including increased prevalence of disease, inflation, and additional identified factors (e.g., presenteeism, costs of childcare). Beyond the economic impact of IBD, these diseases have a significant impact on people living with the disease and their caregivers, including different presentations of disease, different commonly associated extra-intestinal manifestations or comorbid conditions (i.e., affects outside of the bowel, or associated secondary diseases), and different barriers to accessing care.

In this 2023 updated report, we review: Evolving trends in the epidemiology of IBD; updated estimates of indirect and direct costs (including out-of-pocket costs) associated with IBD; information specific to IBD in children, adolescents, and seniors; issues related to IBD pertaining to sex and gender; information specific to risks associated with COVID-19 and cancer related to IBD; an overview of current treatments for IBD; and evolving care models, including access to care.

Key Points

1. The epidemiologic trends of IBD in Canada show similar patterns to those reported in Crohn's and Colitis Canada's 2018 Impact of Inflammatory Bowel Disease in Canada report. The prevalence of disease is continuing to grow rapidly such that approximately 470,000 (1.1% or 1 in 91) Canadians are forecast to be living with IBD by 2035.

2. IBD imparts a significant cost to individuals with the disease, family caregivers of those individuals, the economy, and healthcare systems. In Canada, in 2023, IBD is estimated to cost $5.38 billion in combined direct, indirect, and out-of-pocket costs ($2.05 billion in indirect and out-of-pocket, $3.33 billion in direct), and this may be an underestimate of the true burden.

3. The impact of IBD is different for different portions of the population (e.g., children and adolescents, seniors, Indigenous peoples, immigrants to Canada, members of the LGBTQ2S+ community, or those of disadvantaged socio-economic status); these subpopulations experience different complications of IBD and/or different barriers to accessing care.

4. Several medical therapies used to treat IBD suppress the immune system of those being treated. However, only high-dose corticosteroids (>20mg/day) were found to increase the risk of severe COVID-19 (e.g., hospitalization, ICU admission, death). Continuing medical therapy to maintain IBD remission and receiving booster vaccines against SARS-CoV-2 are important factors in lowering COVID-19 risks.

5. Colorectal cancer occurs 1.5–2 times more often in people with IBD compared to the general population—but the absolute risk of cancer remains low. Regular, high-quality surveillance colonoscopy procedures are important for early detection and management of potential cancers.

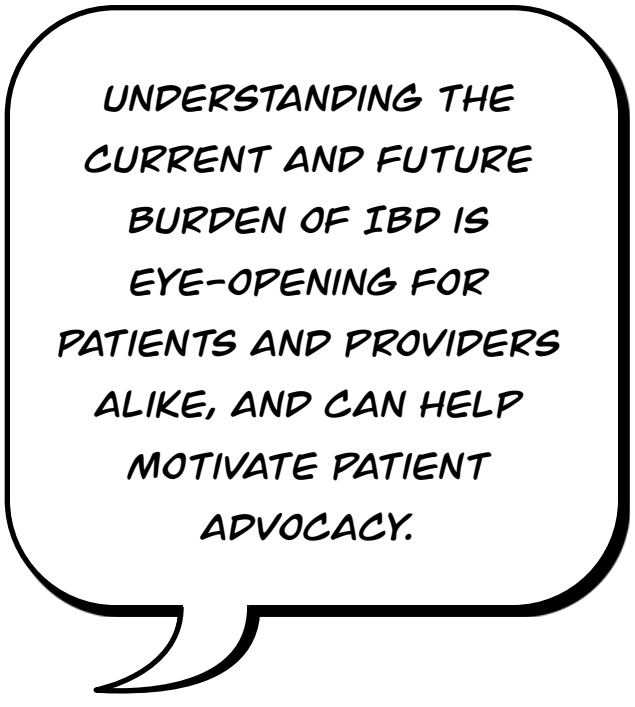
6. Psychiatric disorders are 1.5–2 times more common in people with IBD compared to the general population, and nearly one quarter to one third of people with IBD experience elevated symptoms of depression or anxiety. Clinical guidelines recommend screening those with IBD for mental health concerns and recognize the need for clinical care pathways to ensure appropriate treatment when these concerns are detected.

Introduction

In 2023, more than 320,000 Canadians are estimated to be living with inflammatory bowel disease (IBD). IBD is a chronic disease characterized by periods of relapsing and remitting inflammation of the digestive tract (i.e., periods of flare and remission). It comprises Crohn's disease and ulcerative colitis, though some individuals may be diagnosed with IBD-unspecified. Chronic inflammation and the medications used to treat IBD may increase the cumulative risk of some cancers over that of the general population, though the absolute risk of cancer remains low. Further, because some medications used to treat IBD suppress the immune system, there can be an increased risk of infections, such as SARS-CoV-2 leading to COVID-19. IBD affects portions of our population in different ways: children and adolescents who are diagnosed with IBD will live with long-standing disease since they are unlikely to die due to complications of the disease; seniors who are diagnosed with IBD will face issues around age-related comorbidities (e.g., heart disease or osteoporosis) and polypharmacy; differences in sex and gender are correlated with different healthcare utilization patterns and needs; and different ethnic groups, such as Indigenous peoples or immigrant communities in Canada, experience additional barriers to accessing healthcare.

IBD imparts a significant burden on Canadian healthcare systems in terms of costs and resources; the employment sector in terms of lost productivity; caregivers to individuals living with the disease, such as family members who are faced with out-of-pocket costs related to assisting the individual in accessing healthcare; and those living with the disease, who may experience IBD-related health concerns and out-of-pocket costs for accessing care.

Crohn's and Colitis Canada's 2018 Impact of Inflammatory Bowel Disease in Canada report summarized the burden of IBD in Canada at that time.[1] This new 2023 report updates the Canadian literature over the past five years and expands the topics of the previous report to present updated information; discuss what the future of care may be; and identify knowledge gaps, future research areas, and key policy and advocacy outcomes.



Methods

The Steering Committee of the 2023 Impact of Inflammatory Bowel Disease in Canada report met in 2022 to identify one to three co-leads for each of the chapters comprising the 11 topics of the report: Epidemiology of IBD, Indirect (Individual and Societal) and Out-of Pocket Costs, Direct Health System and Medication Costs, Special Populations—Children & Adolescents with IBD, Special Populations—IBD in Seniors, She Influence of Sex and Gender on Canadians Living with IBD, Mental Health and IBD, COVID-19 & IBD, Cancer & IBD, Treatment Landscape, and Access to & Models of Care. Each of the co-leads identified a working group to research, write, and review the scientific literature published over the last five years. The Steering Committee, along with the various co-leads, made final revisions to the chapters. Research informing each of the chapters was taken from the working groups' specialist knowledge and supported by a systematic literature review. Key points, knowledge gaps and future research directions, and key advocacy points, along with a paragraph entitled, Patient & Caregiver Perspective were informed through engagement of patient and caregiver partners (more information below).

Systematic Review

We conducted systematic literature searches to inform the following chapters of the impact report: Access to & Models of Care, Cancer & IBD, Special Populations—Children & Adolescents with IBD, COVID-19 & IBD, Direct Health System and Medication Costs, Indirect (Individual and Societal) and Out-of-Pocket Costs, Direct Health System and Medication Costs, Epidemiology of IBD, Mental Health and IBD, Special Populations—IBD in Seniors, The Influence of Sex and Gender on Canadians Living with IBD, and Treatment Landscape. Of these, four chapters (Special Populations—Children & Adolescents with IBD, Direct Health System and Medication Costs, Special Populations—IBD in Seniors, and Treatment Landscape) included multiple

systematic reviews to address specific sections within each chapter. Where there was overlap between sub-topics across chapters, the relevant studies from one review were included in additional reviews. Information for the Epidemiology chapter was based on two systematic reviews, one on the epidemiology of pediatric IBD conducted by Kuenzig *et al.*,[2] and one on the epidemiology of adult IBD conducted by Windsor *et al.* in 2022.[3] The specific databases searched varied by the topic of each search. MEDLINE (Ovid) and EMBASE (Ovid) were searched for all systematic reviews. Topic-specific searches also included PsycINFO (Ovid), CINAHL (EBSCO), Cochrane Library (Wiley), and/or medRxiv. All searches were conducted between April and June 2022 and included studies published in 2018 or later, in order to update the 2018 Impact of Inflammatory Bowel Disease in Canada report. The COVID-19 literature search included studies published in 2021 or later, which updated the 2021 Impact of COVID-19 and Inflammatory Bowel Disease in Canada report. These dates were chosen to minimize overlap in identified studies with previous iterations of this impact report.[1,4]

We included any study addressing the specified topic(s) of each review. We included primary studies, clinical practice guidelines, and recommendations. We excluded conference abstracts, studies that were not published in English, study protocols, case series of <5 individuals with IBD, and basic or translational science studies. Editorials, comments, and letters were excluded if they did not include original data. Systematic reviews were included in all reviews. At the specification of chapter authors, narrative reviews were included in some chapters but not others.

InsightScope was used to facilitate the abstract and full-text review process. Abstracts and full texts of studies identified from the literature search were independently screened by two individuals for each chapter. Conflicts at both stages were reviewed by a third reviewer. Study objective and design were extracted for each study by at least two reviewers. Studies pertinent to each chapter of the report were then distributed to authors of the relevant chapters. Included studies were synthesized qualitatively. Additional sources were incorporated based on each working group's areas of expertise.

Patient & Caregiver Partner Engagement

Crohn's and Colitis Canada invited individuals, via email, who had past engagement with the organization to assist in developing the 2023 Impact of Inflammatory Bowel Disease in Canada report. Individuals were included if they were living with Crohn's or colitis or caring for someone with Crohn's disease or ulcerative colitis. The purpose of this partnership was to gather perspectives of patients and caregivers for each chapter including information on: i. content most relevant and meaningful to them as individuals affected by IBD, ii. key findings or take-away messages, iii. knowledge gaps, and iv. advocacy priorities for Crohn's and Colitis Canada. Each chapter within this report contains a Patient & Caregiver Perspective paragraph comprising the key feedback from the partners reviewing each respective article. This paragraph is in the partners' words and is not edited by the writing group of the article or the Steering Committee of the report.

Fifty-four patient and caregiver partners were recruited, and 46 provided their voluntary consent via SurveyMonkey. Of these partners, the majority (38) were living with IBD (53% with Crohn's disease, 21% with ulcerative colitis, 26% did not specify IBD type) and 17% (9) were caregivers to children living with IBD. One patient partner was both living with IBD and a caregiver to a child with IBD.

Partners were located across Canada: 41% (19) residing in Ontario, 13% (6) in Alberta, 9% (4) in Quebec, 7% (3) in Saskatchewan, 7% (3) in British Columbia, 7% (3) in Newfoundland, 6% (3) in Nova Scotia, 4% (2) in Prince Edward Island, 4% (2) in Manitoba, and 2% (1) in New Brunswick. Four partners were Indigenous, from communities within Saskatchewan and Manitoba.

Partners were from across the lifespan, including 36% (17) that were 18–29 years of age, 42% (19) were 30–44 years of age, 4% (2) were 45–59 years of age, 4% (2) were 60–64 years of age, 7% (3) that were 70+ years of age, and 7% (3) did not specify age. The majority (72%) of partners self-identified as being female gender, 24% (11) self-identified as male, 2% (1) self-identified as transgender, and 2% (1) did not specify gender. For most partners (72%), their highest-level education was a post-secondary degree, 4% completed their high school diploma, and 22% did not specify their highest-level of education.

Consensus Meeting

After completion of the draft of each chapter and the patient & caregiver partner engagement, the Steering Committee, working group co-leads, and partner representatives participated in a two-day virtual consensus meeting. During the consensus meeting, the content of the report was reviewed; partner engagement feedback was incorporated; and the wording of the key points, knowledge gaps and future research directions, and key policy and advocacy points were finalized. Drafts were then finalized by each working group and underwent professional editing by the editor of the report. A blind peer review process was facilitated by the *Journal of the Canadian Association of Gastroenterology* and working group leads incorporated anonymous feedback from the peer reviewers to strengthen the chapters.

Report Summary

Epidemiology of IBD

Although there are differences in the epidemiology of IBD across Canadian regions (e.g., between provinces, between rural versus urban areas), Canada is in the third epidemiologic stage of IBD evolution where the rate of increasing incidence (new diagnoses) slows, stabilizes, or even declines, but the prevalence (total number of people living with the disease) of disease rapidly increases—this stage of IBD evolution is known as Compounding Prevalence.[5] Today, it is estimated that approximately 322,600 Canadians are living with IBD, which is approximately 0.82% of our population; this total increases every year with new cases of pediatric-onset IBD being the primary driver since the incidence of pediatric-onset IBD is increasing at an average of 1.23% year over year, but the incidence of adult- or elderly-onset IBD is stable. If the historical trends in the incidence and prevalence of IBD continue, it is estimated that approximately 470,000 Canadians will be living with IBD by 2035, which is approximately 1.1% of our population, or 1 in every 91 people in the country.

IBD was once considered to be a disease of Caucasian people of European descent. Today it is recognized among all populations and is found on every populated continent. It is also diagnosed in immigrants and the children of immigrants to Canada, and among Indigenous peoples in Canada. Several current research projects such as the Crohn's and Colitis Canada Genetic, Environmental, and Microbial project (GEM) are focused on discovering factors that influence the development of IBD; by understanding these factors, this research offers possible strategies surrounding diet, lifestyle, behavioural, and environmental modifications to improve the healthcare and quality of life for those with IBD.

Indirect (Individual and Societal) and Out-of-Pocket Costs

The burden of IBD affects the individual, those who care for the individual, and society through indirect, out-of-pocket costs for things such as medical supplies not covered by insurance (e.g., ostomy supplies, medications for bowel preparation prior to colonoscopy, dispensing fees); allied healthcare; and additional costs pertaining to diet, vitamins, and supplements. Additionally, IBD imparts indirect costs on the individual, those who care for them, and society in the form of lost productivity, premature retirement or death, and an impact on the maximum potential of the individual.

Medical supplies and other patient-borne costs associated with seeking care not covered by insurance account for approximately $536 million in out-of-pocket costs for Canadians, annually. The indirect costs of IBD can be estimated from costs associated with lost opportunity: delayed entry into the workforce, premature retirement or death, and impacts on maximum earning potential. Further, lost opportunity also refers to other, intangible costs of IBD that cannot be measured, such as the impact on quality of life. The indirect costs of IBD in Canada are estimated at $1.51 billion, annually, but this is likely an underestimate. Another type of indirect cost associated with IBD is that incurred by society or the employer; in addition to the reduced earning potential the individual suffers due to lost opportunity, society also bears the cost of things like unemployment or early retirement. Unemployment is the largest contributor to indirect costs of IBD in Canada, estimated to account for $1.14 billion, annually. Even while an individual with IBD is working, employers may bear indirect costs associated with lost productivity through absenteeism (i.e., missed work hours) and presenteeism (i.e., reduced productivity while at work). The costs of absenteeism and presenteeism are estimated at $285 million, annually.

Finally, the costs to caregivers for those with IBD must also be highlighted. People caring for individuals with IBD must also sacrifice time in helping afflicted individuals seek care such as providing transport to clinics or hospitals for infusions or colonoscopies; this potentially increases the burden in terms of absenteeism, for example.

Direct Health System and Medication Costs

The direct costs of IBD to health systems in Canada stem from healthcare utilization and medication costs. Healthcare utilization accounts for costs associated with visits to the emergency department (ED), hospitalizations, surgeries, surveillance, and outpatient visits. Combined with the estimated costs of medications, these costs are somewhere between $2.19–4.47 billion, annually. Although biologic medications made up roughly 50% of these costs in 2017 and likely account for an even greater percentage of healthcare spending today, there has been an overall reduction in costly health services utilization (i.e., surgeries and hospitalizations); however, there is discrepancy in this metric based on different sub-populations.

The overall frequency of children presenting to the ED has increased, but the overall frequency of adults and seniors presenting to the ED has decreased; however, due to an increasing number of Canadians living with IBD, the absolute numbers have increased. Disparities in health services utilization varies by province, but there are also within-province differences such that Indigenous people are more likely than the general IBD population to be hospitalized; children with Crohn's disease of South Asian descent are more

likely to be hospitalized at diagnosis, but subsequently have a similar hospitalization rate to the general IBD population; immigrants to Canada who are later diagnosed with IBD have greater health services utilization, but a lower risk of surgery than the general IBD population; and people with IBD living in rural areas are more likely to visit the ED or be hospitalized than those living in urban centres, but there is no statistical difference in the risk of surgery between the two populations; and those of lower socioeconomic status living with IBD are more likely to be hospitalized, undergo surgery, or require systemic corticosteroids.

Special Populations—Children & Adolescents with IBD

Increasing incidence of IBD in Canada is primarily driven by pediatric-onset disease, and the number of new cases in this population is quickly rising, especially among those under six years old. The presentation of IBD in children and adolescents is different from adult- or elderly-onset disease and comes with a unique set of complications, including the potential for growth stunting, delay of puberty, and deficits in bone development, let alone the mental health costs of having a chronic disease at a young age. Children and adolescents developing IBD frequently have more extensive disease, although those with very early onset IBD (VEO-IBD, presenting under six years of age) are more likely to have colonic disease only.

The unique presentation of disease among children and adolescents comes with unique healthcare needs: the treatment options for pediatrics are limited, partially due to children not typically being included in the initial clinical trials for new biologic and small molecule medications, and thus fewer medications being approved for use in pediatrics. In addition, physicians avoid corticosteroids in this population in favour of dietary therapy or biologics because of the possible side-effects that steroid use can elicit, such as exacerbating growth delay, issues of bone health/development, or exacerbating mental illness. Additionally, roughly 3% of children who develop IBD have a monogenic form of the disease that often presents with other comorbid conditions, immunodeficiencies, or extra-intestinal manifestations.[6] Finally, children with IBD display higher rates of anxiety and depression than other children, and also compared with adults with IBD. The transition between pediatric to adult care is a time when psychosocial and physical development is at a critical timepoint—both research into understanding the risks at this timepoint as well as clinical guidelines to successfully transition the care of these individuals are needed.

Special Populations—Seniors with IBD

By 2035, it is estimated that 1 in 91 Canadians will have IBD; in 2023, that number is already 1 in 88 seniors, up from 1 in 160 seniors in 2018, and the prevalence of IBD in this population continues to increase due to an aging IBD population and new diagnoses among seniors. Seniors with IBD have unique healthcare challenges due to long standing disease (for those diagnosed earlier in life), frailty, and polypharmacy from treatment of comorbid conditions related to aging. The complex healthcare needs of this population are putting additional strain on IBD clinics to provide adequate care; gastroenterologists treating IBD in seniors need to be part of a multidisciplinary team that can avoid adverse effects of polypharmacy and adequately care for longstanding IBD in addition to other effects of aging.

Several treatment options for managing IBD in seniors exist but may be limited by medical therapies that have lost effectiveness over a

longstanding disease course (for those who were diagnosed earlier in life), or by potential side effects. For example, anti-TNF medications may increase the risk of infections, such as pneumonia, but newer biologics such as IL-12/23 inhibitors have better safety profiles regarding infection risk. However, vaccines against preventable infections (e.g., pneumococcus, SARS-CoV-2, herpes zoster) are safe and strongly encouraged to protect seniors with IBD.

In addition to complex healthcare needs, seniors with IBD also face unique barriers to care due to potential mobility restrictions, logistic challenges, or a lack of a support system to advocate on their behalf. While the COVID-19 pandemic rapidly evolved virtual and remote care options that increase the ability to access care for seniors, resources for technological literacy and support are still necessary to prevent modern access options from becoming an additional barrier to care.

The Influence of Sex and Gender on Canadians Living with IBD

Overall, IBD is not considered a disease that is differentiated in terms of sex. However, sex-specific physiologic states such as puberty, menstruation, pregnancy, or andropause/menopause can have effects on an individual's IBD, and IBD can, in turn, impact those states. For example, people with IBD who become pregnant are more likely to experience adverse outcomes, including pregnancy loss, low birth weight, preterm birth, or the need for caesarean delivery. IBD is also a stated reason for some females choosing to remain childless, which may be influenced by uncertainty around safety, lack of disease-specific/medication-specific IBD knowledge around pregnancy, or lack of access to pregnancy in IBD specialists.

Similarly, gender in and of itself is not thought to impact the disease course of IBD, but ascribed gender roles—as correlated with sex-specific healthcare utilization patterns—do show different trends among men and women. For example, women are more likely to seek healthcare than men, but women are also more likely to receive fragmented care or have IBD symptoms confused with female-specific conditions such as menstrual cramping or endometriosis. Because much of the research available on gender differences in healthcare utilization and trends in the care of IBD rely on administrative healthcare databases that characterize included individuals based on sex, there is very little information on healthcare trends among individuals who do not identify as male or female, transgender individuals, or individuals from the queer community, who may also experience barriers to healthcare or be reluctant to seek care.[7]

Although research exists on corollaries between sex- or gender-specific healthcare in IBD, such as an association between oral contraceptive use among females and subsequent IBD diagnosis or trends in seeking healthcare between men and women, there is a lack of research into direct questions of the influence of sex or gender on IBD diagnosis, treatment, or access to care. Due to a large IBD community with highly engaged individuals, along with access to longitudinal healthcare databases, Canadian researchers are well positioned to make advances in this important and necessary area.

Mental Health & IBD

Diagnoses of psychiatric disorders, such as depression and anxiety, are 1.5–2 times more common among those with IBD than the general Canadian population, with a greater prevalence among women and people with Crohn's disease.

Children with IBD are at an additional two times the risk for a psychiatric diagnosis and six times the risk for depression. In addition to the challenges that mental illness imparts on an individual, depression and anxiety are known to negatively impact the disease course of IBD, which is a bidirectional phenomenon where active IBD symptoms can also negatively impact mental health conditions.

Psychological treatments for anxiety and depression have been shown to successfully reduce symptoms and significantly improve the quality of life for those with IBD, including helping to mitigate the effect that active symptoms from these mental health conditions have on IBD activity. Further, a promising area of intervention is on building and strengthening resilience. The evidence surrounding antidepressant therapies for mental health or IBD outcomes is less robust. In adolescents transitioning from pediatric to adult care, strengthening the individual's self-autonomy with regards to disease self-management can ease the transition process and may help prevent negative outcomes for the individual.

Due to the association between mental health concerns and IBD, clinical guidelines now recommend both screening for mental health concerns as part of IBD care as well as having an established clinical care pathway for appropriate treatment when mental health concerns are detected. As it is recommended that gastroenterologists screen for mental health issues, it may be that many gastroenterologists are not equipped to deal with active psychiatric symptoms. Hence, it is further recommended that gastroenterologists be part of a multidisciplinary IBD care team that should include specialists in psychological care.

COVID-19 & IBD

On March 11, 2020, the World Health Organization declared SARS-CoV-2 a global pandemic; on March 12, 2020, Crohn's and Colitis Canada formed the COVID-19 and IBD Taskforce to assess, synthesize, and communicate relevant medical and public health information to the IBD community through a dedicated website (with more than 800,000 visits as of Fall 2022) and a series of 30 community-oriented webinars (viewed over 81,000 times as of Fall 2022). The expertise gained from this intense knowledge translation strategy provides a proven strategy for communication in any future public health emergencies.

Three years into the COVID-19 pandemic, there is robust evidence to suggest that most clinical therapies used to treat IBD do not put those with IBD at greater risk of acquiring COVID-19, or experiencing severe COVID-19, compared to the general population. The exception is that people under 50 years of age experiencing a severe IBD flare, or those who require >20 mg per day of corticosteroids are at increased risk of severe COVID-19. Severe outcomes of COVID-19 are defined as hospitalization, ICU admission, or death. Further, despite the fact that people with IBD were not included in clinical trials for COVID-19 vaccine safety and efficacy, there is now robust data to show that these vaccines are safe and elicit excellent immune responses in those with IBD; however, there is a blunted antibody response for those taking prednisone and those on anti-TNF therapies.

As variants of the SARS-CoV-2 virus continue to circulate in the population and breakthrough infections occur in those who have been previously vaccinated, it is strongly recommended that those with IBD continue to receive booster doses of the

vaccine, especially now that bivalent vaccines are available that specifically target Omicron subvariants of the virus.

Cancer & IBD

IBD increases the risk of colorectal cancer by 1.5–2 times that of the general population, exacerbated by age, duration of disease, extent and severity of colorectal involvement, and family history of colorectal cancer. However, the absolute risk of colorectal cancer does remain low. In addition to effective treatment of inflammation, regular colonoscopy procedures are the cornerstone of colorectal cancer prevention in IBD. Some extra-intestinal cancers are also more common in those with IBD, including melanoma, hepatobiliary cancer (especially in those with comorbid primary sclerosing cholangitis), and lung cancer. Having an extra-intestinal cancer may impact the available options to treat IBD.

Additionally, some immunosuppressive therapies commonly used to treat IBD are associated with increased risks of certain extra-intestinal cancers (i.e., increased risks of lymphoma and non-melanoma skin cancers with thiopurine treatment). However, the absolute risks of these cancers remain exceedingly low and should not be a deterrent to effective treatment, particularly since untreated, active inflammation increases the risks of disease-related complications and intestinal cancers. Active surveillance is recommended for early detection of neoplastic lesions of the skin, cervix, and hepatobiliary system.

Individuals with IBD are living longer due to advances in IBD treatments and general societal health. As such, the cumulative, life-long risk of cancer is increasing in the IBD population. As healthcare practitioners face increasing cancer burden in IBD populations, treatment decisions will become more complex and will need to factor in any potential risks of cancer.

Treatment Landscape

Over the past two decades, several biologic and small molecule advanced therapies have become available to treat IBD. These medications have been shown to be safe and effective in clinical and real-world studies and have radically changed the prospect of long-term disease control for those with IBD. Biosimilar therapies have started to emerge for several classes of biologic medications, bending the cost curve downwards through competitive pricing and increasing access to biologic treatments. Evolving treatment paradigms, including treating to a target of objective disease remission (as opposed to resolving symptoms alone) and introducing combination therapies earlier in the disease course have the potential to further improve long-term prognosis. Being able to identify the right treatment for the right individual at the right time in their disease course to optimize long-term prognosis is an important future goal in IBD management and an active area of IBD research.

Although medical management of IBD has substantially advanced, surgery continues to play an important role, especially in those with stricturing, penetrating, or perianal fistulizing Crohn's disease, medically refractory disease, and colorectal cancer.

Beyond medication and surgical interventions, evidence for alternative therapies that are directed at modifying intestinal bacteria through diet modification, probiotics, and fecal transplants have all shown promise in preliminary studies; however, further research in these areas is needed before there can be widespread recommendation for these alternative or supplemental therapies.

ACCESSING CARE IS A HUGE CHALLENGE NOT ONLY FOR THOSE WITH IBD, BUT ALSO THOSE AWAITING A DIAGNOSIS OF IBD. HAVING AN INTEGRATED COLLABORATIVE MODEL OF CARE WITH AN INTERDISCIPLINARY TEAM WOULD BE A STEP FORWARD IN IBD CARE. GIVING PATIENTS HELP TO NAVIGATE THE MEDICAL SYSTEM, AND HELP PATIENTS FEEL SEEN AND HEARD BY THEIR TEAM.

Access to & Models of Care

The quality of care varies across Canada by geographic differences (e.g., province/territory or urban versus rural living), socio-economic status, and ethnicity (e.g., immigrant or Indigenous communities). Some of the barriers to accessing quality healthcare identified by individuals living with IBD include long wait times for specialist or non-specialist care, the lack of resources surrounding travel times to clinics, and inadequate availability of specialist resources. The latter barrier includes difficulties with access to gastroenterologists, non-invasive surveillance options (e.g., intestinal ultrasound), and allied healthcare professionals to provide help for mental health or other concerns that are frequent among people with IBD. Increasing access to these patient-identified healthcare resources can improve patient-reported outcomes and the quality of life for those living with IBD.

Gaps in accessing care and treatment for IBD, including gaps in psychosocial care, could be addressed partly by implementing standardized quality of care indicators and clinical pathways, such as those proposed by Crohn's and Colitis Canada's Promoting Access & Care through Centres of Excellence (PACE), with a focus on integrated care management by a multidisciplinary care team.

Access to care, not only for those living in rural areas or those who have mobility restrictions but for all individuals with IBD, may be enhanced through the expansion and adoption of virtual health platforms. These platforms could improve communication between individuals living with IBD and their healthcare providers, increase the ability of physicians to implement evidence-based care based on individual data monitoring, and suggest surveillance approaches with the individual's quality of life and ability to engage in shared decision-making as a focus.

Recommendations

- The incidence and prevalence of IBD in Canada needs to be continually monitored and updated to constantly understand the overall burden and change of burden in Canada. These trends should be updated and used as a basis for recommendations to the healthcare systems to adjust for the impending burden.

- Canadian healthcare should evolve to include multidisciplinary care, including access to mental health professionals, dietitians, and other allied healthcare professionals to improve the quality of life for people living with IBD. Additionally, extended health benefit providers should be lobbied to provide additional benefits regarding these costs to reduce overall health expenditures.

- The number of people living with IBD in Canada is increasing. At the same time, the costs of treating each person living with IBD are also increasing. The increasing costs of caring for a rising number of people living with IBD are not sustainable indefinitely. Crohn's and Colitis Canada should advocate for better regulation of the cost of biologic therapies to ensure the financial viability of providing the right medication to the right person at the right time. Both government and private health insurance plans should put financial pressure on the pharmaceutical industry to lower medication costs.

- Rates of pediatric IBD are rising in Canada. These individuals require multidisciplinary and specialized care for their chronic disease. They should have access to expert physicians, nurses, dietitians, social workers, pharmacists, and mental health specialists to treat both the individual and their family, no matter where in Canada they live.

- Ensuring that seniors with IBD have access to gastroenterology care is essential; remote access is also important because there may be barriers to accessing care with some forms of virtual care. Telemedicine should be accessible and be funded to ensure it can be utilized by those who need it (e.g., those with mobility restrictions or living in remote locations).

- Advocacy should aim to support research specifically addressing sex- and gender-related factors on the course of IBD, on the lived experience of IBD, and how to best minimize disparities based on sex and/or gender—including non-binary and other genders. A strong knowledge translation focus on this research will inform clinicians and may positively affect the quality of care they provide.

- Clinical guidelines recommend screening people with IBD for mental health concerns as part of the standard practice in IBD care, recognizing the prominent comorbidity and disease influence, but also noting the importance of having clinical pathways for care if positive. Psychological therapies used to treat anxiety and depression occurring in the context of IBD have been shown to significantly improve quality of life and reduce anxiety and depression for children and adults with IBD; there is less direct evidence in regard to the impact of antidepressant medication on mental health or disease outcomes in IBD.

- Crohn's and Colitis Canada's COVID-19 and IBD taskforce compiled knowledge and communicated with the IBD community through an expert-generated website and frequent webinars for a public audience. This work has set the stage for Crohn's and Colitis Canada to inform the IBD community in the event of any

future public health emergencies. Crohn's and Colitis Canada should continue to advocate policy makers and health authorities during the pandemic for vulnerable, immunocompromised individuals with IBD.

- Additional resources to facilitate shared decision-making discussions are required. Shared decision-making needs to be promoted and facilitated for all aspects of healthcare for individuals with IBD. It is particularly important for communicating and making decisions with respect to cancer care. Shared decision-making should inform treatment choices and cancer risks for IBD, weighing the risks of untreated inflammatory disease against the small, but potentially serious, risks of extra-intestinal cancers with immunosuppressive therapies.

- Strategies to optimize the effectiveness of available therapies, such as introducing biologic therapy early in the course of Crohn's disease, targeting normalization of objective markers of disease remission, and using therapeutic drug monitoring to guide treatment decisions with biologics have the potential to improve long-term prognosis and longevity of current medical treatment options.

- Advocacy for increased government investment in the development, implementation, and evaluation of evidence-based interventions and practices that improve access to IBD care, particularly for equity-deserving populations, is needed. Promising interventions and practices include, but are not limited to, increased specialist staffing in under resourced areas, augmented psychosocial supports, continued virtual health supports, and support for patient navigators.

- For future Impact of IBD in Canada reports, it is recommended that Crohn's and Colitis Canada continue its important work of engaging patient and caregiver partners. Importantly, this community should be engaged at the beginning of the process such that they can help frame the research questions and inform what chapters should be included in the report.

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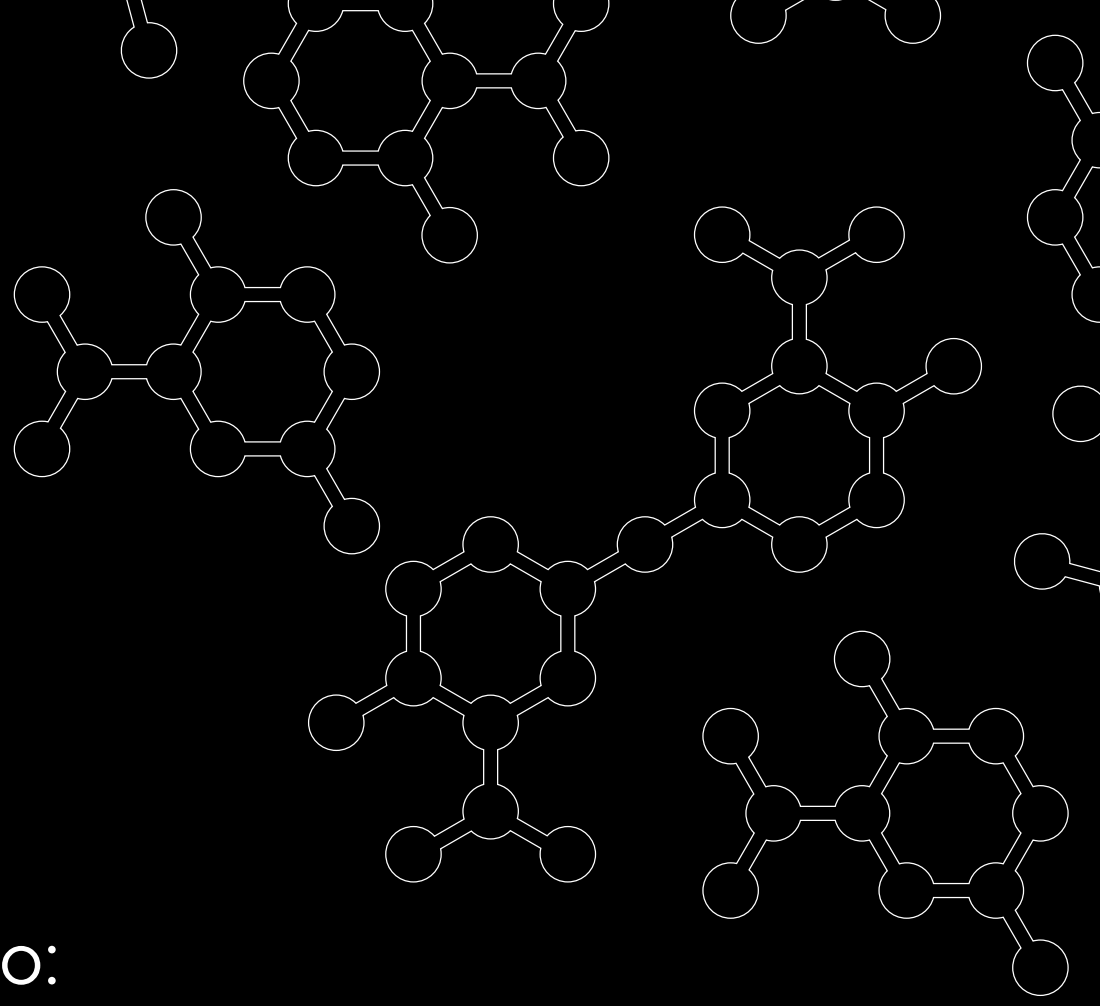


Section Two:

Epidemiology of IBD

Epidemiology of IBD

Abstract

Inflammatory bowel disease (IBD), consisting of Crohn's disease and ulcerative colitis, is recognized across the world, though Canada has among the highest burdens of IBD in the world. The Canadian Gastro-Intestinal Epidemiology Consortium (CanGIEC) led a six-province study that demonstrated the fast-growing prevalence (total number of people living with IBD, see compounding prevalence) of IBD in Canada from 400 per 100,000 Canadians in 2002 to 636 per 100,000 Canadians in 2014. The prevalence in 2023 is estimated at 825 per 100,000 Canadians, meaning that over 320,000 people in Canada are living with IBD. Prevalence is forecasted to rise by 2.44% per year such that 1.1% of the population—or 470,000 Canadians—will be living with IBD by 2035. The overall incidence (people newly diagnosed) of IBD in 2023 is 30 per 100,000 Canadians, indicating that over 11,000 Canadians will be newly diagnosed with IBD in 2023. Incidence is forecast to rise by 0.58% per year up to 32.1 per 100,000 Canadians by 2035. The rising incidence of IBD is largely driven by pediatric-onset IBD, which is rising by 1.23% per year from 15.6 per 100,000 Canadian youth in 2023 to 18.0 per 100,000 Canadian youth in 2035. In contrast, incidence rates among adults and seniors are relatively stable. Understanding the factors that influence people developing IBD has expanded through prospective cohort studies such as the Crohn's and Colitis Canada Genetic, Environmental, Microbial (CCC-GEM) project. Consensus recommendations towards diet, lifestyle, behavioural, and environmental modifications have been proposed by international organizations with the goal of optimizing disease control and ultimately preventing people from developing IBD. Despite these efforts, Canadian healthcare systems will need to prepare for the rising number of people living with IBD.

Key Points

1. IBD evolves across four epidemiologic stages: Emergence (Stage 1), Acceleration in Incidence (Stage 2), Compounding Prevalence (Stage 3), and Prevalence Equilibrium (Stage 4). Canada is currently rooted in the third epidemiologic stage (Compounding Prevalence) where the prevalence of IBD is steadily climbing because the number of new diagnoses each year greatly outpaces mortality.

2. Across all provinces, the prevalence of IBD is significantly increasing. In 2023 it is estimated that the prevalence across the provinces ranges from 720 per 100,000 Canadians in Manitoba (95% CI: 688, 751) to 968 per 100,000 in Alberta (95% CI: 879, 1056). On the other hand, incidence across provinces is heterogeneous. It is significantly increasing in British Columbia and Quebec, stable in Alberta and Ontario, and significantly decreasing in Manitoba and Saskatchewan.

3. In 2023, approximately 322,600 (0.82%, or 8.2 per 1,000) Canadians are estimated to live with IBD. By 2035, that number is expected to rise to 470,000 Canadians (1.1% or 1 in 91); this is similar to the trends reported in the 2018 Impact of IBD in Canada.

4. In 2023, the incidence of IBD is 30 per 100,000 Canadians, meaning that over 11,000 Canadians will be newly diagnosed with IBD in 2023.

5. Overall, the incidence of IBD is rising by 0.58% per year. Pediatric-onset IBD is the predominant driver of rising incidence at 1.23% per year with the incidence remaining stable among adults and seniors.

6. If trends in incidence remain the same over the next decade, then the incidence will climb to 32.1 per 100,000 in 2035; representing 14,000 Canadians newly diagnosed with IBD that year.

7. Information from cohort studies like Crohn's and Colitis Canada's Genetic, Environmental, Microbial project (CCC-GEM) offers potential strategies on guiding diet, lifestyle, behavioral, and environmental modifications to improve the care of IBD.

8. The incidence of IBD in Canada is recognized across race and ethnicity including Indigenous populations and those of South Asian descent.

9. Canadian healthcare systems will need to contend with the ongoing, rising burden of IBD.

Summary of Crohn's and Colitis Canada's 2018 Impact of IBD: Epidemiology

Crohn's and Colitis Canada's 2018 Impact of Inflammatory Bowel Disease (IBD) report on the epidemiology of IBD documented that Canada had among the highest burdens of IBD in the world. In 2018, the prevalence of IBD in Canada was roughly 0.7% of the population, which represented approximately 270,000 Canadians living with IBD, half of whom were living with Crohn's disease. Forecasting projected a steadily rising prevalence towards 1% of the Canadian population over the next decade. By 2030, models estimated that nearly 400,000 Canadians would be living with IBD. The highest rate of new diagnoses was reported in Nova Scotia and the lowest in British Columbia. While IBD can be diagnosed at any age, adolescents and young adults had the highest incidence of disease. In the past, Caucasians of European descent and Ashkenazi Jews were thought to be at highest risk for IBD. However, IBD is now recognized among all races and ethnicities; in particular, among the first-generation children of immigrants to Canada. Consequently, healthcare systems need to prepare for the rising burden of IBD in Canada.

Introduction

Inflammatory bowel disease (IBD), consisting of Crohn's disease and ulcerative colitis, are chronic inflammatory disorders of the intestines. IBD is believed to arise among genetically susceptible individuals who are exposed to environmental exposures that alter their intestinal microbiome.[1] Over 200 genes have been identified that are associated with altering the risk of developing IBD.[2] Most of these genes are involved with the intestinal immune system's interaction with the microbiome—the good bacteria that live in the gut.[3] Environmental exposures (things such as highly processed foods, air pollution, or cigarette smoking), particularly those early in life, that influence the composition and diversity of the microbiome may increase the risk of developing IBD later in life.[4]

The environmental determinates of IBD (i.e., things that influence the risk of developing IBD) are rooted in the westernization and industrialization of society.[5] The incidence of IBD (the number of new diagnoses each year) escalated during the latter half of the 20th century in the early-industrialized world: North America, Western Europe, and Oceania.[6, 7] At the turn of the 21st century, the incidence of IBD has levelled in some regions of the early-industrialized world; however, it has begun to rise dramatically in newly industrialized countries in Asia and Latin America as these countries have begun to undergo westernization and urbanization.[8] Today, IBD is recognized as a global disease.

In countries like Canada, the prevalence of IBD (the total number of people with the disease) has steadily been rising.[9] Decades of rising incidence in conjunction with low mortality means that individuals with IBD are continually added to gastroenterology clinics, whereas few leave.[10] Consequently, healthcare systems must contend with the ever expanding volume of individuals living with IBD.[11]

The purpose of this chapter is to understand the evolution of IBD across epidemiologic stages, highlight the most recent data on the incidence and prevalence of IBD in Canada, and explore how the determinants of IBD may be modified to reduce the incidence of IBD in Canada.

The Four Epidemiologic Stages in the Evolution of IBD across the World

A theoretical framework on the global evolution of IBD across four epidemiologic stages has been proposed (Figure 1).[10] The first epidemiologic stage, Emergence, suggests that in developing countries, IBD arises as sporadic, incident cases in the population. In this stage, both the incidence and the prevalence of IBD are very low. With economic expansion, newly industrialized countries experience advances in healthcare infrastructure and westernization of lifestyle and diet. These societal changes trigger the escalation in the incidence of IBD, transitioning these regions into the second epidemiologic stage, Acceleration in Incidence. During the second epidemiologic stage, the incidence rate rises sharply, whereas the prevalence of IBD remains low in the population. IBD is predominately diagnosed in young individuals and has low mortality. Thus, new cases are continually added to the prevalent base with few dying. So long as incidence exceeds mortality, prevalence will steadily rise, leading to the third epidemiologic stage, Compounding Prevalence. During third epidemiologic stage, the previously sharp rising slope of incidence decelerates; the

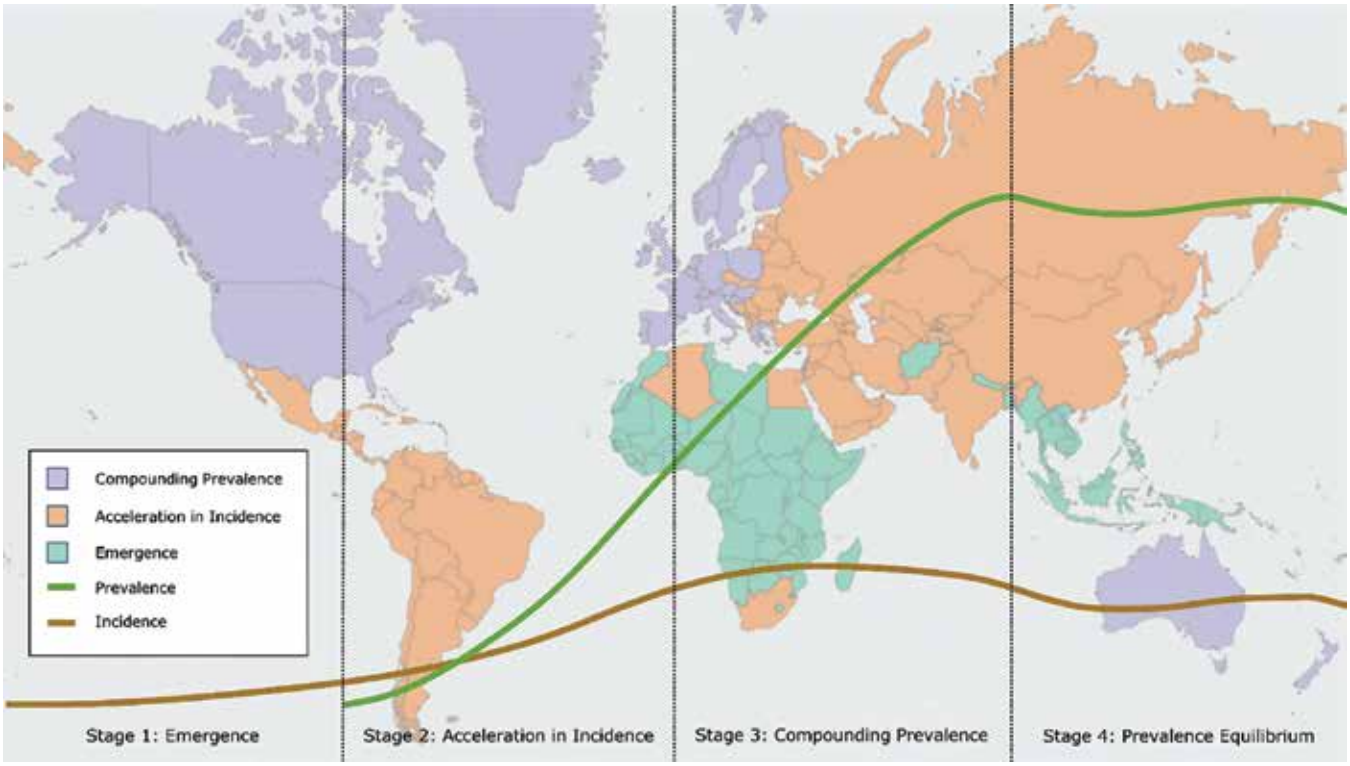


Figure 1: *This figure depicts a stylized track of incidence and prevalence rates in each of the four epidemiologic stages. In Stage 1, Emergence, there is very low incidence due to sporadic disease. In Stage 2, Acceleration in Incidence, incidence rates quickly increase, and prevalence starts to accumulate. In Stage 3, Compounding Prevalence, incidence stabilizes but prevalence continues to climb. In Stage 4, Prevalence Equilibrium, the prevalence of disease begins to stabilize due to stable incidence and an aging population. Every region of the world is currently in one of the first three stages, as depicted by colours in the background map. No region has yet transitioned to Stage 4. (Adapted from Kaplan & Windsor 2021,[10] updated with data from Windsor et al. 2023.[13])*

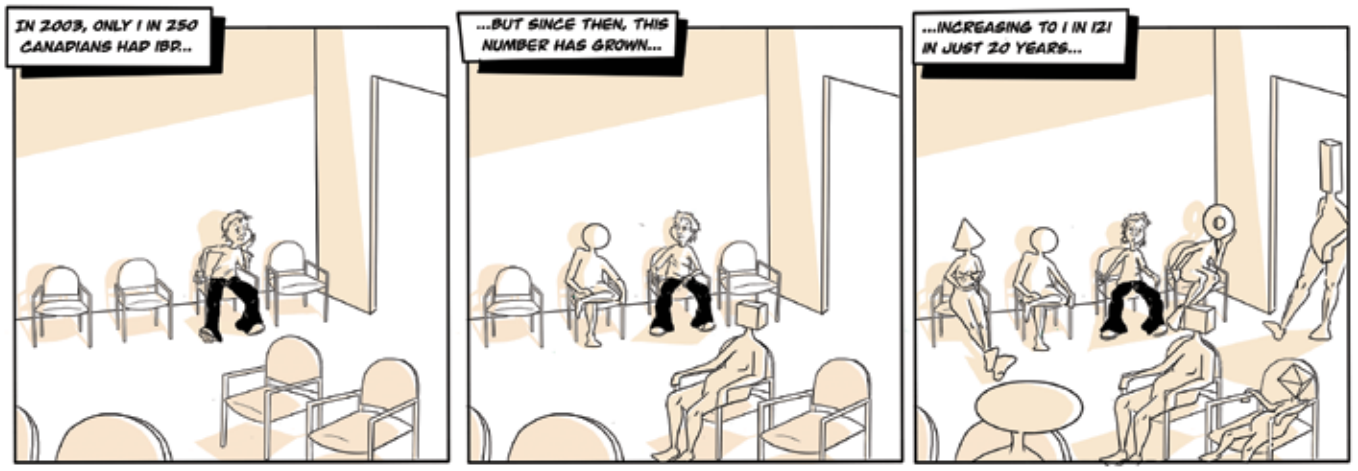
incidence rate may stabilize or even decline in some regions. However, the slope of prevalence increase continues to rise steadily. The fourth epidemiologic stage, Prevalence Equilibrium, is a theoretical stage wherein prevalence begins to stabilize as a result of rising mortality from an aging IBD population. At present, no region has transitioned into the fourth epidemiologic stage.[10]

Understanding how societies transition across the different epidemiologic stages allows us to historically evaluate epidemiologic patterns, estimate the current incidence and prevalence of IBD, and forecast changes in the burden of IBD into the future.[10] Canada was firmly rooted in the second epidemiologic stage during the latter half of the 20th century with steadily rising incidence and relatively low prevalence of IBD.[12] At the turn of the 21st century, the acceleration in incidence began to slow down in Canada, which is now in the compounding prevalence stage of the epidemiologic evolution of IBD.[9]

The Prevalence of IBD Is Steadily Climbing in Canada across All Age Groups

The Canadian Gastrointestinal Epidemiology Consortium (CanGIEC) is a national Canadian network of IBD epidemiologists who analysed provincial cohorts of IBD from six provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, and Quebec) representing over 95% of the Canadian population; this is updated data, separate from a prior forecasting analysis undertaken by the same group.[9, 14] Each of the provinces have data from 2002–2014, but data from Manitoba begins as early as 1987, and data from British Columbia extends to 2019. Overlapping years from the six provinces were used to create a national, statistical model of prevalence in Canada, to derive the average annual percent change (AAPC), and to forecast prevalence to 2035.[14]

The prevalence of IBD steadily increased from 2002 (389 per 100,000 Canadians) to 2014 (636 per 100,000 Canadians; 321 per 100,000 for Crohn's disease, and 315 per 100,000 for ulcerative colitis and IBD-unclassified [IBD-u] together). After 2014, the national prevalence of IBD is forecast to rise by an AAPC of 2.44% per year. The rising prevalence over time is similar for both Crohn's disease and ulcerative colitis. Overall, the prevalence of IBD in 2023 is estimated to be 825 per 100,000 Canadians



(410 per 100,000 for Crohn's disease, and 414 per 100,000 for ulcerative colitis and IBD-u). A 0.82% prevalence represents 322,600 people living with IBD in Canada. By 2035, the prevalence is forecasted to climb to 1.08% of the population, representing 470,000 Canadians living with IBD. Prevalence across all age groups were forecast to significantly increase. The highest AAPC was seen in the elderly, with a prevalence of 841 per 100,000 Canadians in 2014 and 1,534 per 100,000 Canadians in 2035.

Few studies have been done specifically to identify IBD within an Indigenous population in Canada—the main one coming from Saskatchewan.[15] Similar to other prevalence studies in Canada,[16] the prevalence of IBD in Indigenous populations is significantly increasing at 4.2% per year (95% CI: 3.2, 5.2), which is an increase from 64 per 100,000 (95% CI: 62, 66) in 1999 to 142 per 100,000 (95% CI: 140, 144) in 2016.[15]

The prevalence of IBD in Canada is analogous to other countries of the early-industrialized world including, the US, Western Europe, and Oceania, which have reported similar trends in compounding prevalence.[8] For example, forecast models in Scotland suggest that the prevalence of IBD was 0.78% in 2018 and will be approximately 1% of the population by 2028.[17]

The Incidence of IBD Is Rising in Canada, Predominantly Driven by Children with IBD

CanGIEC explored the incidence of IBD provincially (BC, AB, SK, MN, ON, and QC) and in a national model across 2007–2014. Historical data derived from provincial administrative healthcare databases were used to forecast incidence trends into the future.

In 2014, the calculated incidence of IBD across Canada was 28.4 per 100,000 Canadians (calculated in person-years) (13 per 100,000 for Crohn's disease, and 15.4 per 100,000 for ulcerative colitis and IBD-u). After 2014, the national incidence of IBD is forecast to rise by an AAPC of 0.58%. The rise in incidence in Canada is predominantly driven by ulcerative colitis and IBD-u, which are projected to increase by 1.23% per year. In contrast, the incidence of Crohn's disease is forecast to remain stable. Overall, the incidence of IBD in Canada is estimated to be 30 per 100,000 Canadians in 2023, with an incidence of 12.2 per 100,000 for Crohn's disease and 17.5 per 100,000 for ulcerative colitis and IBD-u. These values represent over 11,700 Canadians being newly diagnosed with IBD in the year 2023—approximately 4,800 with Crohn's disease and 6,800 with ulcerative colitis or IBD-u. Moreover, with the projected rise in incidence of 0.58% per year, the incidence of IBD is forecast to be 32.1 per 100,000 Canadians in 2035 (11.5 per 100,000 for Crohn's disease, 20.1 per 100,000 for ulcerative colitis and IBD-u). Consequently, if these trends remain the same over the next decade, then 14,000 Canadians will be newly diagnosed with IBD in 2035.

The incidence of pediatric onset IBD was 13.9 per 100,000 in 2014 and is forecast to rise by 1.23% per year up to 18.0 per 100,000 in 2035. In contrast, the incidence of IBD diagnosed in adults and seniors over the age of 64 has been stable and is forecast to remain stable over the next decade. The incidence of IBD is similar between sexes: 28.9 per 100,000 in females and 30.0 per 100,000 in males in 2023.

Analyzing provinces separately yields varying trends in incidence, in part due to differences in data availability across years. The incidence rates of IBD were stable in Alberta (2007–2017, AAPC: −0.75; 95% CI: −2.29, 0.36) and Ontario (1999–2016, AAPC: 0.83; 95% CI: −1.55, 2.29), increasing in British Columbia (1999–2019, AAPC: 0.71; 95% CI: 0.45, 0.95) and Quebec (2002–2014, AAPC: 0.58; 95% CI: 0.15, 0.95), and decreasing in Manitoba (1987–2014, AAPC: −0.93; 95% CI: −1.51, −0.47) and Saskatchewan (1998–2018 AAPC: −7.72; 95% CI: −21.58, −2.56).[14] Future studies are necessary to explain the differences in incidence trends between provinces.

Historically, the incidence of IBD has been the highest among Caucasians living in Canada. However, at the turn of the 21st Century, IBD is recognized across races and ethnicities including children of immigrants from newly industrialized countries.[18] For example, there was a similar incidence among those of South Asian ethnicity living in Canada compared to the general population.[19] Furthermore, incidence among Indigenous populations in Saskatchewan has remained statistically stable (AAPC: −2.7%; 95%CI: −6.2, 0.8) with a rate of 11 per 100,000 (95% CI: 5, 25) in 1999 and 3 per 100,000 (95% CI: 1, 11) in 2016. Additionally, a higher rate of ulcerative colitis than Crohn's disease among that Indigenous population was observed (ulcerative colitis to Crohn's disease ratio of 1.71) while population-based Canadian studies show equal rates of ulcerative colitis and Crohn's disease.[15, 16] Future epidemiologic studies should evaluate the evolving trends of IBD across race and ethnicity.

Modifying Environmental Risk Factors May Prevent IBD and Help Control Disease Activity

If historical trends continue, the prevalence of IBD in Canada will steadily rise over the next decade to levels that are significantly higher than what we currently see. However, the rising prevalence can be slowed down by interventions aimed to reduce incidence. In order to prevent IBD, we need to learn the underlying determinates that cause IBD and modify those factors that influence people developing IBD. Over the past five years, tremendous insight into the environmental determinants of IBD have been discovered.

Several prospective cohort studies on the environmental risk factors of IBD offer indirect evidence on potential preventative strategies for IBD and for controlling disease activity. The International Organization for the study of Inflammatory Bowel Disease (IOIBD) published dietary guidance for those with IBD.[20] Whole foods such as vegetables, fruits, and omega-3 oils from fish are associated with a reduced risk of developing IBD and sustaining remission in those with IBD.[20, 21] In contrast, foods that should be minimized in those with IBD include saturated and trans fats, red and processed meats, and refined sugars. Moreover, highly processed foods, emulsifier's, and artificial sweeteners may worsen the risk of IBD.[20-22] Most dietary effects are believed to be driven by changes in the composition and diversity of the intestinal microbiome.[20] However, recent Canadian data suggests certain types of fibres may trigger inflammation in some individuals, further complicating our understanding of diet's role in the risk and prognosis of IBD.[23]

IOIBD has also published consensus recommendations towards lifestyle, behavioral, and environmental modifications geared towards care for those with IBD.[24] The key recommendations from that report included avoiding smoking, eating a healthy whole-food diet such as the Mediterranean

diet, minimizing regular use of high-dose non-steroidal anti-inflammatory drugs (NSAIDs), attempting to achieve and maintain a normal body-mass index (BMI), engaging in regular physical activity, and promoting mental health care.[24] Recommendations for the children of those with IBD who are at higher risk of acquiring IBD and population-level interventions geared towards IBD prevention have also been considered. Based on indirect observational research, guidance includes: Never start smoking; minimize NSAIDs in adulthood and antibiotics in childhood; ensure adequate vitamin D; optimize fruits, vegetables, fibre, and fish oils in diet; promote physical activity, regular sleep patterns, stress reduction, and a healthy weight; and breastfeeding where possible.[24]

The lack of randomized controlled interventional studies and high-quality, population-level environmental modification studies is a limitation of current guidelines. Future studies of high-quality, environmental interventions that demonstrate strategies to prevent IBD are necessary to reduce the future incidence of IBD.

The CCC-GEM Project Is Shining Light on the Determinates of IBD

Crohn's and Colitis Canada's Genetic, Environmental, Microbial (CCC-GEM) project is a prospective cohort study that has followed over 5,000 first-degree relatives (parents, siblings, or children) of individuals with Crohn's disease. Since CCC-GEM's inception in 2008, over 120 new diagnoses of Crohn's disease or ulcerative colitis have been made within the cohort. Analyses from the CCC-GEM cohort suggest that Crohn's disease may be identified prior to a clinical diagnosis. Antibodies to microbes[25] and alterations in the intestinal permeability[26] were associated with developing Crohn's disease in the future.

Identifying individuals prior to a clinical diagnosis of IBD opens the possibility of intervening through environmental modifications with the goal of preventing disease development. For example, the subset of the CCC-GEM cohort that followed a Mediterranean diet underwent changes in the microbiome that were associated with reduced intestinal inflammation before the diagnosis of Crohn's disease.[27] Studies such as CCC-GEM help to bridge the knowledge gap around environmental determinants and how we could modify them by identifying possible environmental factors and their effects in a real-world setting. Through the monitoring of thousands of individuals, this study works to identify the environmental determinants, along with interacting genetics, aiming to decrease the incidence of Crohn's disease. This decrease in incidence would in turn decrease the prevalence of the disease and provide a necessary decrease in burden.

Conclusion

Crohn's disease and ulcerative colitis are global diseases, with Canada reporting among the highest prevalence and incidence of IBD in the world. In Canada, the prevalence of IBD climbed from 400 per 100,000 Canadians in 2002 to 636 per 100,000 Canadians in 2014. Today, in 2023, the prevalence is estimated to be 825 per 100,000 Canadians (approximately 0.8% of the population) and is forecast to rise by 2.44% per year over the next decade. In 2023, over 320,000 people in Canada are living with IBD, and the prevalence forecasted to be almost 1.1% of the population by 2035, representing 470,000 Canadians with IBD. The overall incidence of IBD and Canada in 2023 is 30 per 100,000 Canadians, meaning 11,000 new diagnoses of IBD will be made in 2023. Incidence is projected to rise by 0.58% per year, reaching 32.1 per 100,000 Canadians by 2035. The rise in incidence is predominately driven by pediatric onset IBD with relatively stable rates among adults and seniors. Addressing the rising burden of IBD in Canada will require a concerted effort to understand the underlying determinants of IBD and to use this information to prevent disease development.

INCIDENCE AND PREVALENCE OF IBD ARE ON THE RISE SO GREATER INVESTMENT INTO RESEARCH, STREAMLINING DIAGNOSTIC PATHWAYS, AND IMPROVED ACCESS TO AFFORDABLE TREATMENTS NEEDS TO BE PRIORITIZED. GREATER INVESTMENT IN RESEARCH ON THE IMPACT OF IBD AMONG INDIGENOUS POPULATIONS SHOULD BE ADVOCATED FOR.

Knowledge Gap & Future Research Directions

1. The reason for the rising incidence of IBD in children and adolescents, with stable rates in adults and seniors, is not known. Future research should explore environmental factors driving the rising incidence of pediatric-onset IBD.

2. Temporal trends in incidence of IBD varies by province. Future studies should explore the different patterns of incidence rates over time between provinces.

3. Intervention studies on modifiable diet, lifestyle, behavioural, and environmental factors that reduce the incidence of IBD are necessary.

4. Population-level guidelines directed by high-quality, intervention-based research are necessary to support activities that prevent IBD development.

5. The burden of IBD among Indigenous populations and the first-generation children of immigrants are on the rise, but there is a general lack of research in these areas; this should be an area of focus for future research and for changes in health policy to ensure that we accommodate the needs of these populations.

Patient & Caregiver Perspective

Patient partners highlighted the importance of monitoring the IBD prevalence and incidence trends in Canada, especially the rising numbers observed among children. The epidemiology of IBD among specific populations (e.g., Indigenous peoples and first-generation immigrants) also requires the attention of different stakeholders and better awareness of healthcare providers about these numbers and their implications. Based on this epidemiology, the IBD community can inform how healthcare systems could be well-equipped (e.g., outpatient care and after-hours services to avoid visits to the emergency room) and advocate for providing adequate health services. Individuals with IBD can contribute crucial information to help prepare Canadian healthcare systems for reforming and designing efficient and timely IBD care. In addition, patient partners underlined the importance of the risk factors for IBD to, potentially, modify them and diagnose IBD before its clinical onset. If we focus on prevention and early diagnosis of IBD, the growing burden of IBD on the healthcare systems could be diminished, as well as the burden of this chronic condition on the well-being of individuals living with IBD in Canada.

Policy Implications & Key Advocacy Outcomes

1. Due to the increasing prevalence of IBD in Canada, the Canadian healthcare systems need to prepare for the increasing burden (e.g., more gastroenterologists) to ensure afflicted individuals receive high-quality care as needed to manage long-standing disease or flares.

2. Under-represented populations—such as Indigenous populations in Canada and first-generation children of immigrants to Canada—require more research to understand the incidence and prevalence of IBD therein. Current research is lacking, and data needs to be made available in order to better grasp the burden that is imparted on these populations. It is critically important to engage in knowledge translation with these stakeholder groups and to make healthcare providers aware of this information to challenge biases and knowledge gaps.

3. Increased funding needs to be geared towards research that looks at the development of IBD and possible ways to mitigate its development.

4. Cross-organizational partnership is encouraged between Crohn's and Colitis Canada and other agencies to promote healthy lifestyle choices, particularly around diet and other modifiable behaviours that impact the risk of developing IBD.

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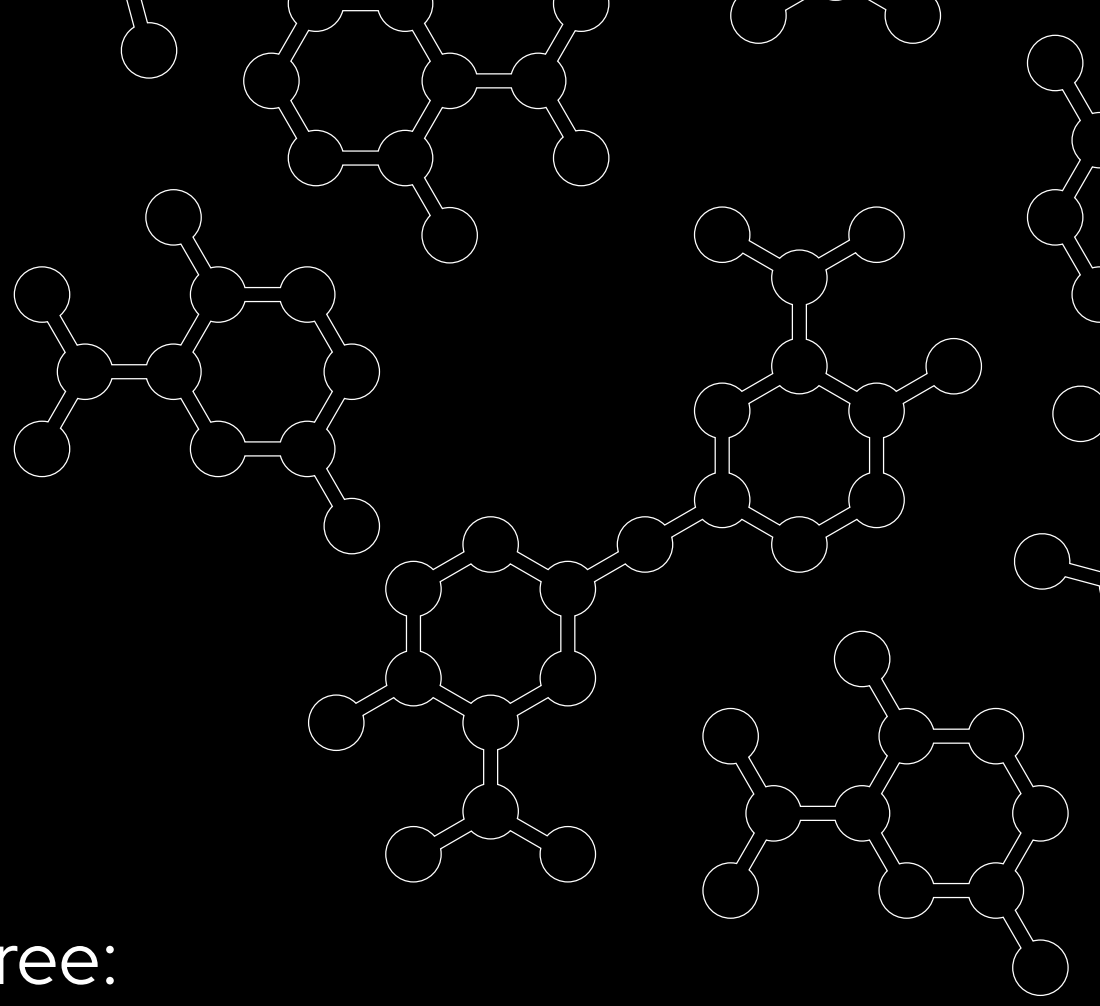


Section Three:

Indirect (Individual and Societal) and Out-of-Pocket Costs

Indirect (Individual and Societal) and Out-of-Pocket Costs

Abstract

People living with inflammatory bowel disease (IBD), and their caregivers, are faced with indirect and out-of-pocket costs that they would not otherwise experience. These costs impact one's ability to contribute to the economy to their fullest potential. The indirect costs of IBD in Canada are estimated to be at least $1.51 billion in 2023 and include costs associated with lost productivity resulting from a combination of missed work (absenteeism), decreased workplace productivity (presenteeism), unemployment, premature mortality, and caregiving costs. Unemployment is the largest contributor to indirect costs ($1.14 billion), followed by costs of absenteeism and presenteeism ($285 million). Caregiving costs for children with IBD are estimated to be nearly $58 million. Canadians with IBD also pay $536 million every year for care that is not covered by universal or supplemental private health insurance; this includes allied healthcare (e.g., care provided by psychologists), medication, and other supportive therapy. Combined, the indirect and out-of-pocket costs of IBD in Canada are estimated at more than $2 billion CAD in 2023. This cost is substantially higher than the estimate of $1.29 billion in Crohn's and Colitis Canada's 2018 Impact of IBD report with differences attributable to a combination of rising prevalence (total number of people living with IBD), inflation, and the addition of presenteeism and caregiving costs to the total indirect costs.

Key Points

1. IBD impacts the ability of people living with the disease (or caring for people living with IBD) from contributing to the economy to their fullest potential.

2. In Canada, the indirect costs of IBD are estimated to be at least $1.51 billion in 2023, though this is likely an underestimate.

3. Costs of unemployment are the largest contributor to indirect costs ($1.14 billion), followed by costs of absenteeism and presenteeism ($285 million).

4. Caregiving costs for children with IBD are estimated to be nearly $58 million.

5. Canadians with IBD pay $536 million out of their own pockets to obtain care, medications, and supportive therapy not covered by universal or private health insurance plans.

Summary of Crohn's and Colitis Canada's 2018 Impact of IBD: Indirect Costs of IBD Care

The annual indirect and out-of-pocket costs were estimated at $1.29 billion in 2018. Decreased workplace productivity was reported as a significant contributor to indirect costs, driven by premature retirement ($629 million CAD), absenteeism ($88 million CAD), and premature death ($34 million CAD). Out-of-pocket expenses borne by people living with IBD were estimated at $541 million. Data on the costs of presenteeism, professional advancement, and caregiving were lacking and therefore not included in the estimate of costs in 2018.

Introduction

The total economic burden of the inflammatory bowel diseases (IBD) comprises both direct and indirect costs (Figure 1). Direct costs include those incurred during the course of providing medical care for people with IBD. Direct costs include the costs of clinic visits, emergency department visits, hospitalizations, surgeries, and medications (see Chapter 4). In Canada, direct costs are largely born by provincially- or territorially-administered universal health insurance, supplemented by private extended health benefit plans. However, many people will have to pay for some portion of their direct medical costs out-of-pocket when they are not covered by governmental or supplemental private insurance, in addition to direct non-medical costs required for individuals to access needed healthcare (e.g., transportation to a clinic appointment). Indirect costs are costs to the individual and society because of the impact that IBD has on a person's ability to contribute to their full potential. This chapter details recent data on the indirect and out-of-pocket costs experienced by people living with IBD in Canada.

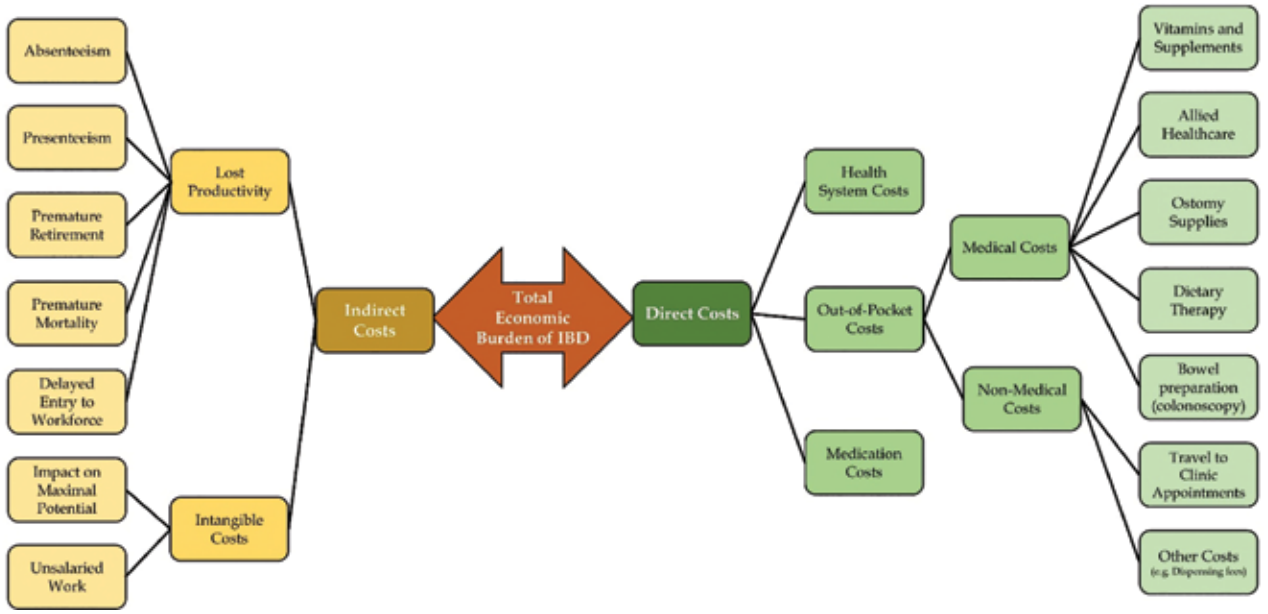
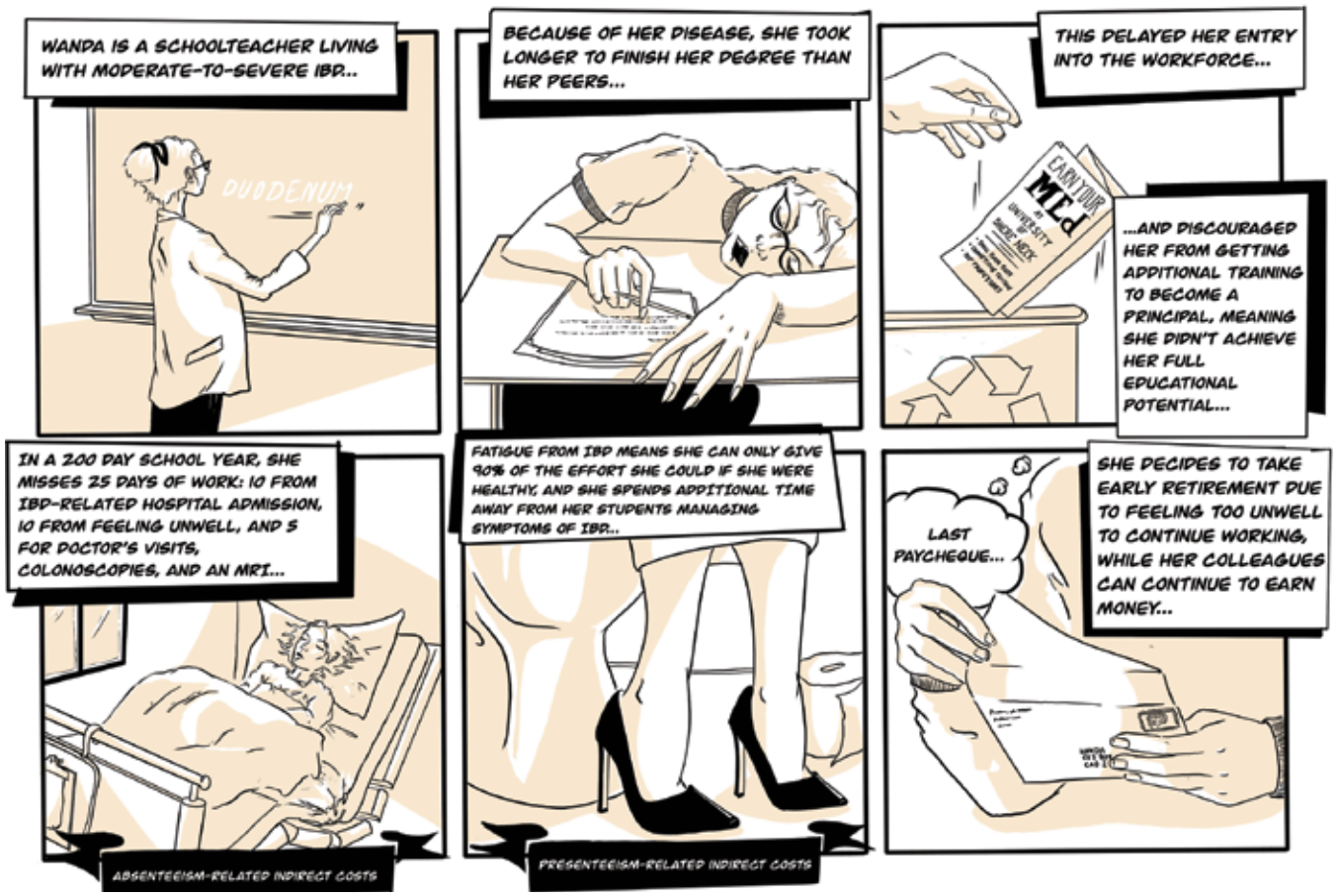


Figure 1: *Component costs contributing to the economic burden of inflammatory bowel disease in Canada. Figure adapted from Garaszczuk et al.*[1]

Indirect Costs

Indirect costs attributable to a disease reflect the impact that living with a disease (such as IBD) has on a person's ability to achieve their full potential for engaging with the world. In this sense, indirect costs of IBD can be thought of as lost opportunity. On the level of the individual living with IBD, indirect costs refer to the costs of what a person is missing out on, either in work or in life, because of IBD. On a societal level, indirect costs refer to the loss to society resulting from the impact that IBD has on a person's ability to fully contribute to their community. Indirect costs are often separated into work-related costs (the loss to the community when a person is unable to work to their full potential) and intangible costs (costs that are difficult to measure, such as the cost to a person from not being able to participate in leisure activities or otherwise enjoy life to their fullest). In addition, the care needs of a person living with IBD can impact the abilities of close family members and friends to contribute to their communities; this is especially true for children, the elderly, and people with severe psychiatric disease or neurocognitive deficits. Therefore, in considering the indirect costs of IBD, the costs incurred by primary caregivers cannot be overlooked.

Indirect costs can often be difficult to quantify precisely. Most attempts to measure indirect costs use the human capital approach, where a person's lost wages are presumed to represent the costs of lost productivity. Further, there are relatively few studies that have focused on the impact that IBD has on one's ability to be optimally productive at work or otherwise contribute to the well-being of society, especially in the Canadian setting.



Work-Related Costs

Absenteeism

Absenteeism costs refer to lost wages due to missed work. Costs related to intermittent absences can directly impact an individual's earnings when they do not have paid sick days or impact employers through costs related to replacing an employee or lost productivity due to an employee's absence. Among respondents with IBD to the Canadian Community Health Survey, those who were employed missed an average of 1.6 (standard deviation: 4.4) days of work over a three-month period; people without IBD missed an average of 1.0 (standard deviation: 3.5) days of work;[2] this equated to an additional 1.1 days (95% CI: 0.7, 1.5) of work missed among people living with IBD at a cost of $270 (95% CI: 163, 377) over three months, after accounting for differences in the probability of employment between people with and without IBD.[2] Extrapolating to a full year, people with IBD miss an additional 4.4 days at a cost of $1,080 every year compared to people without IBD. Based on an estimated 150,775 employed Canadians with IBD, the attributable indirect cost of missed work among people with IBD is estimated to be $163 million annually. This estimate does not capture additional costs related to presenteeism, delayed entry into the workforce, early retirement, or lost opportunity of individuals unable reach their maximum potential.

Several studies have described work-related productivity costs using data from Sweden, where they track healthcare data along with data on access of disability pensions and sick leave pay for the entire population. Sick leave and permanent disability result in 63 days of work missed for people with Crohn's disease (costing $12,719 USD) and 41 days of work missed for people with ulcerative colitis (costing $8,219 USD) per year.[3] Between 2006–2014, the average (mean) number of days of work missed among people with Crohn's disease decreased from 88 days to 61 days.[4] People missed more work days at time of surgery or the start of biologic therapy, but workplace attendance returned to baseline levels within an average (median) of two months following these events.[5] Over the five years following initiation of biologic therapy, workplace attendance was significantly better among individuals continuing on their biologics. Similarly, 44% of people with Crohn's disease missed some work in the first year following diagnosis, but only 9% experienced total work loss five years after diagnosis,[6] likely due to effective therapy.

Among 540 people in the WORK-IBD cohort from the Netherlands, 18% reported missing work in the last week, and 4% had missed at least 50% of workdays.[7] An analysis of a US-based health insurance database suggested the indirect costs related to absenteeism were $5,490 USD per year among people with IBD compared to $3,322 among people without IBD. Women, people with less education, and those of older working age (40–65 years of age) missed more days of work, and people with moderate-to-severe disease and a history of anxiety or depression were more likely to miss work and accrue higher absenteeism costs.[4, 7]

Presenteeism

Presenteeism occurs when an individual is present at work but is unable to work at their full potential. Presenteeism costs estimate the cost associated with this reduction in workplace productivity. Among 762 work-age employed Manitobans with IBD, 37% reported reduced workplace productivity during at least one day in the previous two weeks, with 19% reporting reduced productivity on three or more of the previous two weeks.[8] In the WORK-IBD cohort, 50% of participants reported some degree of productivity loss in the previous week, with 16% reporting severe productivity loss (≥50%

of their usual productivity).[9] The proportion of participants who reported productivity loss of ≥50% was higher in those with Crohn's disease (27%) than in those with ulcerative colitis (12%). Fatigue was reported by 71% as the main reason for their reduced productivity and was the most frequently cited contributor to productivity loss. A Finnish study of 320 individuals followed at an IBD centre estimated the annual indirect costs attributable to presenteeism at €644 per year, €1,079 among people using biologic therapy.[10] Prior to the COVID-19 pandemic, a Dutch study demonstrated improved presenteeism among people with IBD working remotely.[11]

Extrapolating costs estimated in the Finnish study[10] to the Canadian context (adjusting for inflation and purchasing power parities),[12] the total cost of presenteeism among people with IBD is estimated to be $812 (CAD) per person per year, or more than $122 million annually among the 150,775 employed Canadians with IBD.[2]

Impact on Achieving Maximal Educational Potential

A Manitoba study reported no delays in graduating from high school among children with IBD and their non-IBD peers.[13] Marks on standardized testing in mathematics and language arts were similar. Data were less clear on whether the impact of IBD in childhood and adolescence influenced choices in higher education and career training as people reached adulthood.

Disease severity may be related to missed days of school and delays in educational progression in high school. In a study of 675 German and Austrian students with IBD, 10.4% reported repeating a year of school; the repetition rate was highest among individuals who had missed more than two weeks of school related to IBD, or those who had active IBD symptoms.[14] A French study of 104 children and adolescents with IBD reported that they missed 4.8% days of school, with digestive symptoms accounting for a third of missed days and medical appointments and procedures accounting for a quarter of missed days.[15] It is important to recognize that survey results may under-estimate the true burden of IBD on educational attainment and functioning, as the type of parents who are motivated enough to participate in this research may have characteristics that make them more engaged in supporting their children's navigation of school challenges while living with IBD.

Importantly, childhood IBD may have a long-term influence on earning potential. In a study using population-based Swedish healthcare data, the annual salary at 30 years of age among individuals who were diagnosed with IBD during childhood was 5.4% (95% CI: 1.8, 9.1) less than healthy controls.[16] Children who underwent IBD-related surgery or had extensive hospitalization during childhood earned 16.3% (95% CI: 7.9, 24.7) less at 30 years of age than controls without IBD. Whether this earning disparity resulted from decreased education attainment or the impact of ongoing IBD-related disability remains unclear.

Caregiver Costs

Among parents and caregivers of Canadian children with IBD, the average (mean) wages lost annually was $8,367 (standard deviation: $11,912); costs were greatest among parents of females and parents with lower educational attainment and income.[17] In a survey of 120 primary caregivers of American adults with IBD, of whom 79 were fully or partly employed outside the home, 38% experienced absenteeism within the past week (missing nine hours of work on average), and 57% experienced presenteeism, with an 22% average (mean) decrease in productivity.

Among individuals reporting higher levels of caregiver burden, 65% reported absenteeism and 85% reported presenteeism in the previous week.[18] In a multinational European study of 491 children and their caregivers with newly-diagnosed pediatric IBD, workplace productivity of caregivers decreased by 44% around diagnosis, but normalized among caregivers of children whose disease was brought under control.[19] This loss in workplace productivity was also correlated to caregiver-reported quality of life. The estimated cost of caregiver absenteeism and presenteeism in the first year following a child's diagnosis was $7,276 USD.

Applying the most recent Canadian estimate of $8,367 in indirect costs per child with IBD per year to the estimated 6,068 children currently living with IBD in Canada and adjusting for inflation, we estimate the total costs of lost wages among caregivers to be $58 million annually. This cost does not account for lost wages among individuals caring for adults and seniors with IBD and therefore likely underestimates the total indirect costs to caregivers associated with IBD.

Additional Sources of Indirect Costs

Since the 2018 Impact of IBD in Canada report,[20] no additional studies have described the costs of premature retirement or mortality in Canada. Based on data from the Canadian Community Health Survey, people living with IBD are significantly less likely than those without IBD to be employed in the previous three months (70% vs. 80%; adjusted relative risk: 0.92; 95% CI: 0.88, 0.96).[2] With an additional 10% unemployment among people with IBD, we expect 23,124 people with IBD of working age (18–64 years of age) to be unemployed for reasons related to their IBD.[2] With an average (mean) employment income of $52,928,[21] the attributable indirect costs of unemployment among people living with IBD equates to $1.23 billion. This estimate accounts for increases in early retirement and long-term disability among individuals with IBD.

According to data from Statistics Canada, there were 53 deaths with either Crohn's disease or ulcerative colitis listed as the primary cause of death in 2020 among individuals of working age (20–64 years of age in this statistic).[22] Using the average retirement age of 64 years, these 53 individuals will have missed a total of 396 years of future work due to their premature deaths. At an average employment income of $52,928 per year, the cost of premature death in Canada is nearly $21 million annually. This is likely an underestimate as this estimate does not capture deaths where IBD may have been a contributing factor (but not been the primary cause of death) or that occurred due to complications of IBD (e.g., colorectal cancer), its treatment (e.g., an opportunistic infection in someone on immunosuppression), or other chronic conditions that may be elevated among individuals with IBD (see Age-Related Comorbidities).

Estimating the Total Indirect Costs of IBD in Canada

Incorporating costs of absenteeism, presenteeism, unemployment, premature mortality, and caregiving costs, we estimate the total indirect costs of IBD in Canada to be $1.51 billion annually. However, this is likely an underestimate of the true indirect costs of living with IBD in Canada as they do not capture costs related to delayed entry into the workforce, lost opportunity of individuals living with IBD to reach their maximum educational potential, and caregiving costs for adults and seniors with IBD. Additionally, there may be other intangible costs that cannot be assigned a value that increase the societal costs of IBD.

Direct Out-of-Pocket Costs of IBD

Non-medical direct out-of-pocket costs include costs that are incurred in the process of obtaining medical care; they include the costs of parking during a clinic visit, transportation to a medical appointment, or paying a babysitter to watch children while attending an infusion of medication. Medical out-of-pocket expenses include anything the individual must pay for directly, including the costs of medications or health services not covered by insurance (e.g., allied healthcare professionals such as psychologists or dietitians), complementary and alternative medicines (vitamins, supplements, medical cannabis), ostomy supplies, travel to attend appointments, dietary therapy (including exclusive enteral nutrition), and medications for bowel preparation prior to colonoscopy. These costs are a major financial burden for people with IBD[23] and pose barriers to accessing needed care. For example, 55% of people with IBD interviewed

THE STATISTICS REPORTED IN THIS CHAPTER AND RESEARCH PAINT A DISTRESSING PICTURE OF THE SIGNIFICANT COSTS OF IBD AT THE INDIVIDUAL AND SOCIETAL LEVEL. THE RESEARCH DEMONSTRATES THE URGENCY WITH WHICH GOVERNMENTS, RESEARCHERS, AND WORKPLACES NEED TO CONSIDER HOW TO BETTER SUPPORT PERSONS LIVING WITH IBD. NOW IS THE TIME FOR GREATER INVESTMENT INTO INNOVATIVE OUTPATIENT SUPPORTS AND TREATMENT OPTIONS.

in an American study reported cost as the greatest barrier to receiving psychotherapy.[24] Financial barriers to care are described in further detail in Chapter 12. Direct costs borne by the healthcare systems and private insurance plans are discussed in Chapter 4.

A Canadian study reported average (mean) out-of-pocket expenses for 243 children with IBD at $5,236 (standard deviation: $6,931).[17] Travel costs were the highest cost (mean: $2,234, standard deviation: 2,598), followed by over-the-counter medications and other health and food products (mean: $1,894, standard deviation: $3,326), and food purchased during IBD-related appointments (mean: $1,285, standard deviation: $2,172). Tests not covered by provincial healthcare, allied healthcare providers (e.g., psychologists, dietitians), phone calls related to IBD care, and childcare were also included in these total out-of-pocket costs. Families with private health insurance were significantly less likely to be in the highest quartile of out-of-pocket costs (OR: 0.28; 95% CI: 0.08, 0.96).

A survey was conducted in 2022 by Crohn's and Colitis Canada aimed at understanding unmet needs of the IBD community. Respondents reported average (mean) out-of-pocket costs of $1,579 (standard deviation: $2,017). Among the 797 people with IBD responding to the survey, the highest reported costs were prescription medications (mean: $504, standard deviation: $942), vitamins and other supplements (mean: $268, standard deviation: $524), acupuncture or massage therapy (mean: $158, standard deviation: $420), transportation to and from medical appointments (mean: $153, standard deviation: $358), mental health care (mean: $139, standard deviation: $506), and over the counter medications (mean: $128, standard deviation: $270). Only 20% of respondents reported decreasing transportation costs to and from clinic appointments with the shift to virtual care because of the COVID-19 pandemic.

Estimating the Total Out-of-Pocket Expenses for IBD in Canada

Using the estimate of $5,236 for out-of-pocket costs for IBD among the 6,068 children living with IBD in Canada, adjusted for inflation, the total out-of-pocket costs among children with IBD is estimated to be over $36 million. Using the estimate of $1,579 for out-of-pocket costs of IBD among the 316,530 adults and seniors living with IBD in Canada, the total out-of-pocket costs among adults with IBD is estimated to be $500 million. Combining the pediatric and adult out-of-pocket costs, we estimate the total out-of-pocket costs for IBD to be approximately $536 million in 2023.

Conclusions

The indirect and out-of-pocket costs of IBD are substantial: $1.51 billion in indirect costs and $536 million in out-of-pocket costs. Combined, indirect and out-of-pocket costs account for more than $2 billion annually. This cost is a substantial increase compared to the estimated $1.29 billion in indirect and out-of-pocket costs estimated in the 2018 report.[20] The addition of costs associated with presenteeism and caring for children with IBD to the indirect costs, combined with the rising total number of people with IBD in Canada and inflation contribute to these rising costs. Despite these additional data, there remain many costs that are inestimable in the Canadian context, and there are gaps in our knowledge of indirect costs (e.g., caregiving for seniors with IBD).

As the prevalence of IBD continues to rise, the costs of reduced productivity among individuals with IBD and their caregivers will continue to climb. Furthermore, the financial burden associated with out-of-pocket costs places an undue burden on individuals and their families. Our healthcare systems need to evolve to minimize the costs borne by those living with IBD and their caregivers. People with IBD need to be better informed of their rights in the workplace.[25] Systems need to be put in place to remove barriers for gainful employment for individuals with IBD, ensuring they can reach their potential.

Knowledge Gaps & Future Research Directions

1. We need to identify and evaluate strategies to reduce absenteeism and presenteeism among employed Canadians living with IBD. Similarly, we need to identify and evaluate strategies to support students with IBD throughout their educational journeys, including during elementary, secondary, and post-secondary education.

2. We need to describe the short- and long-term cost benefits (to both individuals and the healthcare systems) of providing multidisciplinary care that does not require individuals to pay out of pocket or rely on private insurance.

3. There is a lack of data around the indirect and out-of-pocket costs borne by those acting as caregivers for adults and seniors with IBD, which needs to be described.

4. Additional data are needed to describe the total out-of-pocket costs for people living with IBD, including data on the costs of supplements, ostomy supplies, travel to medical appointments, and dietary therapy.

Patient & Caregiver Perspective

For patient partners, this chapter presents the concerning picture of the significant costs of IBD for individuals living with this condition and their family caregivers. IBD is an expensive chronic condition with costs borne by individuals and Canadian society due to missed work, decrease in productivity, unemployment, and out-of-pocket expenses. Stakeholders must consider how to support persons living with IBD and promote innovative and holistic solutions. As individuals living with IBD face significant barriers to thriving financially, workplace support alternatives (e.g., increased sick time or flexible work-from-home options on flare days), and enhanced benefits and services (e.g., tax breaks or free access to mental health care) need to be promoted to help persons living with IBD and to maximize their full potential in terms of education, earnings, and productivity. Children and young adults living with IBD require early support to be empowered to reach their maximum potential. The indirect healthcare costs of family caregivers (e.g., parents of children with IBD) also require the attention of stakeholders to promote strategies that support them. The experiences and insights of individuals with IBD and their families should guide these initiatives. Furthermore, patient partners emphasized the importance of recognizing that individuals living with IBD, and their families, are still dealing with significant out-of-pocket expenses. These issues require the attention, strategizing, and operationalization of different stakeholders to help reduce these costs and diminish the burden of the disease on the mental health of individuals living with IBD and their families.

Policy Implications & Key Advocacy Outcomes

1. Canadian healthcare should evolve to include multidisciplinary care, including access to mental health professionals, dietitians, and other allied healthcare providers whose care improves the quality of life for people living with IBD. Additionally, extended health benefit providers should be levied to provide additional benefits regarding these costs to reduce overall health expenditures.

2. The costs of supplements, ostomy supplies, and nutritional therapies (e.g., exclusive enteral nutrition) should be covered by universal healthcare programs.

3. Virtual healthcare delivery should be continued beyond the COVID-19 pandemic due to its ability to decrease individual and caregiver costs related to travelling and missed work for medical appointments. Provincial health authorities need to continue remuneration for these services, which decrease indirect and out-of-pocket costs to the individual.

4. Crohn's and Colitis Canada should advocate for workplace programs designed to increase workplace productivity among people living with IBD, including tools to decrease both absenteeism and presenteeism.

5. Crohn's and Colitis Canada should advocate to government for mandatory paid sick days for all individuals, in all sectors.

6. There is a currently lack of understanding among employees and employers in the workplace around what individual rights and workplace accommodations are, regarding chronic disease. Advocacy should target this educational deficit.

7. Crohn's and Colitis Canada should advocate for medical travel tax deduction limits to be increased (in accordance with inflation) and broadening the scope of national tax benefits to include chronic diseases (e.g., Disability Tax Credit, Employment Insurance caregiving benefits). Consistent guidelines concerning qualifications for these credits are needed (from year to year, and across provinces).

8. Crohn's and Colitis Canada should work to partner with social workers, financial/tax experts, and/or lawyers to provide people with IBD financial or legal advice on their rights as citizens with a potentially disabling chronic disease. Practitioners need to understand the financial burden IBD places on an individual and should provide referrals to these experts.

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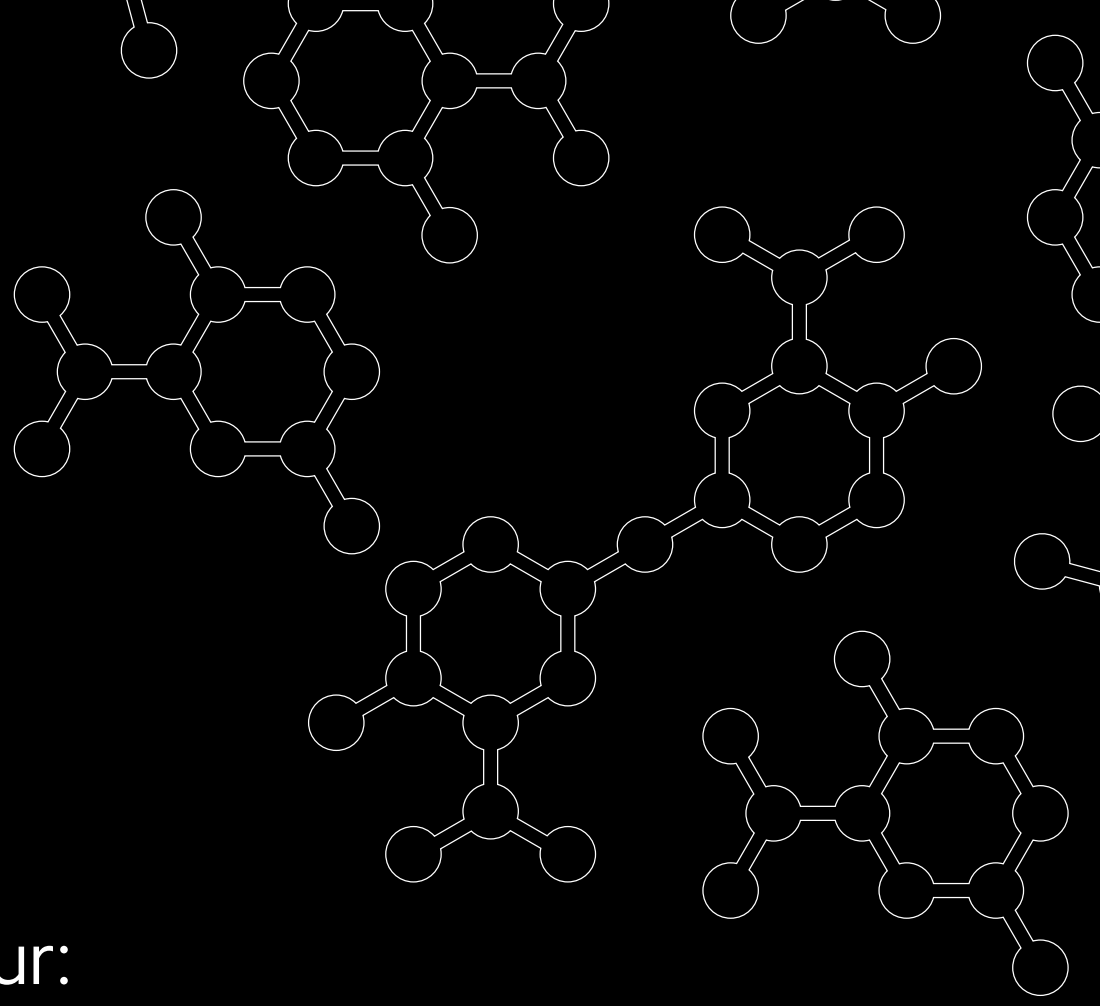


Section Four:

Direct Health System and Medication Costs

Direct Health System and Medication Costs

Abstract

Healthcare utilization among people living with IBD in Canada has shifted from inpatient management to outpatient management; fewer people with IBD are admitted to hospital or undergo surgery, but outpatient visits have become more frequent. Although the frequency of emergency department (ED) visits among adults and seniors with IBD decreased, the frequency of ED visits among children with IBD increased. Additionally, there is variation in the utilization of IBD health services within and between provinces and across ethnocultural and sociodemographic groups. For example, First Nations individuals with IBD are more likely to be hospitalized than the general IBD population. South Asian children with Crohn's disease are hospitalized more often than their Caucasian peers at diagnosis, but not during follow-up. Immigrants to Canada who develop IBD have higher health services utilization, but a lower risk of surgery compared to individuals born in Canada. The total direct healthcare costs of IBD, including the cost of hospitalizations, ED visits, outpatient visits, endoscopy, cross-sectional imaging, and medications are rising rapidly. The direct health system and medication costs of IBD in Canada are estimated to be $3.33 billion in 2023, potentially ranging from $2.19 billion to $4.47 billion. This cost is an increase from an estimated $1.28 billion in 2018, likely due to sharp increases in the use of biologic therapy over the past two decades. In 2017, 50% of total direct healthcare costs could be attributed to biologic therapies; the proportion of total direct healthcare costs attributed to biologic therapies today is likely even greater.

Key Points

1. People living with IBD in Canada are admitted to hospital and undergo surgery less often than in past decades, but these individuals have an increasing number of outpatient visits.

2. The frequency of emergency department (ED) visits among adults and seniors with IBD have decreased. Children with IBD are visiting EDs more often. Despite presenting to the ED for reasons related to their IBD, gastroenterologist consults during their ED visit and follow-up are uncommon.

3. The utilization of IBD-specific health services (outpatient visits, ED visits, and hospitalization) and medications, as well as the likelihood of undergoing surgery, vary both within and between provinces.

4. First Nations individuals with IBD are more likely to be hospitalized than the general IBD population. Additional within and between province studies are needed to better understand healthcare and medication utilization and the risk of surgery in First Nations individuals with IBD.

5. South Asian children with Crohn's disease are hospitalized more often at diagnosis than their Caucasian peers. However, these differences diminish during follow-up.

6. Immigrants to Canada who develop IBD have higher health services utilization, but a lower risk of surgery compared individuals born in Canada.

7. People with IBD of low socioeconomic status are more likely to be hospitalized, undergo surgery, and require systemic steroids.

8. People with IBD living in rural areas are more likely to be hospitalized and visit the ED than people living in urban areas, but there is no difference in their risk of surgery.

9. The total direct healthcare costs of IBD—costs of hospitalizations, ED visits, outpatient visits, endoscopy, cross-sectional imaging, and medications—in Canada have risen rapidly and are estimated to be $3.33 billion in 2023 relative to market list price; these costs may be as low as $2.19 billion or as high as $4.47 billion.

10. Biologic medications contributed approximately 50% of direct healthcare costs in 2017; the proportion of total direct healthcare costs attributed to biologic therapies today is likely even greater.

Summary of Crohn's and Colitis Canada's 2018 Impact of IBD: Direct Costs & Health Services Utilization

In 2018, annual healthcare costs (including healthcare utilization and medication) of IBD in Canada was estimated to be at least $1.28 billion, but this was acknowledged as likely an underestimate due to its reliance on a Manitoba costing study using data from 2006, which reflected an era where far fewer individuals were treated with biologic therapy. Direct healthcare costs for IBD are more than double that of individuals without IBD. Prescription drug costs accounted for 42% of these costs and were continuing to rise with increasing use of biologic therapy. The introduction of biosimilars into the marketplace was anticipated to reduce these costs. People with IBD had increasing access to gastroenterologists, yet many lacked timely access, with most individuals waiting longer than six months between symptom onset and diagnosis. Seniors, individuals living in rural areas, and non-immigrants had less access to specialist care, which was associated with better IBD outcomes. One in five adults with Crohn's disease and one in eight adults with ulcerative colitis were hospitalized every year. Surgery rates were declining. However, within 10 years of diagnosis, one in three people with Crohn's disease still required a surgery, and one in six people with ulcerative colitis required a colectomy.

Introduction

Canadians living with inflammatory bowel disease (IBD) have frequent interactions with the healthcare system, including being admitted to hospitals, undergoing diagnostic testing (endoscopy, laboratories, imaging), and receiving ambulatory and long-term care. Nearly all Canadians are eligible for universal healthcare plans that cover the majority of costs from these interactions. Most provinces also cover medication costs for seniors, individuals on social assistance, or those who are otherwise unable to afford needed medications. When these and other costs (e.g., costs associated with care provided by allied healthcare providers such as psychologists or dietitians) are not covered by health plans, individuals must pay out-of-pocket or purchase private insurance. These costs, borne both by individuals and the healthcare system, comprise the direct costs of IBD.

Provincial healthcare budgets are limited. Nevertheless, Canadian healthcare systems must be prepared to address the needs of a growing IBD population. Understanding the healthcare needs of people with IBD ensures Crohn's and Colitis Canada can advocate for the resources people with IBD need. Therefore, it is critical to understand how much care is being used by Canadians with IBD, how this is changing over time, the inequities in healthcare utilization, and associated costs in order to provide equitable, high-quality care for people with IBD. This chapter outlines the direct costs of IBD borne by the Canadian health systems, including medication costs (covered either through government or private pharmacare programs). For the direct costs borne by individuals (including medication costs paid out-of-pocket by a person with IBD), see Chapter 3.

Hospitalizations

The frequency of hospitalization for IBD has steadily decreased in most Canadian regions over the past few decades, likely resulting from a combination of evolving treatment paradigms in IBD and health system pressures (Table 1).[1-6] In Ontario, hospitalizations among children with IBD declined at a slower rate than among children without IBD (with IBD, average annual percentage change [AAPC]: −2.6%; 95% confidence interval [CI]: −3.3%, −1.8%; matched controls, AAPC: −4.3%; 95% CI: −5.4%, −3.3%).[3] Hospitalizations in adults with IBD also decreased in Ontario, but the introduction of biologic therapy did not alter the rate at which hospitalizations were decreasing in people with Crohn's disease.[4]

Table 1: Trends in hospitalization rates in Canadian people with inflammatory bowel disease

Study	Province	Years	Age Group	Cohort Type	Definition of Hospitalization	IBD Type	Hospitalization Rates	Time Trend (95% CI)
Coward *et al.*[5]	Alberta	2002–2014	All ages	Prevalent	IBD-specific (admission directly resulting from IBD)	IBD	2002: 16.8 per 100 people (95% CI: 16.4, 17.2) 2014: 8.7 per 100 people (95% CI: 8.5, 9.0)	AAPC: −3.77% (−4.63, −3.08)
					IBD-related (admission for IBD or a symptom or comorbidity associated with IBD)	IBD	2002: 22.6 per 100 people (95% CI: 22.1, 23.1) 2014: 13.4 per 100 people (95% CI: 13.2, 13.7)	AAPC: −3.09% (−3.65, −2.62)
					All reasons	IBD	2002: 35.3 per 100 people (95% CI: 34.7, 35.9) 2014: 24.9 per 100 people (95% CI: 24.5, 25.2)	AAPC: −2.12% (−2.31, −1.93)
Targownik *et al.*[1]	Manitoba	2005–2015	All ages	Prevalent	IBD-attributable (difference in the total number of hospitalizations when comparing people with and without IBD)	CD	2005: 19.08 per 100 PY 2015: 11.75 per 100 PY	AAPC: −3.0% (−3.7, −2.3)
						UC	2005: 8.11 per 100 PY 2015: 7.89 per 100 PY	AAPC: 0.3% (−0.5, 1.1)
					Urgent IBD-specific (hospitalizations including an overnight stay with a most-responsible diagnosis of CD or UC)	CD	2005: 6.21 per 100 PY 2015: 3.19 per 100 PY	AAPC: −6.0% (−7.5, −4.3)
						UC	2005: 2.63 per 100 PY 2015: 1.96 per 100 PY	AAPC: 0.4% (−2.0, 2.7)
Dheri *et al.*[3]	Ontario	1994–2012	Pediatrics (<18 years)	Incident	All reasons	IBD	—	AAPC: −2.6% (−3.3, −1.8)
						CD	—	—
						UC	—	—
					IBD-specific (hospitalizations with a most responsible diagnosis of IBD)	IBD	—	AAPC: −2.5% (−3.2, −1.8)
						CD	—	AAPC: −3.0% (−3.8, −2.1)
						UC	—	AAPC: −1.1% (−2.5, 0.003)
					IBD-related (hospitalizations with IBD or its signs, symptoms, and extra-intestinal manifestations as a most responsible diagnosis)	IBD	—	AAPC: −1.7% (−2.4, −1.0)
						CD	—	AAPC: −3.0% (−3.8, −2.1)
						UC	—	AAPC: −1.4% (−2.8, −0.0004)

Table 1: Trends in hospitalization rates in Canadian people with inflammatory bowel disease *(continued)*

Study	Province	Years	Age Group	Cohort Type	Definition of Hospitalization	IBD Type	Hospitalization Rates	Time Trend (95% CI)
Murthy *et al.*[4]	Ontario	1995–2012	Adults (>18 years)	Prevalent	IBD-related (visits with either CD or UC as the most responsible comorbid, or primary interservice or interhospital transfer diagnosis)	CD	—	**Pre-infliximab:** OR:[b] 0.980 (0.975, 0.985) **Post-infliximab:** OR:[b] 1.00 (0.998, 1.01)
						UC	—	**Pre-infliximab:** OR:[b] 0.976 (0.973, 0.979) **Post-infliximab:** OR:[b] 1.22 (1.07, 1.39)
Rahman *et al.*[2]	Ontario	2003–2014	All ages	Prevalent	CD was the most responsible diagnosis for the admission	CD	2003: 154 (95% CI: 150, 159) per 1,000 2014: 104 (95% CI: 101, 107) per 1,000	32.4% decrease over the course of the study
Verdon *et al.*[6]	Québec	1996–2015	Not stated	Incident	IBD-related	CD	1996–2010: 19%[a] 2011–2015: 45%[a]	—
						UC	1996–2010: 21%[a] 2011–2015: 44%[a]	—

Abbreviations: AAPC, *average annual percentage change*; CD, *Crohn's disease*, CI, *confidence interval*, IBD, *inflammatory bowel disease*; PY, *person-years*; OR, *odds ratio*; UC, *ulcerative colitis*

[a]*Hospitalization rates among biologic users only.*

[b]*Quarter analyzed as a continuous variable; odds ratio* (OR) *compares the odds of hospitalization per quarter change in time.*

Costs of Hospitalization

Hospitalization costs directly attributable to Crohn's disease decreased between 2005–2015, from $2,565 to $1,426 per person with Crohn's disease per year; hospitalization costs attributable to ulcerative colitis remained steady (costs in 2015 Canadian dollars [CAD]).[1] In Alberta, British Columbia, and Saskatchewan, hospitalization costs ranged from $2,372 to $4,472 per person with IBD per year (Alberta and British Columbia costs in 2020 CAD; Saskatchewan costs in 2013 CAD).[7, 8] Hospitalization costs accounted for 35%–45% of health system costs in 2009, decreasing to 22%–28% in 2015.[7] In these studies, hospitalization costs were averaged over all people with IBD, regardless of whether they were hospitalized. Costs of inpatient admissions for Manitoba children with IBD decreased from $365,252 in 2004 to $61,600 in 2017 ($p<0.01$); per-person hospitalization costs were not reported (costs in 2018 CAD).[9] The authors attributed this decrease in hospitalization costs to a reduction in IBD-related surgeries.

Surgeries

When medications are not working or IBD-related complications occur (e.g., strictures, fistulae, abscesses, or colorectal cancer), individuals with IBD may require surgery. The type and location of surgery depends on disease location and phenotype. The most common surgery in Crohn's disease is an intestinal resection,[2] most often an ileocecal resection.[10] People with ulcerative colitis may require a colectomy with or without the creation of an ileal pouch-anal anastomosis (typically a J-pouch in more recent years). Within five years of diagnosis, 12% (95% CI: 8%, 15%) of children with Crohn's disease required an intestinal resection and 12% (95% CI: 10%, 14%) of children with ulcerative colitis required a colectomy.[11, 12] One third of Ontario seniors required intestinal resection within five years of a Crohn's disease diagnosis, and one in five Ontario seniors required a colectomy within five years of an ulcerative colitis diagnosis.[11]

As IBD management has evolved, surgery rates have decreased (Table 2).[1-4, 9, 10, 13] However, these declining trends existed prior to the introduction of biologics, and their introduction into the market have not appreciably changed the rate at which surgeries are decreasing.[4]

Table 2: Trends in surgery rates in Canadian people with Crohn's disease and ulcerative colitis

Study	Province	Years	Age Group	Cohort Type	IBD Type	Surgery Rates	Time Trend (95% CI)
Dittrich *et al.*[10]	Alberta (Edmonton)	1996–2013	Adults (≥18 years)	Prevalent	CD	1996: 5.8 per 100 patients 2013: 1.4 per 100 patients	AAPC: −8.4% (−9.6, −7.3)
El-Matary *et al.*[9]	Manitoba	1995–2017	Pediatrics	Incident	IBD	1995–2003: 5.2 per 100 PY 2004–2017: 1.8 per 100 PY	RR: 0.34 (0.20, 0.59)
Targownik *et al.*[1]	Manitoba	2005–2015	All ages	Prevalent	CD	2005: 1.88 per 100 PY 2015: 1.27 per 100 PY	AAPC: −3.6% (−6.0, −1.2)
				Prevalent	UC	2005: 0.85 per 100 PY 2015: 0.83 per 100 PY	AAPC: 1.7% (−2.0, 5.4)
Dheri *et al.*[3]	Ontario	1994–2012	Pediatrics (<18 years)	Incident	CD	—	AAPC: −6.0% (−7.3, -4.6)
					UC	—	AAPC: −3.0% (−5.2, −0.7)
Murthy *et al.*[4]	Ontario	1995–2012	Adults (>18 years)	Prevalent	CD	—	**Pre-infliximab:** OR:[b] 0.984 (0.975, 0.99) **Post-infliximab:** OR:[b] 1.10 (0.81, 1.50)
					UC	—	**Pre-infliximab:** OR:[b] 0.993 (0.975, 1.01) **Post-infliximab:** OR:[b] 0.933 (0.540, 1.61)
Rahman *et al.*[2]	Ontario	2003–2014	All ages	Prevalent	CD	**All inpatient surgeries:** 2003: 53 (95% CI: 50, 55) per 1,000 2014: 32 (95% CI: 30, 34) per 1,000 **Intestinal resections:** 2003: 41 (95% CI: 39, 43) per 1,000 2014: 23 (95% CI: 22, 25) per 1,000 **All outpatient surgeries:**[a] 2003: 8 (95% CI: 7, 9) per 1,000 2014: 12 (95% CI: 10, 13) per 1,000	**All inpatient surgeries:** 39.6% decrease over the course of the study **Intestinal resections:** 44% decrease over the course of the study
Abou Khalil *et al.*[13]	Québec	1998–2011	Not stated	Prevalent	UC	1998–2004: 36 per 1,000 PY 2005–2011: 30 per 1,000 PY	HR:[c] 0.81 (0.70, 0.95)
Verdon *et al.*[6]	Québec	1996–2015	Not stated	Incident (proportion with surgery within five years of diagnosis)	CD	**1st surgeries:** 1996–2010: 8% 2011–2015: 15% **2nd surgeries:** 1996–2010: 18% 2011–2015: 21%	—
					UC	1996–2010: 6% 2011–2015: 10%	—

Abbreviations: AAPC, *average annual percentage change*; CD, *Crohn's disease*; CI, *confidence interval*; IBD, *inflammatory bowel disease*; PY, *person-years*; OR, *odds ratio*; RR, *relative risk*; UC, *ulcerative colitis*

[a]*Includes stricture dilations and stricturoplasty (61.6% in 2014) and fistula or perianal surgeries (36.9% in 2014)*

[b]*Quarter analyzed as a continuous variable; odds ratio (OR) compares the odds of hospitalization per quarter change in time.*

[c]*Comparing across eras*

Emergency Department Visits

The frequency of Crohn's disease-related emergency department (ED) visits decreased from 141 (95% CI: 137, 146) in 2003 to 101 (95% CI: 99, 104) per 1,000 individuals with an existing diagnosis of Crohn's disease in 2014.[2] Trends were similar in adults and seniors.[2] ED visits among children increased for IBD-related reasons (AAPC: 1.5%; 95% CI: 0.7%, 2.3%) as well as for all causes (AAPC: 1.0%; 95% CI: 0.1%, 1.9%),[3] while the frequency of all-cause ED visits among children without IBD remained stable (AAPC: −0.2%; 95% CI: −0.6%, 0.2%).[3] The average cost of an ED visit in Winnipeg, Manitoba was $650 (costs in 2017 CAD); costs were primarily driven by imaging and specialist consults.[14]

Sixty percent of ED visits among people with IBD occur outside of traditional office hours.[14] One third of people visiting the ED are admitted to hospital.[15] Those not admitted to hospital averaged 5.2 IBD-related ED visits over a three-year period; half had seen their gastroenterologist in the past year.[15] Gastroenterologists were only consulted during 19% of first IBD-related ED visits,[15] but the likelihood of seeing a gastroenterologist increased with repeat visits.[14] People seen by a gastroenterologist during their ED visit were significantly more likely to have follow-up with a gastroenterologist following discharge from the ED (79% vs. 27%).[15]

Outpatient Care

On average, people with IBD have an additional 3.7 outpatient visits per person per year compared to people without IBD.[16] Between 2005–2015, the number of IBD-attributable outpatient visits in Manitoba increased from 573 to 681 per 100 person-years among individuals with Crohn's disease and from 376 to 522 per 100 person-years among individuals with ulcerative colitis.[1] The frequency of IBD-specific outpatient visits was stable among Ontario children diagnosed with IBD before 2005 (AAPC: 0.6%; 95% CI: −0.04%, 1.2%), but increased by 4.0% (95% CI: 3.1%, 4.9%) per year among those diagnosed since 2005.[3] Since 2005, the frequency of all-cause outpatient visits for children without IBD decreased by 0.7% per year (95% CI: 0.0002%, 1.4%) but increased by 2.1% per year (95% CI:1.2%, 3.0%) among children with IBD. Each year, an individual with IBD accrued an average of $1,663 (British Columbia) and $1,898 (Alberta) in costs related to physician visits; these costs remained stable over time (costs in 2020 CAD).[7]

Impact of Specialist Care on IBD Outcomes

While people with IBD living in rural areas were more likely to visit the ED than those living in urban areas, this association was not mediated by geographic differences in access to specialist care.[17] People with IBD living in an Ontario Local Health Integration Network—with fewer gastroenterologists per capita and fewer people receiving regular follow-up care with a gastroenterologist—were more likely to visit the ED.[18] Among Ontario seniors, having a gastroenterologist as the primary provider of IBD care was not associated with IBD-specific ED visits, hospitalizations, or intestinal resection in Crohn's disease, even when controlling for community-level availability of gastroenterologists.[11] Ontario seniors whose ulcerative colitis care was managed by a gastroenterologist were less likely to require a colectomy (odds ratio [OR]: 0.78; 95% CI: 0.63, 0.97) and more likely to take immunomodulators (OR: 1.69; 95% CI: 1.41, 2.02).[11]

Endoscopy and Non-Invasive Imaging

People with IBD are significantly more likely to undergo abdominal imaging.[19] One third of people with IBD had one or more procedure of abdominal x-ray, barium enema, or abdominal/pelvic CT; <10% of matched controls without IBD had ever undergone these procedures. Almost 40% of people with IBD had an abdominal ultrasound compared to 18% of matched controls while 11.5% of people with IBD and 1.1% of controls had an abdominal/pelvic MRI. These estimates are derived from health administrative data, which currently do not provide the information needed to describe the recent increases in point-of-care bowel ultrasounds within outpatient IBD clinics. Additional information on the utilization of point-of-care bowel ultrasounds and barriers to universal access to this imaging modality are provided in Chapter 12.

The proportion of people with an abdominal CT for Crohn's disease increased by 11% (95% CI: 9%, 11%) per year between 1999–2007, then decreased by 2% (95% CI: 2%, 3%) per year until 2017.[19] The proportion of people with an abdominal MRI for Crohn's disease increased by 25% (95% CI: 21%, 29%) per year between 1999–2007 and by 34% (95% CI: 29%, 40%) per year between 2007–2012. The use of abdominal MRI continued to increase after 2012, but at a slower pace (6% per year, 95% CI: 3%, 10%). The use of abdominal ultrasounds decreased by 2% per year (95% CI: 1%, 3%) between 1999–2007, then increased by 3% per year (95% CI: 2%, 4%). Trends in abdominal CT and ultrasound for ulcerative colitis mirrored those of Crohn's disease. Abdominal MRI was much less common in ulcerative colitis and its use increased at a slower pace than in Crohn's disease.

Medication Use

Using provincial health administrative data to describe how many people in a province are taking a type of therapy can be challenging due to differences in how these data are captured. In Alberta and Manitoba, information is available on all medications filled at any outpatient pharmacy in the province. In others (e.g., Ontario, Quebec), data are limited to outpatient prescriptions for those eligible for provincial drug plans; in these provinces, individuals ≥65 years of age and those on social assistance are eligible for provincial drug plans as well. Individuals who need assistance to cover costs associated with expensive medications (e.g., biologics) may also be eligible for provincial drug plans, but off-label use of biologics are often funded by compassionate use programs of pharmaceutical companies, and therefore the dose/interval of their use may not be accurately reflected in provincial drug databases.

Corticosteroids

Among individuals eligible for provincial drug coverage in Quebec, there has been no change in corticosteroid use,[6] while a small decrease in corticosteroid use has been noted in people with Crohn's disease in Edmonton, Alberta (AAPC: −1.9%; 95% CI: −3.0%, −0.7%).[10]

Biologics

Multiple Canadian provinces have reported the rapidly increasing use of biologics to treat IBD. Between 1996–2013, biologic use increased by 36.2% (95% CI: 31.3%, 41.5%) per year among individuals with Crohn's disease in Edmonton, Alberta.[10] Among those eligible for drug coverage in Ontario, infliximab use increased from 2.2% (95% CI: 1.0%, 3.4%) to 16.2% (95% CI: 14.1%, 18.4%) between 2003–2017; adalimumab use increased from 0% to 2.5% (95% CI: 1.7%, 3.4%) during the same time frame.[2] In Quebec, 4% of individuals diagnosed with Crohn's disease before 2011 and

eligible for provincial drug coverage received a biologic within five years of diagnosis compared to 16% of those diagnosed after 2010.[6] Biologic usage among people with ulcerative colitis in Quebec similarly increased from 2% among those diagnosed before 2011 compared to 13% among those diagnosed after 2010.[6] This rapid increase in biologic use likely results from an increasing recognition of the importance of shifting treatment paradigms, which include earlier introduction of biologic therapy and aiming for short- and long-term control of both clinical and objective markers of disease activity (e.g., endoscopic or cross-sectional imaging, fecal calprotectin). The evolving paradigm of IBD management is outlined in Chapter 11.

Immunomodulators

Among people in Quebec with IBD eligible for provincial drug coverage, thiopurine use significantly increased when comparing the pre-biologic (before 2011) and biologic eras (after 2010) (Crohn's disease, 21% to 24%; $p<0.001$; ulcerative colitis, 13% to 16%, $p<0.001$); the proportion of people on methotrexate also increased but was much smaller.[6] Between 1996–2013, immunomodulator use increased by 5.0% per year (95% CI: 2.7%, 7.4%) among people with Crohn's disease in Edmonton, Alberta.[10] The increasing use of immunomodulators is likely due to their use in combination therapy along with a biologic, rather than the use of immunomodulators on their own.

5-aminosalicylates (5-ASA)

Fewer people with Crohn's disease in Quebec diagnosed after 2010 filled prescriptions for 5-ASAs as compared to the individuals diagnosed in 2010 or earlier (21% vs. 33%).[6] Forty percent of people with ulcerative colitis used 5-ASAs, and rates did not change over the course of the study.

Medication Costs

Medications accounted for approximately 50% of all IBD direct healthcare costs in 2016[7] and are expected to make up an even larger proportion of total costs as the number of individuals on biologics increases and newer biologics become available. Total direct healthcare costs (including medication costs) in the year following a biologic start in Manitoba were $42,876 per person per year, compared to $5,153 in the year prior to the biologic start; costs were sustained among those staying on their biologic (costs are in 2015 CAD).[20] Medication costs in Saskatchewan significantly increased from an average of $660 (95% CI: $595, $732) per person per year in 1999/2000 to $6,530 (95% CI: $6,024, $7,078) in 2016/2017 (costs are in 2013 CAD).[8] Similar increases in cost were reported in Manitoba between 2005–2015, where costs of anti-TNFs increased from $181 per person per year to $5,720 per person per year (costs are in 2015 CAD).[1] These costs were averaged among the total population of people with IBD and were not specific to those receiving anti-TNF therapy.

Anti-TNF therapies dispensed for any reason (e.g., IBD, rheumatoid arthritis, psoriasis), cost Canadian taxpayers nearly $1 billion in 2019; this cost estimate accounted only for anti-TNFs taken by those eligible for provincial drug programs (3.9% of biologics dispensed).[21] The introduction of biosimilars for infliximab (2015) and adalimumab (2021) may help stem the increasing costs of biologic therapy. However, the less expensive biosimilars have not been widely adopted. In 2019, only 15.5% of anti-TNFs dispensed for any condition were biosimilars.[21] Some provinces have introduced policies to encourage biosimilar use, including requiring that all new anti-TNFs started be biosimilars and/or instituting non-medical mandatory switching of people from an originator biologic to a biosimilar. Non-medical mandatory

switch policies would result in costs savings due to decreased medication expenditures.[21, 22] However, these cost savings would be accompanied by a loss of effectiveness in 84% of simulations, corresponding to a loss of 0.13 (95% CI: 0.07, 0.16) quality-adjusted life years over a five-year time frame.[23] The estimated cost savings over five years of $46,194 (95% CI: $42,420, $50,455) of a non-medical switch program does not account for indirect costs (e.g., decreased workplace productivity) that would accompany a decrease in effectiveness. Additionally, potential cost savings from anti-TNF biosimilars will be partially offset by increasing use of newer classes of biologic therapy that are at least as expensive as anti-TNF medications. For additional information about the efficacy and safety of biosimilars, see Chapter 11.

Variation in Health Services, Medication Utilization, and Surgery

While all Canadians are eligible for universal healthcare coverage, there remains significant variation in healthcare utilization among Canadians living with IBD. Two studies have specifically investigated this variation in healthcare utilization. The first compared variation in health services utilization and surgery within the first five years following IBD diagnosis among children treated at pediatric centres in Alberta, Manitoba, Nova Scotia, and Ontario.[12] The second compared health services, medication utilization, and surgery among seniors in Ontario across healthcare networks.[11]

The proportion of children with IBD who were hospitalized varied significantly across pediatric centres (I^2: 84%, τ: 0.1556),[12] but the risk of hospitalization among seniors was similar across healthcare networks (median odds ratio [MOR]: 1.0).[11] The risk of colectomy among children with ulcerative colitis did not vary across pediatric centres (I^2: 0%, τ: 0); the risk of intestinal resection in children with Crohn's disease did vary (I^2: 81%, τ: 0.042).[12] The opposite was true in Ontario seniors: There was significant variation in the risk of colectomy among seniors with ulcerative colitis (MOR: 1.37, p=0.01) but not in the risk of intestinal resection among seniors with Crohn's disease (MOR: 1.32, p=0.08).[11]

Children with IBD varied in the frequency at which they visited an ED (I^2: 99%, τ: 1.33), largely attributable to between-province differences.[12] Among Ontario seniors with IBD, there was variation in the likelihood that they visited an ED at the time of IBD diagnosis (MOR: 1.30, p=0.023), but not within five years after diagnosis (MOR: 1.02, p=0.49).[11]

The utilization of some medications but not others varied among Ontario seniors treated in different healthcare networks. The use of both corticosteroids and immunomodulators within five years of IBD

diagnosis varied (corticosteroids, MOR: 1.26, p=0.006; immunomodulators, MOR: 1.46, p=0.001).[11] In contrast, there was no significant variation in the use of biologics among seniors (MOR 1.15, p=0.34).[11]

While we cannot determine if variability in health service utilization, medication utilization, and surgery results from differential access to the healthcare system or other factors that shift an individual's likelihood of seeking healthcare, it is important that we recognize that there are differences in access to and provision of care that may impact long-term outcomes. Canadian studies have aimed to compare health services and medication utilization across sociodemographic (defined by socioeconomic status and rural/urban residence) and ethnocultural groups (including First Nations individuals, those of South Asian descent, and immigrants to Canada).

Socioeconomic Differences

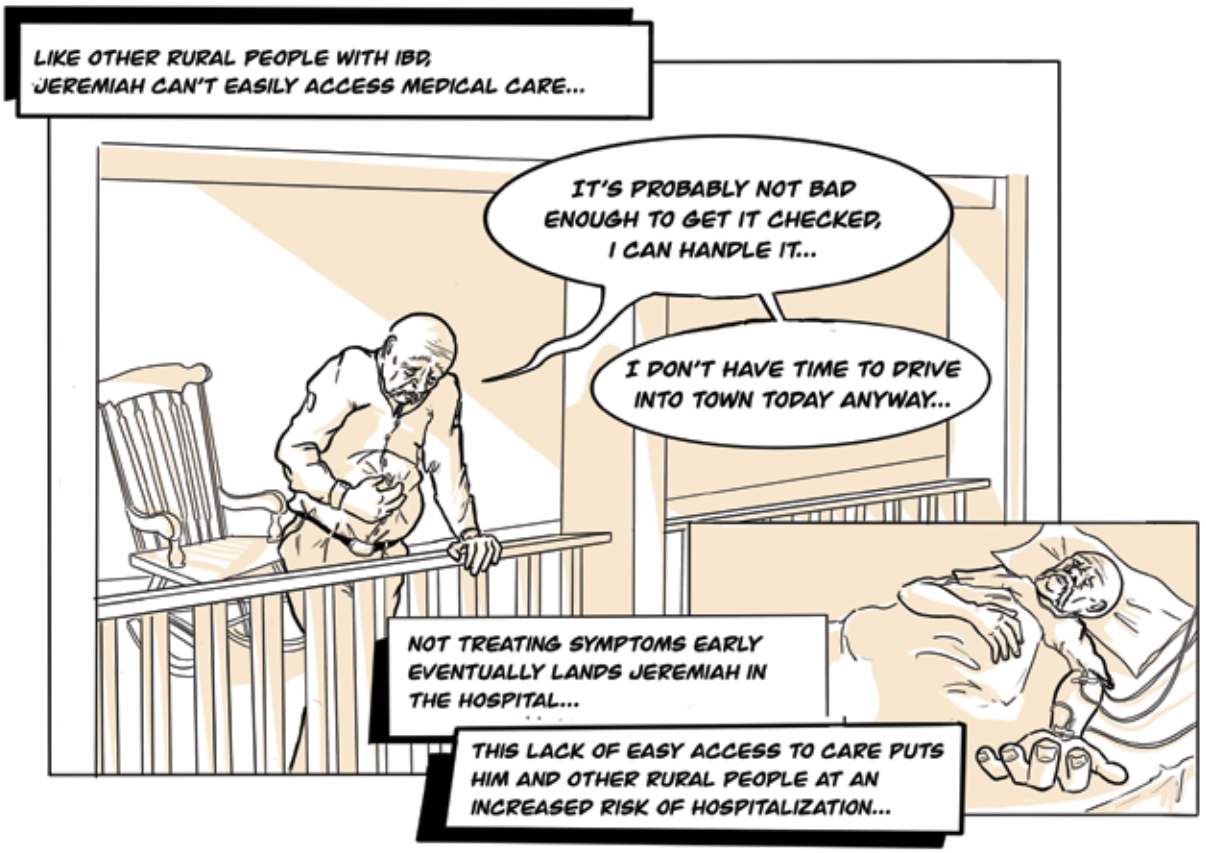
A Manitoba study used health administrative data to compare health services utilization among people with IBD classified as having low socioeconomic status compared to those of higher socioeconomic status.[24] In this study, individuals with low socioeconomic status met at least one of the following three criteria: (1) received Employment and Income Assistance; (2) registered with Child and Family Services or had a child registered with Child and Family Services; or (3) lived in an area defined as being in the highest fifth based on the Socioeconomic Factor Index version 2. Individuals with IBD classified as having low socioeconomic status were more likely to be hospitalized (any reason, relative risk [RR]: 1.38; 95% CI: 1.31, 1.44; IBD-specific reasons, RR: 1.28; 95% CI: 1.18, 1.39). People classified as low socioeconomic status also had an increased the risk of being admitted to an intensive care unit (RR: 1.94; 95% CI: 1.65, 2.27). Low socioeconomic status was associated with an increased risk of surgery among people with existing IBD diagnoses (hazard ratio [HR]: 1.11; 95% CI: 1.00, 1.23) but not people with newly-diagnosed IBD (HR: 1.12; 95% CI: 0.99, 1.27). People with IBD and low socioeconomic status had more all-cause outpatient visits (RR: 1.10; 95% CI: 1.06, 1.13) but not IBD-specific outpatient visits (RR: 1.04; 95% CI: 0.98, 1.10). Socioeconomic status was not associated with seeing a gastroenterologist (RR: 1.02; 95% CI: 0.94, 1.10). Low socioeconomic status was associated with increased use of corticosteroids (RR: 1.11; 95% CI: 1.01, 1.21) but not biologic use (RR: 1.03; 95% CI: 0.91, 1.16).

Individuals Living in Rural and Urban Areas

Data from multiple provinces have described differences in healthcare utilization among people with IBD living in rural and urban regions.[17, 25] People with IBD living in rural regions had more IBD-specific hospitalizations than those in urban regions (Alberta/Ontario/Manitoba combined, incidence rate ratio [IRR]: 1.17; 95% CI: 1.02, 1.34; Saskatchewan, IRR: 1.22; 95% CI: 1.09, 1.37).[17, 25] People living in urban and rural areas had similar risk of first intestinal resection for Crohn's disease and colectomy for ulcerative colitis,[17, 25] but the association with needing a second surgery among people with Crohn's disease varied by province (Ontario, OR: 1.55; 95% CI: 1.16, 2.08; Alberta, OR: 1.14; 95% CI: 0.73, 1.80; Manitoba, OR: 0.80; 95% CI: 0.39, 1.66).[17] People with IBD living in rural areas present to EDs significantly more often than those living in urban areas for IBD-specific reasons (IRR: 1.53; 95% CI: 1.42, 1.65).[17] Only unscheduled visits to EDs were counted; any scheduled visits (e.g., for biologic infusion) did not contribute to the increased number of visits among those living in rural areas. There was no difference in the time to endoscopy for people living with IBD rural versus urban areas in Saskatchewan (HR: 0.94; 95% CI: 0.87, 1.00); however, people living in rural areas had fewer endoscopies during the course of the study (IRR: 0.92; 95% CI: 0.87, 0.98).[25]

The frequency of IBD-specific outpatient visits was similar among people living in urban and rural areas of Alberta, Manitoba, and Ontario (IRR: 0.99; 95% CI: 0.88, 1.01).[17] Furthermore, individuals living in rural areas were less likely to have ever seen a gastroenterologist for IBD-specific reasons (Alberta, Manitoba, and Ontario, OR: 0.46; 95% CI: 0.32, 0.65; Saskatchewan, OR: 0.60; 95% CI: 0.51, 0.70), and they had fewer IBD-specific gastroenterology visits (Saskatchewan, IRR: 0.89; 95% CI: 0.83, 0.95).[17, 25] The differences in the likelihood of having seen a gastroenterologist varied by age: No differences were noted in children with IBD (<10 years of age at diagnosis, OR: 0.97; 95% CI: 0.77, 1.20; 10–18 years of age at diagnosis, OR: 0.70; 95% CI: 0.47, 1.04) and the largest differences were seen in individuals ≥65 years of age at diagnosis (OR: 0.35; 95% CI: 0.26, 0.46).

People living with IBD in rural and urban areas of Saskatchewan were equally likely to be treated with biologic and immunomodulator therapies (biologic, HR: 0.89; 95% CI: 0.78, 1.01; immunomodulator, HR: 0.93; 95% CI: 0.84, 1.03).[25] Similarly, there were no differences in the likelihood of becoming steroid dependent among these two groups (OR: 0.94; 95% CI: 0.79, 1.12).[25] Rural living for people with Crohn's disease, but not for people with ulcerative colitis in Saskatchewan made them more likely to be prescribed 5-ASAs (Crohn's disease, HR: 1.13; 95% CI: 1.02, 1.26; ulcerative colitis, HR: 1.06; 95% CI: 0.97, 1.16).[25]



First Nations Individuals

A study using health administrative data in Saskatchewan compared health services and medication utilization among First Nations individuals with IBD not living on reserves to the general IBD population.[26] After adjusting for rural/urban residence, First Nations individuals with IBD in Saskatchewan were more likely than the general IBD population to be hospitalized for IBD-specific reasons (HR: 1.33; 95% CI: 1.01, 1.75). First Nations individuals living with IBD might have a different risk of surgery compared to the general IBD population (Crohn's disease, HR: 0.93; 95% CI: 0.51, 1.70; ulcerative colitis, HR: 1.30; 95% CI: 0.83, 2.05). Endoscopy rates were similar among First Nations individuals and people from the general population when adjusting for rural/urban residence (HR: 1.14; 95% CI: 0.92, 1.41) but not in the unadjusted model (HR: 1.25; 95% CI: 1.01, 1.54).

There might be differences in biologic and immunomodulator therapy between First Nations individuals with IBD and people with IBD from the general population (biologic therapy unadjusted for rural/urban residence, HR: 0.58; 95% CI: 0.34, 0.99; biologic therapy adjusted for rural/urban residence, HR: 0.65; 95% CI: 0.38, 1.11; immunomodulator therapy adjusted for rural/urban residence, HR: 0.79; 95% CI: 0.55, 1.55).[26] First Nations individuals were less likely to be prescribed 5-ASAs (HR: 0.56; 95% CI: 0.45, 0.71); this was consistent for Crohn's disease and ulcerative colitis.[26] Because of the relatively small numbers of First Nations individuals living with IBD, these estimates are imprecise and further studies within and across provinces are needed. Unfortunately, there is also a lack of research addressing IBD among Indigenous communities in Canada more broadly.

South Asian Individuals with IBD

The risk of hospitalization/surgery was compared among South Asian and non-Jewish Caucasian children using data from the Canadian Children Inflammatory Bowel Disease Network (CIDsCaNN)—a cohort study of children newly diagnosed with IBD across 12 Canadian pediatric hospitals.[27] South Asian children with Crohn's disease were more likely to be hospitalized at diagnosis (OR: 3.30; 95% CI: 1.36, 8.03), but the odds of hospitalization were similar among South Asian and Caucasian children with ulcerative colitis (OR: 1.09; 95% CI: 0.51, 2.30). In the 18 months following diagnosis, there were no differences in the risk of hospitalization across ethnic groups (Crohn's disease, HR: 1.30; 95% CI: 0.57, 2.98; ulcerative colitis, HR: 0.80; 95% CI: 0.40, 1.60). There were no differences in initial induction or maintenance therapy when comparing South Asians and Caucasians. However, South Asian children with Crohn's disease were more likely to receive a steroid course during follow-up (HR: 3.41; 95% CI: 1.11, 10.5); no differences were noted among children with ulcerative colitis (HR: 1.46; 95% CI: 0.78, 2.73).

Immigrants to Canada

Health services utilization among immigrants to Canada was compared to Canadian-born individuals using Ontario health administrative data linked to data from Immigration, Refugees, and Citizenship Canada.[28] Canadian immigrants had more IBD-specific outpatient visits (IRR: 1.24; 95% CI: 1.15, 1.33), ED visits (IRR: 1.57; 95% CI: 1.30, 1.91), and hospitalizations (IRR: 1.19; 95% CI: 1.02, 1.40). Immigrants to Canada were also more likely to have seen a gastroenterologist for IBD-specific care (OR: 1.37; 95% CI: 1.34, 1.40). Immigrants to Canada were less likely to require surgery (Crohn's disease, HR: 0.66; 95% CI: 0.43, 0.99; ulcerative colitis, HR: 0.52; 95% CI: 0.31, 0.87). When adjusting

for increased specialist care among immigrants to Canada, the association between immigration status and surgery was no longer significant in Crohn's disease (HR: 0.87; 95% CI: 0.57, 1.31); immigrants to Canada with ulcerative colitis were still less likely to require surgery (HR: 0.56; 96% CI: 0.33, 0.93). These findings were generally similar regardless of region of origin.

Estimating the Total Direct Costs of IBD in Canada

A Manitoba study reported significantly increasing total direct healthcare costs (including the costs of outpatient care, hospitalizations, surgeries, and medication) among people with IBD, from $3,354 per person per year in 2005 to $7,801 in 2015 (costs in 2015 CAD).[1] The increase in costs have been even greater for pediatric IBD, increasing from $1,811 per person per year in 2004 to $14,792 per person per year in 2017 (costs in 2020 CAD); the cost of caring for children without IBD did not change over the course of the study.[9] The average direct costs among children in Ontario diagnosed at less than 17 years of age between 2013–2019 was $14,451 (standard deviation: 14,665) in the first year following diagnosis.[29] People with higher healthcare costs were more likely to have Crohn's disease, have an ED visit at the time of diagnosis, be of older age at diagnosis, and have one or more healthcare encounters for a mental health concern. A Saskatchewan study reported an annual increase of 9.5% (95% CI: 8.9, 10.1) in total direct costs, increasing from $1,879 (95% CI: $1,686, $2,093) per person in 1999 to $7,815 (95% CI: $6,733, $7,667) per person in 2016 (costs in 2013 CAD).[8]

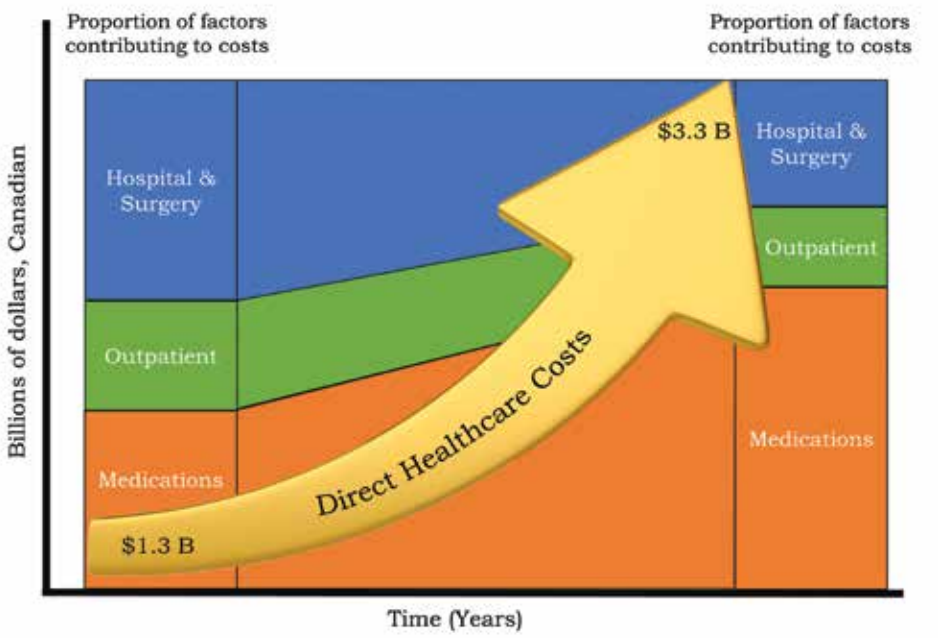


Figure 1: *The rising costs of IBD care in Canada.*

In a study combining health administrative data from Alberta, British Columbia, and Manitoba, the total estimated direct costs for individuals with IBD were $10,336 (95% CI: $6,803, $13,869) in 2016/2017, a significant increase from $7,000 (95% CI: $5,389, $8,610) in 2009/2010 (costs in 2020 CAD).[7] Extrapolating the 2016/2017 per person cost from these three Western provinces to the estimated 332,598 Canadians living with IBD, the total direct costs across Canada in 2023 are estimated to be $3.33 billion. Based on the confidence interval surrounding the estimated cost per person, these costs may be as low as $2.19 billion or as high as $4.74 billion. This estimate includes health system costs, as well as medication costs. However, medication costs are difficult to estimate because the listed price of biologics are not necessarily the negotiated cost paid for by public and private drug insurances. This calculation used the listed price of biologic therapies, which may not represent the actual cost spent by payers (through private health insurance plans, government programs, or out-of-pocket by individuals themselves).

In 2018, we estimated the direct costs of IBD in Canada to be at least $1.28 billion,[30] based on an estimated 270,000 people living with IBD in Canada and an estimated per person cost was based on Manitoba data from 2006 ($4,731 per person per year after adjusting for inflation to 2018 CAD).[31] This was the most conservative estimate available at the time. A Quebec study estimated the annual per person cost of ulcerative colitis between 2005–2011 to be more than double that of the Manitoba study ($8,900; $9,690 after adjusting for inflation to 2018 CAD).32 Had the Quebec study been used to estimate total costs, the cost of IBD in 2018 would have been estimated to be $2.62 billion. Both the Manitoba and Quebec studies provide data from a time when anti-TNF therapies were used less frequently than they are now, and newer biologic therapies (e.g., ustekinumab, vedolizumab) were not yet available. Additionally, neither study provided a complete picture of the total health system costs of IBD in Canada: The Manitoba study did not include the costs of ED visits and the Quebec study only included the subset of medication costs covered by the provincial government (i.e., medication costs were limited to those for seniors and individuals of lower socioeconomic status). The estimated health system costs in 2018 were likely a substantial underestimate, supported by more recent research on the costs of IBD in Canada.[1, 33]

The current cost estimates are derived from health administrative data from three Canadian provinces (Alberta, British Columbia, and Manitoba), then meta-analyzed to provide a pooled per person cost.[7] This cost estimate includes ED data (where available) and medication costs for all individuals, irrespective of their eligibility for provincial pharmacare. Thus, this cost estimate may be more representative of the total IBD costs—though estimates are needed from the remaining seven provinces and all three territories. However, this may still underestimate the current costs of IBD since the proportion of individuals living with IBD on biologic therapy has likely continued to increase since 2017. The growing number of people with IBD, including the increasing number of individuals receiving expensive biologic therapy coupled with low biosimilar uptake, and inflation also contribute to the increased estimate of the total direct healthcare costs in Canada. These increasing costs of IBD are not unique to Canada. Steadily increasing use of biologic therapy has drastically increased the costs of care around the world.[4, 34, 35]

Figure 1 provides a depiction of the rising costs of IBD care in Canada along with the changing relative proportions of those costs made up by hospitalizations and surgeries, outpatient care, and medications.

Conclusions

Variation and inequities in health services utilization exist across sociodemographic and ethnocultural groups. Since timely access to specialist care is vital for reducing adverse outcomes (e.g., needing to visit the ED), efforts need to focus on ensuring equitable access to high-quality specialist care. Novel models of care for IBD, with the goal of improving outcomes (including reduced reliance on EDs) are described in Chapter 12.

Patterns of health services utilization among people living with IBD in Canada are shifting. People with IBD are being admitted to hospital and undergoing surgery less frequently; this is accompanied by increasing outpatient visits and increasing use of biologic therapy. The costs associated with hospitalizations are decreasing (Crohn's disease) or remaining stable (ulcerative colitis). As the use of expensive biologic therapies continues to increase rapidly, medication costs will eclipse all other health system costs.

The costs of IBD to the healthcare systems, to people living with IBD, and to society are substantial. Over the course of a single year, direct health system and medication costs for IBD are estimated to be $3.33 billion. As the total number of people living with IBD continues to rise and as more biologic and targeted therapies at a higher price point than traditional therapies are introduced into the marketplace, the costs of caring for people with IBD will continue to rise (especially through increased costs of prescription medications). Canadian healthcare systems must prepare for the growing number of people with IBD and the costs of caring for these individuals. The costs of therapies need to become more affordable.

Knowledge Gaps & Future Research Directions

1. While we know that there are ethnocultural, sociodemographic, and geographic inequities in access to and utilization of healthcare services by people living with IBD, our knowledge of these inequities concerning tools used to monitor disease proactively (e.g., cross-sectional imaging such as MRI and intestinal ultrasound) is limited. Understanding potential inequities is important for strategies designed to ensure that all individuals living with IBD have timely access to high quality care that will improve their long-term outcomes.

2. Studies on the health system impacts of biologic therapies have not demonstrated system-level improvements in health services utilization (e.g., hospitalizations and surgeries) and costs of managing IBD. Future studies evaluating the impact of biologic therapy should not only focus on the impact on the healthcare systems but on broader society, including the impact of biologic therapies on disability spending, workplace productivity, and other economic benefits resulting from a healthier IBD population.

3. Much of the data describing variation in care for people with IBD come from regions with relatively high access to specialist care. Data on access to and utilization of health services among individuals living in rural and remote regions, including the territories, and in provinces with limited access to specialist gastroenterology care is sparse and should be a focus of future research.

4. With the emergence of many biosimilars and new competitive advanced therapies (e.g., small molecules, biologics), we should expect that the absolute and relative costs of caring for individuals with IBD will change over time. We need better, transparent data to be able to accurately calculate these changing patterns.

5. Our knowledge of the costs of IBD are derived from a subset of provinces. Differences in health system administration are likely a significant source of disparity in data across provinces. In order to better understand the evolving costs of IBD, national data on the costs of IBD—including the true costs of medications to private and public insurance plans and individuals paying out of pocket for their medications—are needed.

Patient & Caregiver Partner Perspective

Patient partners underlined that the data presented in this chapter show the distressing picture of the significant direct healthcare costs of IBD (and the inequities). Timely access to outpatient care is essential to prevent negative disease outcomes and healthcare costs. The evidence of IBD healthcare utilization differences depending on where you live, income, or ethnicity is an issue that requires close attention and interventions. For example, rural residents and First Nations individuals with IBD face barriers to accessing primary and specialized care, which could result in suboptimal medication management, more emergency department visits, hospitalizations, and surgeries. Improving access to care for individuals with IBD could help reduce healthcare costs in the short and long term. There is an urgency to consider how to support individuals living with IBD to access innovative and holistic healthcare and treatment options. The Canadian healthcare systems need to prepare for the growing number of people with IBD and the costs of caring for them. Since biologic medications account for about 50% of the direct costs of IBD, patient partners also emphasized the need for universal pharmacare in Canada and for developing more research about biosimilars. Upcoming studies and reports could assess the impact of biosimilars on the trends of direct healthcare costs in Canada. The costs of therapies for IBD need to become affordable for individuals, healthcare systems, and society overall.

Policy Implications & Key Advocacy Outcomes

1. Crohn's and Colitis Canada should advocate for better regulation of the cost of biologic therapies to ensure the financial viability of providing the right medication to the right person at the right time. Both government and private health insurance plans should provide financial pressure on the pharmaceutical industry to lower medication costs.

2. Despite increasing utilization of cross-sectional imaging that does not expose people living with IBD to ionizing radiation (e.g., MRI, abdominal ultrasound), people living with IBD have limited timely access to these types of imaging. Improving access for people living with IBD to timely imaging for diagnosis and management is important for managing disease before complications arise and will be beneficial for the long-term outcomes of these individuals by reducing costs to individuals, their caregivers, and the healthcare system.

3. Better access to healthcare resources is needed for individuals living in rural and remote communities and in provinces/territories with limited availability of gastroenterologists, including continued use of virtual healthcare beyond the pandemic.

4. Efforts should be made to reduce geographic, ethnocultural, and other sociodemographic inequities in access to and utilization of health services among people living with IBD, particularly high-quality specialist care, which is important for improving the long-term outcomes of IBD.

5. Crohn's and Colitis Canada should advocate for universal pharmacare that includes timely access to the most effective IBD medications with the goal of improving the short- and long-term well-being of people living with IBD.

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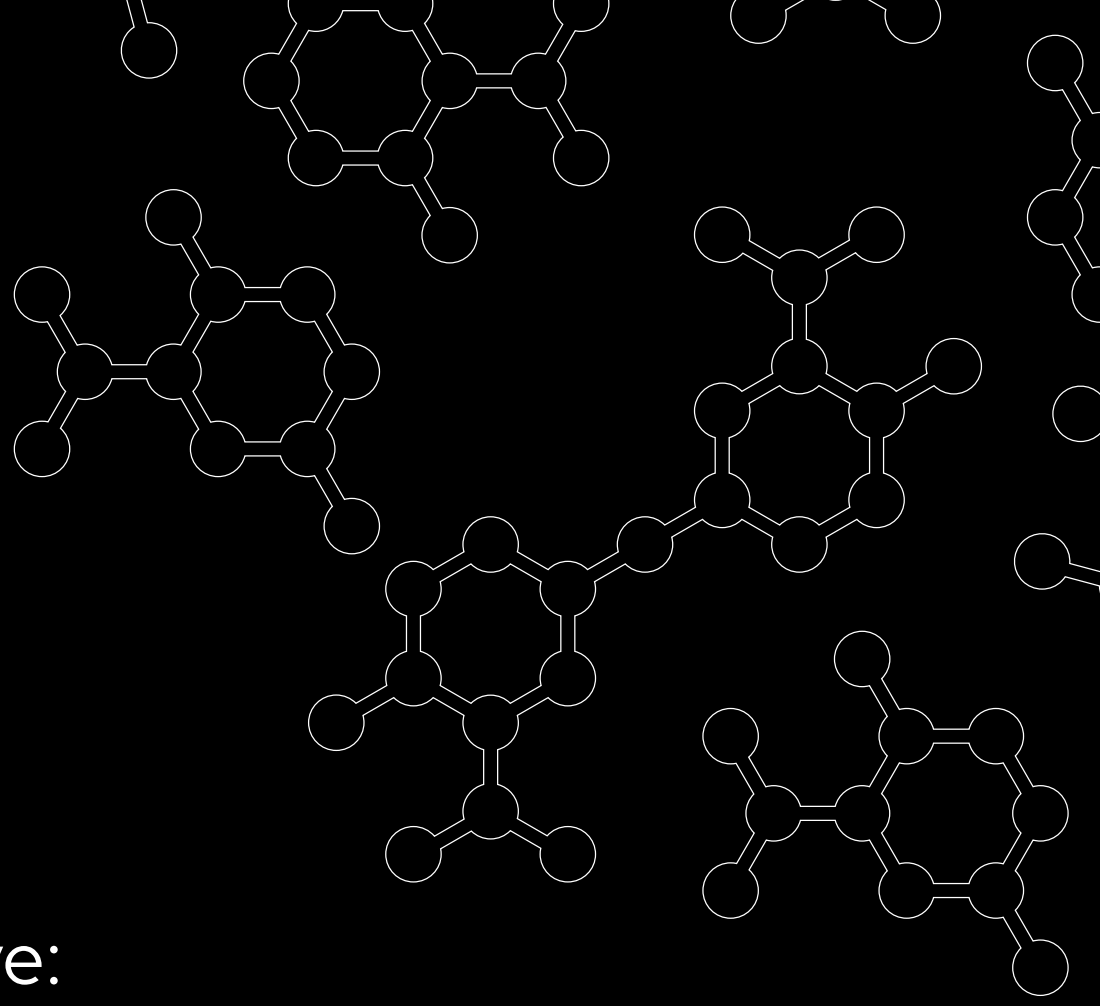


Section Five:

Special Populations– Children & Adolescents with IBD

Special Populations—Children & Adolescents with IBD

Abstract

Rates of inflammatory bowel disease (IBD) in Canadian children and adolescents are among the highest in the world, and the rate of new diagnosis is rising most rapidly in children under five years of age. These young children may have either a typical form of IBD with multi-factorial etiology, or they may have a monogenic form—caused by a single gene mutation. Despite the growing number of children in Canada living with this important chronic disease, there are few available medical therapies approved by Health Canada due to the omission of children from most clinical trials of newly developed biologics. As a result, off-label use of medications is common, and physicians have learned to use existing therapies more effectively. In addition, most Canadian children are treated in multidisciplinary, specialty clinics by physicians with extra training or experience in IBD, as well as specialist nurses, dietitians, mental health care providers, and other allied health professionals. This specialized clinic approach has facilitated cutting edge research, led by Canadian clinicians and scientists, to understand the causes of IBD, the optimal use of therapies, and the best ways to treat children from a biopsychosocial perspective. Canadians are engaged in work to understand the monogenic causes of IBD; the interaction between genes, the environment, and the microbiome; and how to address the mental health concerns and medical needs of adolescents and young adults transitioning from pediatric to adult care.

Key Points

1. The number of new diagnoses (incidence) of children with IBD is rising rapidly in Canada, particularly in those with onset under six years old (Very Early Onset IBD [VEO-IBD]).

2. Our understanding of the etiology of childhood-onset IBD, and the reasons for its rising incidence is still rudimentary. More research into the interaction between environmental factors, genetics, the gut microbiome, and the immune system may allow us a better understanding of treatment and preventive opportunities.

3. IBD presenting in childhood is different from IBD presenting in adulthood. Children have more extensive disease, higher rates of acute severe colitis, and are at risk for linear growth delay, puberty delay, and bone development deficits. In addition, children with VEO-IBD are more likely to present with isolated colonic disease. These differences have important implications on treatment choice, such as avoiding corticosteroids in favour of dietary therapy or biologics.

4. Children with IBD and their families have unique healthcare needs. These may result from differences in physical manifestations of IBD, as well as important differences in mental health (higher rates of anxiety and depression), and social well-being (stress on the child and family, missed school for the individual, missed work for caregivers).

5. The treatment options for children with IBD are limited, especially considering there are fewer choices for Health Canada approved medications and biologics. However, ongoing research aims to provide a better understanding of how to use available treatments more safely and effectively.

6. There is a growing need to understand how to optimize medical therapy in children to achieve better prognoses. A precision health approach to treating IBD holds great promise for the future.

7. The transition period from pediatric to adult care is one where adolescents and young adults with IBD may be at risk for physical and psychosocial difficulties. More research is required to understand the risks to these individuals, and the best way to avoid them.

8. Approximately 3% of children with IBD have a monogenic form of the disease; this is more common in children who present with VEO-IBD (7.8%) than those diagnosed between 6–18 years of age (2.3%). Canadian researchers are leading international studies to understand the causes of this monogenic form of IBD, and new therapies may be developed to treat these children.

9. It is important for physicians and the public to recognize that IBD can occur in young children and access to specialist diagnosis and multidisciplinary care should be facilitated by the healthcare systems.

Summary of Crohn's and Colitis Canada's 2018 Impact of Inflammatory Bowel Disease in Canada: Special Populations—Children with IBD

The incidence (new cases) and prevalence (total cases) of pediatric IBD in 2018 was high in Canada, and rates of Very Early Onset IBD (diagnosis under six years of age) were rising rapidly. Children with IBD present differently from adults and face unique health challenges such as growth failure, osteoporosis, more extensive disease, and difficulty adapting to a chronic disease during adolescence. The mental health and psychosocial well-being of children with IBD and their families are of utmost importance. Nevertheless, inadequate resources were provided for this important care. Treatments for pediatric IBD differ from adults, and there was a lack of data from clinical trials to support the use of many medications frequently used to treat children. There are gaps in our knowledge of why pediatric IBD is rising in Canada; the best ways to provide medical, dietary, and psychosocial care to children and their families; and how to reduce variation in care to individuals with IBD.

Introduction: Children and Adolescents with Inflammatory Bowel Disease

Unlike adult IBD, the incidence of pediatric IBD continues to rise across the globe.[1] In addition, rates of new diagnoses seem to be rising most rapidly in children under six years old, those classified as having Very Early Onset IBD (VEO-IBD).[1, 2] Just as in adults, Canada has among the highest rates of pediatric IBD in the world. The incidence (the annual number of new diagnoses) of childhood-onset IBD is 9.68 per 100,000 children, ranging from 7.22 per 100,000 in Manitoba to 15.18 per 100,000 in Nova Scotia.[2] The prevalence (total number of people living with the disease) of children under 16 years of age living with IBD is 38.25 per 100,000.[2] While this is lower than the prevalence in adults, children face unique biological and psychosocial needs when living with this chronic disease, and there are far fewer medical therapies approved for use in children by Health Canada. This situation makes the care of children with IBD, and the challenges faced by these children and their families, important healthcare concerns in Canada. This chapter reviews some important concepts in pediatric IBD in order to identify the needs for clinical care and research in this important population.

Environmental Risk Factors

The causes of IBD are not completely understood. The current hypothesis is that in genetically susceptible individuals, an environmental trigger (or triggers) will result in an inappropriate immune response. Disturbance of the normal gut microbiome (i.e., dysbiosis) may be associated with this dysregulated immune response. This response may be caused by inflammation, may result from environmental exposures, or both.[3]

The associations between many environmental factors and IBD have been investigated. In the pediatric age group, harmful factors include early exposure to antibiotics.[4-6] Among the protective factors, breastfeeding was protective against Crohn's disease (odds ratio [OR]: 0.71; 95% confidence interval [CI]: 0.59, 0.85) and ulcerative colitis (OR: 0.78; 95% CI: 0.67, 0.91).[7] Living conditions during childhood may affect disease development, with a generally protective role for rural residence.[8] Residential greenspace during the childhood period was associated with a lower risk of developing pediatric-onset IBD (hazard ratio [HR]: 0.77; 95% CI: 0.74, 0.81).[9] Living near a farm with animals, bed sharing, and having pets during childhood had protective roles against IBD.[10] Fruit intake protected against Crohn's disease (OR: 0.57; 95% CI: 0.44, 0.74) and ulcerative colitis (OR: 0.69; 95% CI: 0.49, 0.96).[10] No evidence of association between carbohydrate, sugar, protein, or fat intake and either ulcerative colitis or Crohn's disease was noted. However, studies in adults have demonstrated an association between high fat diets and IBD.[11] In Manitoba, mode of delivery (vaginal or cesarean section) at birth did not seem to affect IBD development.[12] The association between air pollution and developing IBD is controversial.[13] A UK study demonstrated an association in people with IBD onset under 23 years old,[14] while a Canadian study did not find an association between regional air pollution and developing pediatric-onset IBD.[15]

Differences between Pediatric and Adult IBD

There are substantial differences in disease location, phenotype, and severity in pediatric-onset IBD compared to adult-onset IBD. Reduction in growth rate,[16, 17] a decrease in bone mineral deposition,[18] and delay in puberty[17, 19] are the consequences of pro-inflammatory cytokines released from the inflamed intestine.[20] Such complications may be present at the time of diagnosis, particularly in children with Crohn's disease. However, greater awareness of IBD in children will hopefully result in less diagnostic delay, which has been associated with better growth and development.[21, 22] Adequate treatment of the inflammation, particularly with biologics, is now usually effective to address these complications before they become permanent.[23]

Figure 1 demonstrates the frequency of disease phenotype for Crohn's disease and ulcerative colitis derived from the inception cohort of the Canadian Children IBD Network.[24] Overall, children typically have more extensive disease, which is more often considered severe; this is particularly well-documented for ulcerative colitis. Extensive or pancolitis is most common in pediatric-onset ulcerative colitis, whereas left sided disease is more common in adults. The most common disease phenotype in children with Crohn's disease is inflammatory ileocolonic disease as compared to adulthood-onset Crohn's disease where ileocecal disease is most common.[25] Finally, males develop Crohn's disease more frequently than females in the time before puberty, but rates gradually become an equal ratio of male to female after puberty.[26]

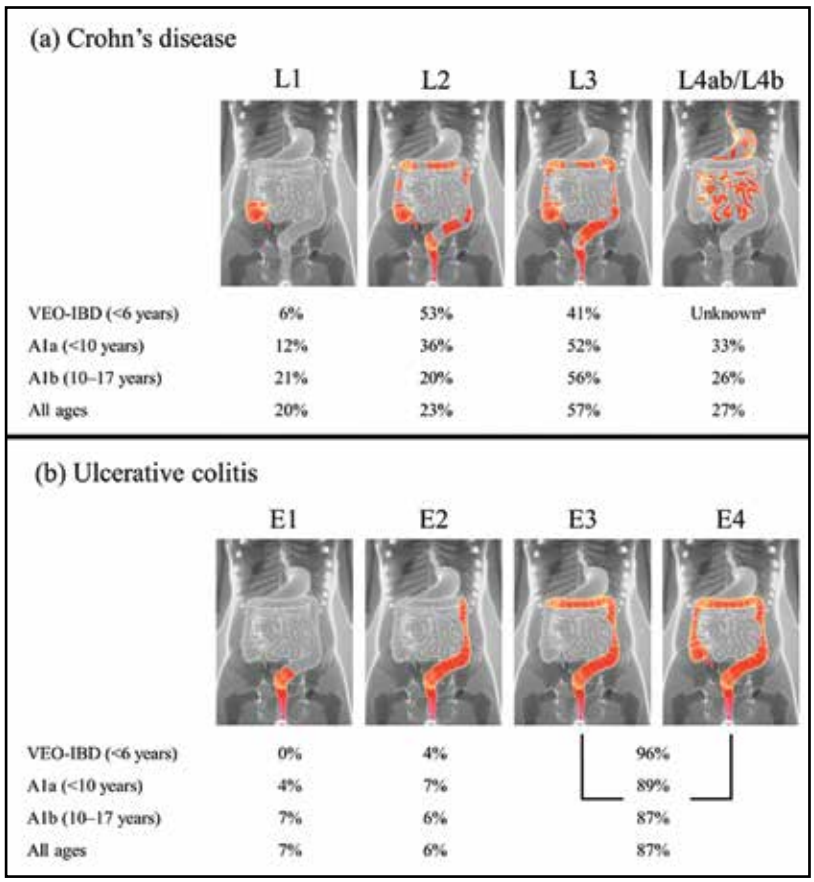


Figure 1: *Location of childhood-onset (a) Crohn's disease and (b) ulcerative colitis according to the Paris modification of the Montreal Classification.[27] Adapted from Dhaliwal et al.[24] Rows in Crohn's disease add up to more than 100% as an individual can have multiple disease locations (e.g., L1/L2/L3 and L4ab/L4b denoted in the literature as L1+L4b, for example).*
[a]*Frequency of L4ab/L4b phenotype was unknown in individuals with VEO-IBD because magnetic resonance enterography was not performed in this age group.*

Treatment of Pediatric IBD

While medical therapies, including biologics and nutritional therapy, are highly effective in pediatric IBD, treating children represents significant challenges. Only two biologics (infliximab and adalimumab) are currently approved by Health Canada for use in children, resulting in high rates of immunomodulator use and off-label use of other biologics.[28] Children are typically excluded from initial clinical trials of biologics and other therapies, and pediatric trials only occur once use in adults has been approved by regulators. Therefore, approval for pediatric use of medications is typically delayed by years, which has long been identified as a gap in the care of children with IBD.[29, 30] This problem is particularly pronounced for VEO-IBD, the group with the most rapid increase in new diagnoses.[2, 28] A recent meeting of the Food and Drug Administration in the US determined ways in which clinical trials in children with IBD could be facilitated, hopefully improving the process in the future.[31] Even when therapies are approved for use in children, dosage and monitoring do not follow adult guidelines, and data guiding the best use of these treatments are lacking.[32] However, some improvements in our use of treatments in children with IBD are described below.

A gap in our use of medications to treat children with IBD is understanding the outcomes of greatest relevance to children and their families; these were previously not well-reflected in pediatric trials, which used disease activity scales as their primary outcomes. However, this situation is improving. The International Organization for the study of IBD (IOIBD) recently updated the STRIDE-II guidelines, which now also include pediatric-specific targets for outcomes (normalization of growth, pediatric-specific disease activity scores, and mucosal healing objectives).[33] In addition, pediatric clinical trials are evolving to include objective measures such as mucosal healing, as well as patient-centred outcomes such as improvements in function, disability, and health-related quality of life.[34] These initiatives will likely change the design and conduct of pediatric clinical trials in the future, making them more relevant to children with IBD and their families, as well as pediatricians.

In the meantime, we have learned to use existing pediatric therapies more effectively. Use of biologics earlier in the course of disease is increasingly common in Canada, including use of anti-TNF biologics as first-line therapy in children.[35] A recent randomized clinical trial confirmed that this strategy is superior to conventional therapies (defined as corticosteroids and/or exclusive enteral nutrition) in achieving short- and long-term outcomes in children with Crohn's disease, indicating the need to revise our treatment approach.[36] A recent trial in children with Crohn's disease using adalimumab found that proactively monitoring drug levels in the blood and adjusting the dose to meet the targeted range resulted in better outcomes after 72 weeks of therapy,[37] indicating the need for an individualized approach to the treatment of each person. In addition, it is clear that some children require larger doses of biologics when weight-based dosing is used (when the individual's weight is used to determine the amount of medication per dose they should receive).[32] Body surface area-based dosing (a calculation for the amount of medication needed per dose based on both the height and weight of the individual) has been demonstrated to be more effective in young children with IBD, and frequently results in exposure to higher doses of biologics and levels of medication within the blood than weight-based dosing.[38, 39]

There has been renewed interest in various dietary therapies and their effects on gut inflammation and microbiome. The Crohn's Disease Exclusion Diet (CDED) combined with partial enteral nutrition has been shown as effective as exclusive enteral nutrition

for inducing remission of Crohn's disease and was better tolerated by children.[40] The CDED is based on the removal of various elements of the Western diet thought to promote gut inflammation, such as animal fats, processed foods, dairy, and wheat and has been associated with partial correction of an altered gut microbiome.[41] It was also demonstrated to be effective for inducing and maintaining remission in a pilot study of adults with Crohn's disease.[42] Dietary therapies and other methods of manipulating the gut microbiome to induce remission and aid with healing are currently being trialled in Canadian centres.[43] Finally, fecal microbial transplant is the subject of a Canadian clinical trial in children with ulcerative colitis.[44] For further information on the role of diet and nutrition in the treatment of pediatric IBD and on fecal microbial transplant, see Chapter 11.

Another key theme of pediatric IBD care in the past five years has been trying to predict which children are at increased risk for negative outcomes. Multiple studies have identified risk factors for hospitalizations, surgeries, and complications from Crohn's disease,[45-48] as well as hospitalization or colectomy from ulcerative colitis.[49] For example, a recent retrospective Canadian study found that female sex, 5-ASA medication use, immunomodulator use (instead of anti-TNF biologics), granulomas and eosinophils on biopsies, elevated inflammatory markers during clinical remission, and lower infliximab levels in the blood during clinical remission were associated with clinical relapse.[50] Two recent systematic reviews from the Pediatric IBD-Ahead group summarized the literature on risk prediction for children with Crohn's disease and ulcerative colitis.[51, 52] While this body of literature is useful to identify those at increased risk, observational research cannot prove that treating earlier or more aggressively will avoid long-term medication loss of efficacy. In addition, most of these risk factors have been difficult to validate in external, prospective cohort studies.[53] In light of these barriers, research into a precision health approach to IBD care has become a priority. Precision health is defined as the integration of genetics, proteomic, metabolomic, microbiome, environmental, and sociodemographic characteristics to create a personalized approach to the care of each individual living with IBD.[54]

Multidisciplinary care (involving physicians, nurses, dietitians, and mental health care providers) has been identified as an important way in which negative outcomes can be avoided in children and adolescents with IBD.[55, 56] Studies have identified mental illness as a significant predictor of non-adherence to medications,[57] and of high direct healthcare cost among children with IBD.[58] Nevertheless, access to multidisciplinary care varies widely among pediatric IBD care providers in Canada, with access to mental health care being widely considered inadequate, even in large pediatric centres.[59]

In summary, regulatory approval of medications for the treatment of pediatric IBD lags behind approval in adults, and a regulatory framework for drug approval and labelling in pediatrics is overdue.[60] In addition, drug cost reimbursement (whether by private or public payors) should change to reflect the latest scientific evidence rather than relying on old research and the clinical trials that resulted in initial regulatory approval. Nevertheless, Canadian pediatric IBD care providers have spearheaded new and unique ways of using existing therapies, more effectively making use of anti-TNF biologics, while learning more about the off-label usage of newer medications and dietary therapies. As such, the outcomes of children with IBD have improved markedly over the past 20 years, with reduced rates of hospitalization and surgery.[61] However, providing multidisciplinary care may result in better clinical outcomes, quality of life, and direct healthcare costs in children with IBD.

Impact on Individuals, Parents, and Caregivers

The impact of any pediatric chronic disease—especially IBD—on children and young adults, their parents, and their families can be substantial. Although incurable, thanks to newer biologics, treatment approaches, and specialized care, most children with IBD can largely remain well and be expected to live a full and happy life. However, coping with the diagnosis of IBD, and its associated active and recurrent symptoms, treatment costs, and potential adverse events can be challenging. Children spend the majority of their time within a larger family system, and family functioning is bound to influence a child's adjustment to IBD.[62] Considering physical and psychological burdens of IBD, it is not surprising that these individuals are at risk of struggling and coping from a mental health perspective.[63] Mental health concerns of children with IBD is addressed in detail in Chapter 8.

Parents play an important part in managing their children's IBD. They help with explaining the disease to their children, medication adherence, scheduling different medical appointments, and establishing a successful relationship with physicians. Balancing these roles may increase the stress on parents and caregivers. Hence, parents of children with IBD were found to experience greater emotional distress, depression, and reported a lack of emotional support, as compared to parents of healthy children.[63] There is a positive correlation between parental stress and internalization of symptoms (depression, anxiety, and physical symptoms due to these mental states) among children with IBD.[63] More parental stress was associated with more severe disease and lower health-related quality of life among their children with IBD.[63] Conversely, more parental involvement was associated with higher rates of adherence to treatments for IBD.[64]

Education and Future Employment

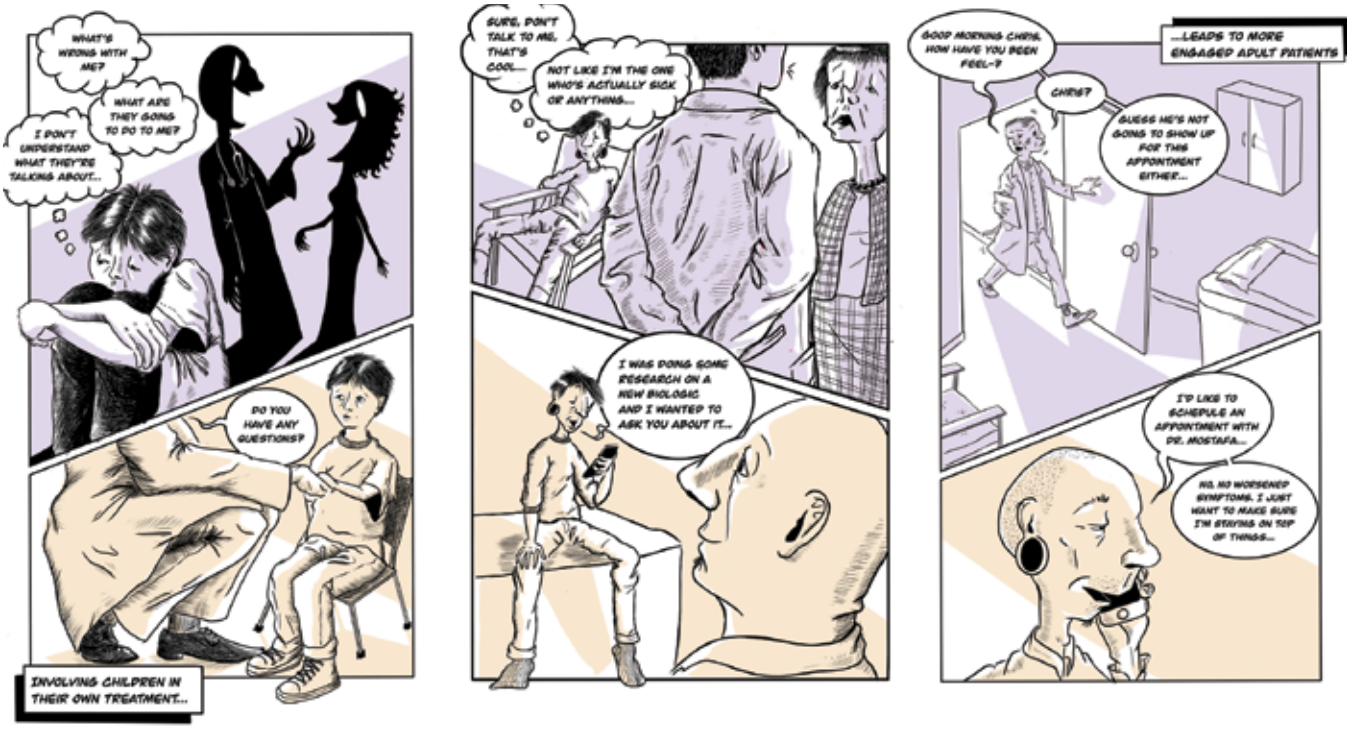
Missing school days due to IBD-related causes—such as attending clinics and hospitalizations—was common in children with IBD, especially in those with active disease.[65] Parental satisfaction with education of children with IBD attending advanced secondary education was also found to be lower in a cross-sectional study, especially in individuals with active disease.[66] However, despite these challenges, Manitoba children with IBD had school performance equal to those of other children as long as they did not struggle with mental illness.[67]

Data on employment and income potential in people with pediatric-onset IBD is not consistent across studies. A recent Swedish population-based study found that people with childhood-onset IBD reported lower income between ages of 20–30 compared to healthy controls, especially in those who needed prolonged periods of hospitalizations or surgery.[68] Conversely, a Canadian study reported higher future long-term adulthood earnings in people with pediatric-onset IBD compared to healthy controls.[69] The difference between the two studies may be related to the difference in design and income data sources; administrative data were used in the Scandinavian study whereas a cross-sectional survey was administered in the Canadian study. The Canadian study had a longer study period, but smaller sample size. Both studies, however, showed no difference in future unemployment and marital status in those with pediatric-onset IBD as compared to the general population.[68, 69]

Transition from Pediatric to Adult Care

Transition in care is defined as the purposeful and planned movement of adolescents and young adults (AYAs) with a chronic medical condition to adult-oriented healthcare systems/care providers.[70, 71] Children in Canada transition from pediatric to adult healthcare services between the ages of 14–18, with ultimate transfer to adult care around the time the child turns 18 years of age. There are inherent differences between pediatric- and adult-care models: Pediatric care is family focused, multidisciplinary, and has caregiver involvement for consent and guidance, while adult care typically has a single provider and adult providers expect that the individual will be capable of making decisions independently from their parents or caregivers.[72, 73] One stressor faced by children and adolescents with IBD (and other chronic diseases) is the everyday developmental transitions from childhood to adulthood, including changes in school structure, employment, general psychosocial growth, and changes in insurance coverage from the parents' plan to the individual's own coverage.[74, 75] These developmental transitions are particularly important for children with a chronic disease as they are amplified by the transfer from pediatric to adult healthcare systems.

There is no standard of care for transitioning adolescents with IBD in Canada, and success of transition is defined differently by individuals, parents, and healthcare providers.[76] However, Crohn's and Colitis Canada recently partnered with the Canadian IBD Transition Network to produce expert consensus statements on best-practices for transitioning AYAs with IBD.[77] Transition for AYAs with special healthcare needs has been identified as a health services priority area.[78] Studies have demonstrated a higher economic burden among young adults with pediatric-onset IBD, including increased all-cause total healthcare costs and the



highest utilization of emergency services of any sub-population.[79, 80] In a healthcare era plagued by economic constraints, ensuring positive healthcare outcomes via the most cost-efficient healthcare delivery is a priority. In Ontario, adolescents with IBD had more visits to the emergency department (ED) after transfer to adult gastroenterology care.[81] However, these ED visits were not associated with an increased risk of hospitalization, suggesting that they were not due to a severe flare of IBD, and might have been avoided with adequate access to outpatient care and education regarding appropriate ED use.[81, 82] In Canada, care of children and adolescents with Crohn's disease is almost exclusively provided in pediatric IBD centres affiliated with academic pediatric hospitals.[59] However, in a recent multi-centre Canadian study of adolescents aged 16–19 years, only 26.6% of adolescents treated in pediatric centres met criteria for readiness to be transferred to adult care.[83] In addition, these individuals had a significant burden of mental health concerns.[83]

Crohn's and Colitis Canada has partnered with the Leona M. and Harry B. Helmsley Charitable Trust to evaluate an intervention to smooth the transition from pediatric to adult care.[84] This randomized controlled trial of a biopsychosocial and educational intervention stands to provide the highest level of evidence of an intervention to improve transition for individuals with IBD.

VEO-IBD and Monogenic IBD

VEO-IBD is defined as IBD diagnosed before the age of six years.[85] The highest percentage increases in annual new cases of IBD in Canada have been observed in this age group.[2] The majority of these young children have complex IBD, that is Crohn's disease or ulcerative colitis developing due to genetic and environmental factors.[86] However, over the last two decades, advances in genomic analyses have discovered multiple monogenic causes of chronic IBD-like diseases. These are immune disorders resulting from genetic mutations and are associated with severe inflammation of the gastrointestinal tract, often not responsive to conventional IBD therapy. In addition, these individuals often have organs and systems affected outside of their gastrointestinal tract (such as immune system deficiency, skin, bones, and lungs).[87] A recent Canadian study that included over 1,000 children with IBD reported results of whole exome sequencing of the 68 genes known to cause monogenic IBD. They reported that 3.4% of the cohort overall, but 13.8% of children younger than two years at diagnosis (infantile-onset IBD), and 7.8% of children with VEO-IBD were found to have a disease-causing mutation in one of these genes.[86] Hematopoietic stem cell transplantation (HSCT) can cure several of these disorders such as certain protein deficiencies (e.g., X-linked inhibitor of apoptosis protein deficiency) and chronic granulomatous diseases (genetic disorders that make white blood cells ineffective against certain bacteria and fungi) as it can correct the immune defects in these orders.[88] Unfortunately, HSCT is ineffective for epithelial barrier dysfunctions (e.g., nuclear factor-kappa B essential modulator deficiency) as it cannot change the expression of these proteins on the intestinal epithelium.[88] Some of these disorders, however, may respond to specific medications (e.g., mevalonate kinase deficiency may respond to IL-1 receptor antagonists).[89]

Canadian researchers are leading an international consortium to find new genetic causes and treatments for VEO-IBD (NEOPICS: the InterNational Early Onset Paediatric IBD Cohort Study).

Knowledge Gaps & Future Research Directions

1. Understanding the causes of childhood-onset IBD and the reasons for its increased rate of new diagnoses in Canada and worldwide will help us identify potential treatments and preventive strategies to improve outcomes and reduce the risk.

2. Much more research is required to understand the mental health, psychosocial, educational, and employment implications of having IBD on children and their families, and therefore the resources required to improve their quality of life.

3. Better interventions are required to improve the transition from pediatric to adult care for adolescents and young adults with IBD.

4. Children with IBD have access to a limited number of approved therapies. We must learn to use these therapies more effectively and efficiently.

5. A precision medicine approach for treating IBD may help improve outcomes of all children with IBD, including those with monogenic forms.

READING A CHAPTER THAT TOUCHES ON BOTH THE BIOLOGICAL AND PSYCHOSOCIAL ASPECTS OF IBD MADE ME FEEL VERY UNDERSTOOD. I FOUND THAT THIS CHAPTER GAVE A VERY GOOD UNDERSTANDING OF THE IMPACT OF IBD IN THE PEDIATRIC POPULATION, BUT ALSO GAVE A GREAT IMPRESSION ON WHAT REMAINS TO BE DONE TO IMPROVE THE PATIENT EXPERIENCE.

Patient & Caregiver Perspective

Patient partners recognized that even though the cases of IBD are rising in children, there are limited medication options available in this age group as they are often not included in clinical trials. It gave them hope to learn more about single gene mutations that may cause a subset of IBD because new therapies may be developed to directly treat this form of IBD. It was identified by patient partners that there was no standardized transition process from pediatric to adult care across Canadian provinces. Patient partners suggested that greater emphasis should be placed on implementing consistent and individualized transition plans across the country. The identification that greater research was needed in the areas of causes and risk factors towards the development of IBD as well as medical treatments, mental health, and psychosocial implications to improve patient and family experience and quality of life provides patient partners with feelings of recognition and hope for the future.

Policy Implications & Key Advocacy Outcomes

1. Rates of pediatric IBD are rising in Canada. These individuals require multidisciplinary and specialized care for their chronic disease. They should have access to expert physicians, nurses, dietitians, social workers, pharmacists, and mental health specialists to treat both the individual and their family, no matter where in Canada they live.

2. The development of IBD in childhood has lifelong implications for the individual and family, and we need to better educate healthcare providers, policy-makers, and the general public about the challenges faced by those with childhood-onset IBD.

3. Crohn's and Colitis Canada should advocate for the inclusion of children and adolescents in industry-sponsored and investigator-initiated clinical trials to allow for a better understanding of medication efficacy in young people, and for earlier regulatory approval of these new medications.

4. Advocacy efforts should also focus on improved funding of research to understand how to better use available treatments in children with IBD in order to improve outcomes.

5. Specific attention should be given to creating an evidence-based standard of care for those transitioning from pediatric to adult care.

6. Education/awareness should be provided to the public, afflicted individuals, and healthcare providers—especially primary care providers—so that children with IBD can be identified, referred to a specialist, and diagnosed quickly and appropriate care pathways followed.

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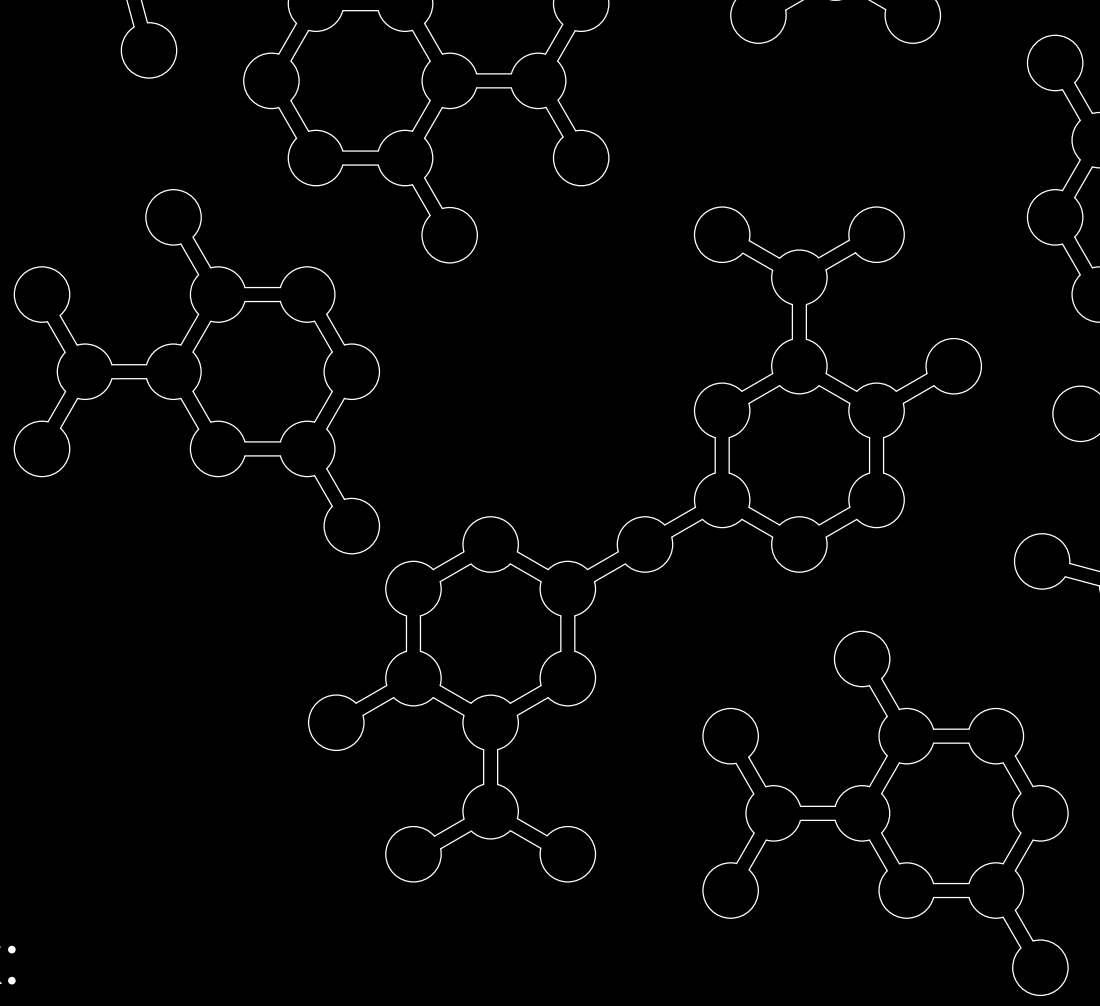


Section Six:

Special Populations– IBD in Seniors

Special Populations—IBD in Seniors

Abstract

Approximately one out of every 88 seniors has IBD, and this is expected to increase in the future. They are more likely to have left-sided disease in ulcerative colitis, and isolated colonic disease in Crohn's disease; perianal disease is less common. Other common diagnoses in the elderly must also be considered when they initially present to a healthcare provider. Treatment of the elderly is similar to younger persons with IBD, though considerations of the increased risk of infections and cancer must be considered when using immune modulating drugs. Whether anti-TNF therapies increase the risk of infections is not definitive, though newer biologics, including vedolizumab and ustekinumab, are thought to be safer with lower risk of adverse events. Polypharmacy (the effect of taking multiple medications for multiple disorders) and frailty are other considerations in the elderly when choosing a treatment, as frailty is associated with worse outcomes. Costs for IBD-related hospitalizations are higher in the elderly compared with younger people. When elderly individuals with IBD are cared for by a gastroenterologist, their outcomes tend to be better. However, as elderly people with IBD continue to age, they may not have access to the same care as younger people with IBD due to difficulties with using or accessing technology.

Key Points

1. In 2023, one out of every 88 elderly individuals has IBD, with the total number of seniors with IBD expected to increase in coming years due to more seniors being diagnosed with IBD and an aging IBD population.

2. Although the evidence is conflicting, anti-TNF use is potentially associated with an increased risk of infection, such as pneumonia.

3. Newer biologic therapies, including vedolizumab and ustekinumab, are promising therapies for the elderly with fewer adverse events related to infections.

4. The complex healthcare needs of an aging IBD population is placing additional stress on specialist gastroenterology clinics to adequately care for these individuals.

5. Increasing comorbidities and frailty evident in the elderly may impact their ability to handle the symptoms of IBD, and in turn, may impact possible treatment options.

6. The elderly are more likely to be using multiple prescription drugs (polypharmacy) and hence there is greater likelihood for drug interactions and potential adverse drug-related side effects.

7. The complex healthcare needs of this population require multidisciplinary healthcare teams in order to adequately care for the various medical complications of aging.

8. It is particularly challenging for the elderly to access care due to mobility restrictions, logistical challenges, or lack of advocacy support. Therefore, virtual access (either by video or phone) should be offered as an option.

9. Vaccines, including the pneumococcus and COVID-19 vaccines among others, can provide protection against infections in the elderly with IBD.

Summary of Crohn's and Colitis Canada's 2018 Impact of IBD: Special Populations—IBD in Seniors

In 2018, one out of every 160 seniors had inflammatory bowel disease (IBD); 15% of all people with IBD are diagnosed over the age of 65. Seniors diagnosed with Crohn's disease are more likely to have isolated colonic disease without fistulae, compared with those diagnosed at a younger age. The use of thiopurines was associated with a higher risk of lymphoma, when compared to those under the age of 50 exposed to thiopurines. The use of anti-TNF therapy was lower for both Crohn's disease and ulcerative colitis, compared with younger people with IBD. Individuals between the ages of 65–79 with IBD had higher healthcare costs when compared with age-matched controls without IBD.

Introduction

In Canada, one out of every 88 seniors is diagnosed with IBD, and the total number of seniors living with IBD is only increasing. Seniors diagnosed with this chronic disease face distinct challenges in treatment due to other co-existing conditions, the effects of taking multiple medications, frailty, and an increased risk of infections and cancer. Further, their IBD presentation (the type and location of disease and natural history of the disease) differs from adults with IBD. Vaccines are an important tool to prevent or decrease the severity of infections in seniors with IBD, including vaccines against SARS-CoV-2—the virus that causes COVID-19. The treatment and management of seniors with IBD is quite challenging due to these many factors and makes it an important healthcare concern in Canada as the population continues to age.

Epidemiology

While the majority of individuals with IBD are diagnosed as teenagers or young adults, as many as 10–15% are diagnosed over the age of 60.[1] In 2023, we estimate one out of every 88 elderly individuals in Canada has IBD (1.14% of seniors), with the total number of seniors living with IBD increasing by 2.76% (95% CI: 2.73, 2.79) per year; this is due to a combination of new diagnoses and the aging of individuals diagnosed with IBD earlier in life.[2] The rate of new IBD diagnoses among seniors is 28.7 (95% CI: 24.4, 33.0) per 100,00 person-years and is not changing over time (average annual percentage change: 0.66; 95% CI: −0.55, 1.52).[2] A retrospective study of people with ulcerative colitis in South Korea revealed that ulcerative colitis-related and all-cause mortality, was higher in the elderly-onset group compared to the non-elderly group.[3] Diagnosing IBD in the elderly can be challenging as other conditions mimicking IBD must be ruled out;[4] these include colorectal cancer, ischemic colitis, segmental colitis with associated diverticulosis, radiation enteritis or colitis, and microscopic colitis.[4] Elderly people with IBD are at increased risk of mortality, based on data from a Swedish national register study.[5]

Phenotype

Elderly people with Crohn's disease are most likely to have isolated colonic disease; penetrating or perianal disease is rare.[1, 6, 7] The rate of progression to stricturing or penetrating disease is either similar, or lower, than in adults with Crohn's disease.[6] In those with ulcerative colitis, left-sided disease is the most common presentation.[6] (For a diagram of areas that Crohn's disease and ulcerative colitis can affect, see Figure 1 in Chapter 5.)

Surgery

Based on a systematic review and meta-analysis, the cumulative five-year risk of surgery in people with Crohn's disease over the age of 60 is 22.6%. This same study reported that the cumulative five-year risk of surgery in elderly people with ulcerative colitis was 7.8%.[6] The five-year risk of surgery was similar in seniors and adults with IBD. Age over 60 years was found to be associated with a decreased risk in using prophylactic therapies after an ileocecal resection (odds ratio [OR]: 0.20; 95% CI: 0.05, 0.76).[8] In a study of 148 individuals hospitalized with moderate-to-severe ulcerative colitis, those over 60 years of age, mostly on intravenous corticosteroids, experienced more loss of treatment efficacy compared with those younger than 60 years old, leading to more colectomies (28.4% vs 12.2%).[9]

Disease-Related Complications

In one study by Rozich *et al.*, there was no difference in disease-related complications (IBD-related surgery, hospitalization, treatment escalation, clinical flare, or disease complication) in elderly individuals (those 60 years of age or above) with either new or existing IBD compared with adults aged 18–59 years with IBD (adjusted hazard ratio [aHR]: 0.85; 95% CI 0.58, 1.25).[10] Elderly individuals were also less likely to experience treatment-related complications (including serious infection, malignancy, or death) (aHR: 0.58; 95% CI: 0.39, 0.87). A retrospective study from 13 hospitals in Hong Kong revealed that those with elderly-onset IBD had an increased risk of cytomegalovirus colitis (OR: 3.07; 95% CI: 1.92, 4.89), herpes zoster (shingles) infection (OR: 2.42; 95% CI: 1.22, 4.80), cancer development (OR: 2.97; 95% CI: 1.84, 4.79), and IBD-related hospitalizations (OR: 1.14; 95% CI: 1.09, 1.20), compared with people with adult-onset IBD.[7] In a large US cohort study using health administrative data from Veterans Affairs, the rate of shingles was higher in people with IBD (only among those treated with 5-ASA medication) when compared to those without IBD (aHR: 1.72; 95% CI: 1.51, 1.96); within the group with IBD, age was a risk factor for developing shingles.[11] A retrospective study assessing a nationwide database in the US reported that when compared with middle-age (40–64 years old) and younger individuals (younger than 40), elderly persons (older than 64 years) with IBD were more likely to be hospitalized due to serious infections (elderly: 14.6%, middle-age: 10.6%, younger: 8.4%), and cardiovascular complications (elderly: 9.9%, middle-age: 4.3%, younger: 0.8%).[12] In a market-scan database study from the US, 63,759 individuals with IBD were identified, and infections were higher in the elderly group (65 years or older) (incidence rate [IR]: 16.95 per 100 person-years vs 10.49 per 100 person-years), with pneumonia (39.8%), sepsis (13.2%), and candidiasis (12.9%) being the most common infections.[13] Individuals with IBD-related hospitalizations who are 65 or older have increased odds of mortality (OR: 3.91; 95% CI: 2.50, 6.11), compared to those with IBD who are 19–64 years old (after controlling for comorbidities and complications), and this risk is even more pronounced when compared with those between 19–35 years old (OR: 17.42; 95% CI: 8.92, 33.99).[14]

Treatment

The medical management of elderly individuals with IBD is similar to younger people with IBD. However, age, polypharmacy, comorbidities, and risk of frailty complicate disease management. Therapeutic efficacy is thought to be similar between the elderly and younger people with IBD, but one must balance the increased risk of infection, potential drug interactions, and heightened risk of malignancy.[15]

Mesalamine has been demonstrated to be an effective treatment for the inducing and maintaining remission in mild-to-moderate ulcerative colitis, though evidence is lacking for its use in Crohn's disease. Despite this, mesalamine is used in more than two-thirds of elderly people with both ulcerative colitis and Crohn's disease.[16, 17] Thiopurines are a convenient oral medication in maintaining remission in both Crohn's disease and ulcerative colitis, with one study indicating approximately 20% of the cohort being exposed to a thiopurine within five years of IBD diagnosis.[18]

In a systematic review and meta-analysis comparing elderly-onset individuals with IBD (those aged over 60 years) with adult-onset individuals with IBD, the use of corticosteroids was shown to be similar between these two groups, though the use of immunomodulators and biologics was lower in the elderly group for both Crohn's disease and ulcerative colitis.[6]

Efficacy/Effectiveness

Data on the effectiveness of anti-TNF therapy in the elderly are conflicting (Table 1). Compared to younger people with IBD, older persons had lower persistence on their anti-TNFs, were less likely to achieve corticosteroid-free remission at 12 months (31% vs 67%, $p<0.001$), and were more likely to experience loss of anti-TNF effectiveness.[19, 20] Adverse events, rather than lack of effectiveness, were more often the reason for stopping anti-TNF therapy in older adults; thiopurine use was associated with lower risk of loss of effectiveness.[20] Conversely, a pooled analysis of data from randomized trials assessing anti-TNF use in ulcerative colitis reported no significant differences in efficacy of anti-TNF in both inducing and maintaining remission between the older cohort (aged 60 years or greater) and younger cohort (aged under 60 years) (OR: 1.05; 95% CI: 0.33, 3.39).[21] Infliximab exposure, including levels and antibodies, is thought to be the same in elderly persons; hence, similar trough concentrations (the amount of the medication in the blood stream just before another dose) can be used to guide therapy.[22] A post hoc analysis of the Randomized Evaluation of an Algorithm for Crohn's Treatment (REACT) study, including the subset of participants over 60 years of age with Crohn's disease, showed no differences in achieving corticosteroid-free clinical remission between early use of combination therapy (anti-TNF agent and thiopurines) and conventional treatment (<60 years, risk ratio [RR]: 1.06; 95% CI: 0.98, 1.15; ≥60 years, RR: 1.09; 95% CI: 0.90, 1.33, $p=0.78$).[23]

Table 1: Effectiveness of IBD Therapies Between Elderly and Non-Elderly Persons with IBD

IBD Therapy	Study	Definition of Effectiveness	Comparison Groups	Type of IBD	Effectiveness
Anti-TNF	Porcari *et al.*[19]	Persistence of therapy at 12 months Corticosteroid-free remission	≥60 years old vs <60 years old	IBD	Lower persistence in older cohort: Ulcerative colitis (p<0.001) Crohn's disease (p=0.004) Corticosteroid-free remission: 31% vs 67%, p<0.001
	Cheng *et al.*[21]	Clinical remission	≥60 years old vs <60 years old	Ulcerative colitis	Induction: OR : 0.78; 95% CI: 0.51, 1.19 Maintenance: OR : 0.65; 95% CI: 0.41, 1.06
	De Jong *et al.*[20]	Discontinuation due to lack of effectiveness (combination of primary and secondary non-response)	≥60 years old vs <40 years old	IBD	SHR: 1.11; 95% CI: 0.63, 1.95
	Kantasiripitak *et al.*[22]	Infliximab levels and antibodies	≥65 years old vs <65 years old	IBD	Infliximab levels at weeks 2, 6, and 14 were similar: p=0.90, p=0.757, p=0.121, respectively Similar rates of antibodies
	Singh *et al.*[23]	Corticosteroid-free clinical remission	≥60 years old vs <60 years old	Crohn's disease	Corticosteroid-free remission: RR: 1.09; 95% CI: 0.90, 1.33
Vedolizumab	Ibraheim *et al.*[24]	Clinical response, clinical remission, and corticosteroid-free remission at 52 weeks	≥60 years old	IBD	Clinical response: 52% Clinical remission: 38% Corticosteroid-free remission: 32%
	Khan *et al.*[25]	Corticosteroid-free remission, IBD-related hospitalization, and IBD-related surgery	≥60 years old vs <60 years old	IBD	Corticosteroid-free remission: 40.1% vs 46.8%, p=0.2374 IBD-related hospitalization: 11.3% vs 11.2%, p=0.9737 IBD-related surgery: 3.9% vs 3.9%, p=0.9851
	Cohen *et al.*[26]	Corticosteroid-free clinical remission and endoscopic remission at 52 weeks	≥60 years old vs ≤40 years old	IBD	Corticosteroid-free remission: Crohn's disease: p=0.45 Ulcerative colitis: p=0.54 Endoscopic remission: CD p=0.74 and UC p=0.52

IBD Therapy	Study	Definition of Effectiveness	Comparison Groups	Type of IBD	Effectiveness
Vedolizumab vs anti-TNF	Pabla *et al.*[27]	Five-year surgical intervention and IBD-hospitalization free survival, endoscopic remission between vedolizumab and anti-TNF users	≥60 years old (anti-TNF users reference group)	IBD	Surgical intervention: *p*=1.0 IBD-hospitalization: *p*=0.21 Endoscopic remission: 65.7 vs 45.2%, *p*=0.02
	Adar *et al.*[28]	Clinical remission at 3, 6, and 12 months between vedolizumab and anti-TNF users	≥60 years old (anti-TNF users reference group)	IBD	Clinical remission at 3 months in Crohn's disease: 41% vs 56%; OR: 2.82, 95% CI: 1.18, 6.76. In ulcerative colitis: 35% vs 43%; OR: 1.74; 95% CI: 0.74, 4.13 Clinical remission at 6 months: 45% vs 54%, *p*=0.23 Clinical remission at 12 months: 54% vs 58%, *p*=0.63
Ustekinumab	Garg *et al.*[29]	Complete clinical remission, and mucosal healing	≥65 years old vs <65 years old	Crohn's disease	Clinical remission: 28.2% vs 52.6%, *p*=0.03 Mucosal healing: 26% vs 30%, *p*=0.74

Abbreviations: *CD = Crohn's disease*; *OR = odds ratio*; *RR = risk ratio*; *UC = ulcerative colitis*

Vedolizumab, a gut-specific monoclonal antibody, is considered effective in the elderly,[24,30] comparable with younger persons.[25] In a retrospective study of 144 individuals with IBD who were 60 years old or older, compared with 140 individuals who were 40 years old or younger, there were no differences in clinical or endoscopic response between the two groups (week 52 remission in Crohn's disease: 40% vs 35%, *p*=0.7, week 52 remission in ulcerative colitis: 48% vs 51%, *p*=0.84).[26] In a retrospective study of people over 60 years old comparing 108 people on vedolizumab with 104 on anti-TNF therapy, there was no difference in surgical intervention or the risk of IBD hospitalization. However, vedolizumab was discontinued less frequently than anti-TNF therapy (25.9% vs 51.9%, *p*=0.02). In those who underwent endoscopic evaluation, the group taking vedolizumab had higher endoscopic response (80.0% vs 59.3%, *p*=0.02) and endoscopic remission rates (65.7% vs 45.2%, *p*=0.02).[27] A retrospective study of people aged over 60 years treated with either anti-TNF or vedolizumab found that more individuals with Crohn's disease (but not ulcerative colitis) on anti-TNF therapy were in remission at three months, though there was no difference between anti-TNF therapy and vedolizumab in either Crohn's disease or ulcerative colitis at six and 12 months.[28]

Ustekinumab, an antibody directed towards IL-12/23, has similar efficacy in all age groups.[31] In a retrospective study of 117 people with Crohn's disease, mucosal healing was similar in the elderly cohort (aged greater than 65 years) compared to those aged under 65 years (26% vs 30%, *p*=0.74).[29]

Safety

Thiopurines

Thiopurine use in people over 65 years of age is associated with both an increase in non-melanoma skin cancers,[32] and lymphoproliferative disorders,[33] when compared to thiopurine users under 50 years of age. Exposure to thiopurines also increases a person's risk of infections.[34] A cohort study of 48,752 individuals with IBD from Spain, revealed that elderly people (aged greater than 60 years) using thiopurines had higher rates of myelotoxicity, digestive intolerance, and hepatotoxicity, and that thiopurines were more likely to be discontinued than in those under 60 years of age (67.2% vs 63.1%).[35]

A nationwide retrospective study of people with IBD with a mean age of 63.0 years, using the Veterans Affairs dataset, revealed that exposure to thiopurines (OR: 0.962; 95% CI: 0.230, 4.027) or anti-TNF therapy (OR: 0.581; 95% CI: 0.174, 1.939) was not associated with an increased risk of contracting COVID-19.[36] For more information on the impact of COVID-19 on people with IBD, see Chapter 9.

Biologics

Anti-TNF use in older people with IBD has been associated with serious infections (aHR: 3.92; 95% CI: 1.185, 12.973), when adjusting for age at diagnosis and number of comorbidities.[37] A prospective IBD registry revealed elderly people (aged greater than 60 years) on anti-TNFs had higher rates of serious adverse events (incidence rate ratio [IRR]: 2.06; 95% CI: 1.42, 3.00), and serious infections (61.2 vs 12.4 infections per 1,000 person-years) compared with a younger cohort (aged under 40 years).[20] A retrospective study of individuals with IBD using the American Veteran Affairs dataset revealed anti-TNF therapies are associated with an increased risk of pneumonia and hospitalization; though this was not stratified by age, 36.5% of people in this study were over 64 years of age.[38] In a meta-analysis, elderly people with IBD (aged 60 years or greater) exposed to biologics were at increased risk of both serious infections (random effects summary relative risk: 2.70; 95% CI: 1.56, 4.66; I^2 = 57%) and opportunistic infections (random effects summary relative risk: 3.16; 95% CI: 1.09, 9.20; I^2 = 73%), though quality of evidence was low to very low.[39]

In a pooled analysis of data from randomized trials assessing anti-TNF use, elderly people (aged 60 years or greater) with ulcerative colitis had a higher increased risk of serious adverse events, but this increase in risk could not be attributed to anti-TNF therapy.[21] In a systemic review and meta-analysis in those with immune-mediated inflammatory diseases (IBD, rheumatoid arthritis, and psoriasis), those 60 years age or greater on biologics had an increased risk of infection compared with younger people on biologics, and an increased risk compared with older individuals not on biologics.[40]

Vedolizumab has a lower risk of infection-related complications,[41] and is therefore considered safe in all ages.[42] In a retrospective study of people with IBD on vedolizumab, there were more infections in the elderly group (12% vs 2%), though the authors noted the increased number of infections could be related to age or underlying disease.[26] In a cohort of 497 individuals with IBD over 64 years of age, vedolizumab was as safe as 5-ASA medications with a similar risk of severe infections (38.5 vs 30.6 events per 1,000 person-years).[43] In a study of people over 60 years of age, comparing vedolizumab with anti-TNF therapy, there was no difference in serious infections (log rank, p=0.43).[27] In people over 60 years of age, there was no difference in the risk of infection comparing participants on anti-TNF or vedolizumab (20% vs 17%, p=0.54); pneumonia was the most common infection.[28] Another study included people with IBD aged 65 years or older: Those on vedolizumab had a lower

rate of infection-related hospitalizations (aHR: 0.47; 95% CI: 0.25, 0.86), compared to those on anti-TNF therapies.[44]

Malignancies were infrequent in people over 60 years of age, with no differences seen between anti-TNF and vedolizumab when assessing skin cancers (0.8% vs 1.0%, p=0.86) and other malignancies (3% vs 1%, p=0.27).[28] In the GEMINI long-term safety study, the number of malignancies observed was similar to the general population.[45] The risk of malignancy (excluding non-melanoma skin cancers) among people with IBD over 64 years of age was similar among people with IBD receiving vedolizumab and 5-ASA medications (17.6 vs 15.6 events per 1,000 person-years).[43]

Ustekinumab is also considered safe for treating IBD. In a retrospective study of 117 individuals with Crohn's disease on ustekinumab, there were no differences in infections (5.2% vs 7.7%, p=0.7), infusion reactions (2.6% vs 6.4%, p=0.77), or post-surgical complications (p=0.99) in those over 65 years of age compared with those under 65 years of age.[29]

Combination Therapy (Anti-TNF and Thiopurine)

In those over 60 years old with Crohn's disease, there were no differences in infection risk when comparing early use of combination therapy (anti-TNF and thiopurine together) and conventional treatment.[23] In a large US study using health administrative data from Veterans Affairs, the incidence of herpes zoster (shingles) infection was higher in people with IBD when compared to those without IBD (aHR: 1.72; 95% CI: 1.51, 1.96), with the highest risk being observed in those over 60 years of age on combination thiopurine and anti-TNF therapy.[11]

JAK-inhibitors

Tofacitinib is known to increase the risk of herpes zoster (shingles) infection.[46] Tofacitinib is also known to increase the risk of venous thromboembolism, especially in those with known risk factors, independent of the risk posed by ulcerative colitis (one person with deep vein thrombosis, IR: 0.04; 95% CI: 0.00, 0.23, four people with pulmonary embolism, IR: 0.16; 95% CI: 0.04, 0.41).[47]

Age-Related Comorbidities

IBD itself is associated with an increased risk of certain comorbidities, and as individuals with IBD age, they are more likely to develop these and other age-related comorbidities. In a longitudinal study, spanning 21 US state inpatient databases and accounting for almost half of the population, older individuals are more likely to have two or more comorbidities, based on the Charlson Comorbidity Index, compared with younger individuals (39% versus 4%).[12] Individuals with IBD also have an increased risk of ischemic heart disease (RR: 1.244; 95% CI: 1.142, 1.355).[48]

People with IBD are at increased risk of osteoporosis, and while corticosteroid use is a known risk factor as well, this risk cannot be attributed to steroid use alone.[49] A population-based study from Manitoba revealed that comorbidities were increased both pre- and post-IBD diagnosis.[50] In those over 65 years of age, after being diagnosed with IBD, there was an increased risk of cardiac disease (HR: 1.24; 95% CI: 1.07, 1.43), cerebrovascular diseases (HR: 1.19; 95% CI: 1.01, 1.40), peripheral vascular disease (HR: 1.36; 95% CI: 1.14, 1.62), chronic obstructive pulmonary disorder [COPD] (HR: 1.38; 95% CI: 1.12, 1.70), cancer (HR: 1.21; 95% CI: 1.04, 1.40), and diabetes (HR: 1.17; 95% CI: 1.01, 1.35), among other comorbidities.

A cohort study of 1,480 individuals with IBD in China looked at those over 60 years old compared with those under 60 years old and found that older people had an increased incidence of cancer (26.9 vs 9.51 per 1,000 person-years), with colorectal cancer being the most common.[51] People in the elderly group had a shorter time from IBD diagnosis to developing cancer, and the presence of diabetes was a risk factor in the progression to cancer.

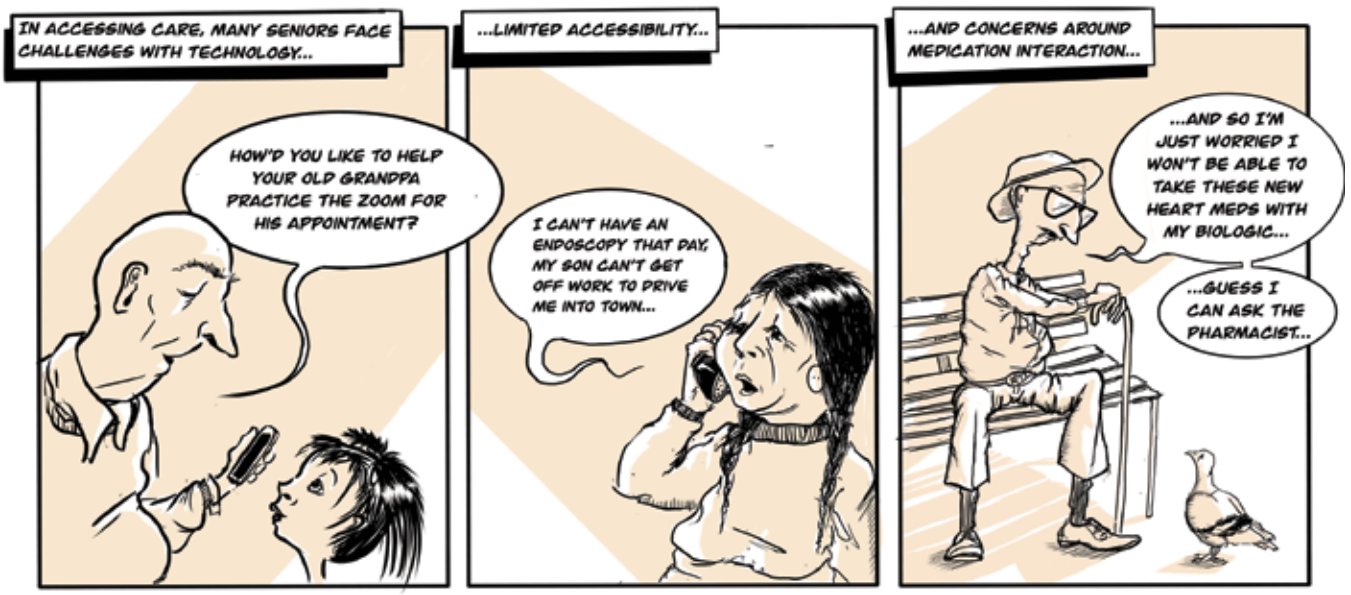
Polypharmacy—being on multiple medications simultaneously—is also an issue in the elderly, perhaps contributing to non-adherence with IBD therapies. A retrospective study of 393 individuals with IBD over 64 years old were prescribed an average (mean) number of 7.0 drugs.[52] Frailty is also more common in the elderly, and this is associated with worse outcomes in IBD, including mortality (aHR: 1.57; 95% CI: 1.34, 1.83), prolonged hospitalization (median nine days vs median five days, $p<0.01$), and readmission for severe IBD (aHR: 1.22; 95% CI: 1.16, 1.29).[53, 54] One study showed that frailty, when present pre-treatment, was associated with an increased risk of infections (19% vs 9% for anti-TNF and 17% vs 7% for immunomodulators, $p<0.01$ in both groups).[55] It is unknown, however, if pre-treatment frailty is a predictor on IBD outcomes by drug class. More evidence is needed in this field.

Deficits in the geriatric assessment (a tool designed to test a number of factors including physical health, mental health, cognitive function, and others) are common in the elderly with IBD, which are associated with a lower health-related quality of life (based on the short IBD questionnaire, which showed a mean score in those with severe deficits 50.7 vs 58.4 in those with moderate deficits, and 62.3 without deficits, $p<0.001$), and those with active disease are more prone to having deficits (39.9% clinically active disease in severe deficits, 27.7% in moderate deficits, and 14.9% in those without deficits, $p=0.001$).[56]

Access to Care

Unfortunately, there are not many studies assessing access to care in seniors. A population-based study in three provinces (Manitoba, Ontario, and Alberta) reported people with IBD over 65 years of age in rural households were less likely to receive care from a gastroenterologist for their IBD compared to seniors in urban areas (OR: 0.35; 95% CI: 0.26, 0.46).[57] A retrospective study assessing Veterans Health Administrations data in the US showed a higher level of continuity of care within one year was associated with being over 65 years old, compared with a younger cohort; this is important because a lower level of continuity of care in their study was associated with worse outcomes.[58]

As virtual care becomes increasingly common in managing IBD, it may be difficult for older individuals to access their IBD care, online questionnaires, or digital applications due to a decrease in technological literacy. One study showed that the self-reported mean information technological literacy scores worsened with advancing age.[59] Further information on virtual care models can be found in Chapter 12. Utilization of gastroenterology care in those with elderly-onset IBD varies, and those treated by gastroenterologists or in networks with more gastroenterologists have better outcomes.[60] In the same study, surgery in people with Crohn's disease was not associated with availability of gastroenterologist or access to specialist care, though there was variation in the five-year risk of colectomy in people with ulcerative colitis.[60] Care by a gastroenterologist was associated with immunomodulator and biologic use within five years, as compared to those whose primary provider was not a gastroenterologist.[60]



Costs

A retrospective analysis from 2007–2016 of pharmacy and administrative claims data in the US revealed that elderly people with IBD had higher costs of care when compared to those with IBD aged 35–44 years.[61] Nguyen *et al.* reported that persons 65 years old or older had longer hospital stays than those who were middle-aged and younger (median stay seven days compared with six days and five days, respectively), as well as an increased mortality.[12] These results ultimately led to significantly higher hospitalization costs for older individuals with IBD, with an average (mean) cost of $15,078 USD versus $12,921 USD and $10,070 USD, respectively. Despite this, older individuals with IBD were less likely to undergo gastrointestinal surgeries, or IBD-related procedures. A population-based study within Manitoba revealed that mean costs directly attributable to Crohn's disease and ulcerative colitis were lowest in those over 65 years old, when compared with younger cohorts.[62] More information on costs borne by the healthcare systems directly related to IBD is in Chapter 4.

Vaccines

Elderly people with IBD are at increased risk of opportunistic infections,[63] and vaccines are an important layer of protection. It is recommended that those over 50 years of age receive the recombinant herpes zoster vaccine (against shingles), and that those over 65 years of age receive the pneumococcal vaccine (against pneumonia).[64] Therapies to treat IBD are associated with an increased risk of infection; for example, anti-TNF inhibitors are associated with an increase in pneumonia, but being vaccinated against pneumococcus viruses is associated with a reduced risk of pneumonia.[65] While receiving the recombinant herpes zoster vaccine can help reduce one's risk of acquiring shingles, individuals with IBD are still at increased risk of acquiring the infection even after getting vaccinated, compared with those who do not have IBD.[66] Older age (this threshold varied in studies, from over 50 to over 65 years) is associated with an increased uptake of influenza and pneumococcal vaccines, although they were less likely to get the live-attenuated herpes zoster vaccine.[67]

Individuals with immune-mediated inflammatory diseases (including IBD) aged over 60 years on immunomodulators or biologics who received COVID-19 vaccines had reduced odds of a positive antibody response following either mRNA or adenovirus-vector vaccines,[68] and antibody levels decline in seniors at a faster rate than in younger populations. In people with IBD vaccinated with mRNA or non-viral vector vaccines, being over age 60 was associated with lower anti-SARS-CoV-2 antibodies and a lack of antibody response.[69, 70] More on overall vaccine response to COVID-19 vaccines can be found in Chapter 10.

Conclusion

The total number of seniors living with IBD is increasing, and this provides many different challenges due to the presence of comorbidities, frailty, polypharmacy, and an increased risk of infections and malignancies. While treatment approaches are similar to non-elderly people with IBD, the use of biologics in real-world cohorts is lower in elderly people with IBD. Whether anti-TNF therapy is associated with an increased risk of infections is controversial, and newer biologics including vedolizumab and ustekinumab are thought to have a more favourable safety profile when treating elderly individuals with IBD. Access to care for seniors can be difficult, as technology advances with online questionnaires and digital applications on smartphones, though outcomes are better when seniors' IBD is treated by a gastroenterologist. Vaccines are an important mechanism to prevent infections and should be offered to all elderly individuals with IBD.

Knowledge Gaps & Future Research Directions

1. It is important to better define the natural history of IBD in the elderly, and how it differs from other age groups with IBD.

2. A better understanding of how to optimize biologic therapies when treating elderly individuals with IBD is needed.

3. The magnitude of infection risk with older advanced therapies (e.g., anti-TNF) and newer advanced therapies (e.g., anti-IL-23, integrin inhibitors) needs to be defined for the elderly, including those with multiple comorbidities. Randomized trials should include a larger number of elderly individuals with IBD so that efficacy and safety can be better defined.

4. Further studies are needed on how and why costs are different in the elderly population with IBD, and regarding cost-effective measures in lowering both their direct and indirect costs.

5. An understanding of the spectrum of technology literacy among seniors with IBD is important as we enter an era of increased virtual care and remote monitoring of IBD status.

6. The financial, social, and time costs for family members of elderly people with IBD is not defined, but, in some cases, can rival or exceed that for family members of children with IBD. This can be especially problematic for family members of the elderly individuals with mobility and/or cognitive issues.

7. Research into optimizing multidisciplinary care for seniors living with IBD, including communication and shared decision making among different medical specialists, healthcare providers, and social services, is required.

Patient & Caregiver Partner Perspective

Patient partners acknowledged that the number of seniors with IBD is increasing due to new diagnoses: Partly because of new diagnoses in older adults, and partly because adults who already have IBD are aging. Patient partners recognize that the management of IBD in seniors is complicated due to the presence of underlying conditions, polypharmacy, frailty, and lack of access in some areas to specialized care/gastroenterologists. Some medications may be safer to use and offer fewer adverse effects than others in the senior population. Encouraging vaccinations in seniors with IBD is important in protecting against infections. Seniors with IBD want to be engaged in their own care and encouraging greater access to care can assist with that engagement. Virtual technology can be used as one method to enhance access; however, support may be needed for its use and connecting virtually may not be preferred by all. Another means to enhance care assess is to offer greater in-home care services for seniors. IBD in seniors is a growing public health issue requiring greater research and coordinated, interprofessional resources to address complex care needs to allow seniors to make informed decisions about their care. Partners stressed the importance of self-advocacy or having someone to advocate on their behalf for their care needs.

Policy Implications & Key Advocacy Outcomes

1. Ensuring that seniors with IBD have access to gastroenterology care is essential; remote access is also important because there may be barriers in some forms of virtual care. Telemedicine should be accessible and be funded to ensure it can be utilized by those who need it (e.g., those with mobility restrictions or living in remote locations).

2. There is a need for services to allow seniors, or someone advocating for the senior, to review their medications with a pharmacist as needed.

3. A social worker or support system for peer advocates/support is needed to ensure seniors have sufficient resources to purchase their medications and food, and to be a healthcare advocate for those who cannot provide/advocate for themselves.

4. Senior-specific support groups would be useful to help individuals not feel isolated.

5. Support should be provided for house-bound—physically or by choice—individuals by increasing access to in-home care (where possible).

IBD IN SENIORS IS A GROWING HEALTH ISSUE IN CANADA; THIS CHAPTER AND RESEARCH IS EXTREMELY HELPFUL IN HELPING TO DEFINE THE PROBLEM AT HAND AND THE ROAD AHEAD.

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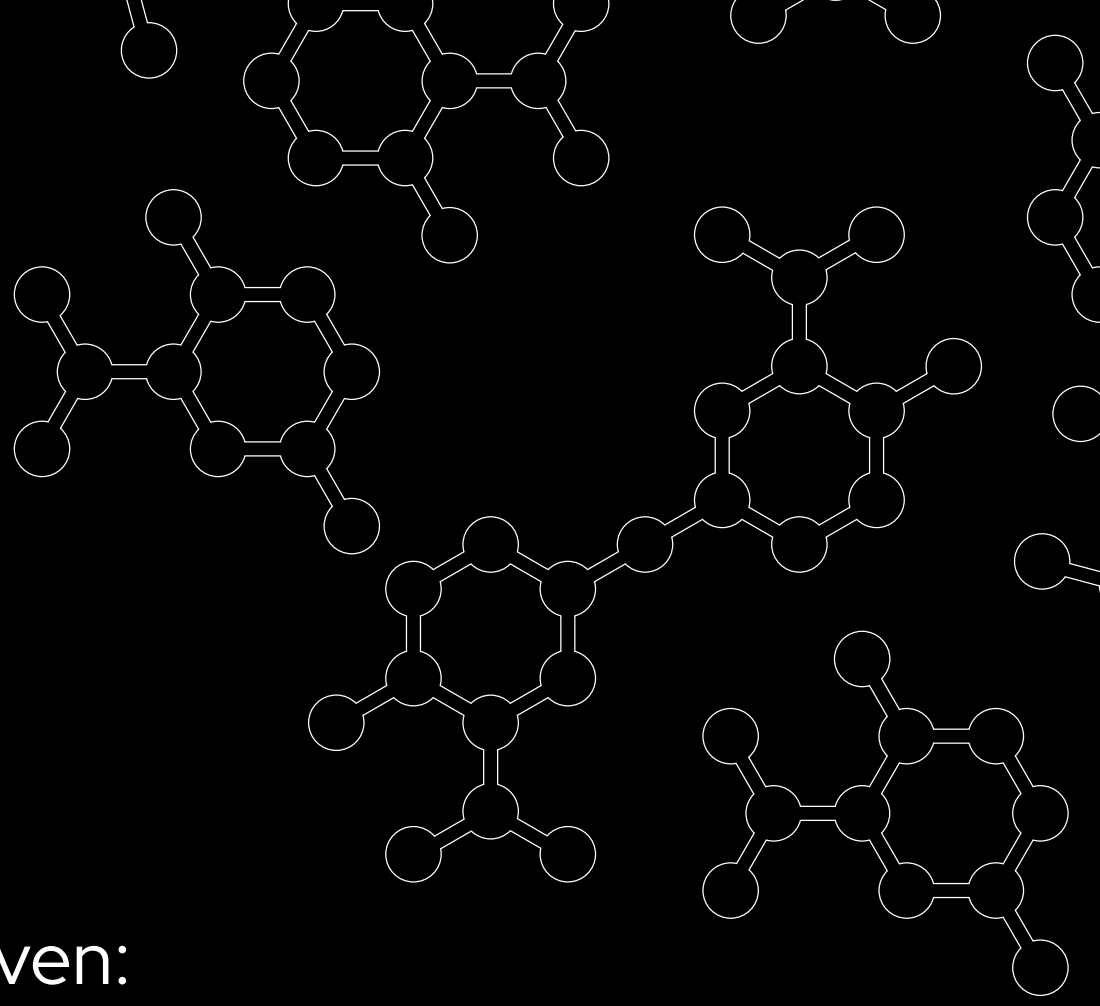


Section Seven:

The Influence of Sex and Gender on Canadians Living with IBD

The Influence of Sex and Gender on Canadians Living with IBD

Abstract

Sex (the physical and physiologic effects resulting from having specific combinations of sex chromosomes) and gender (sex-associated behaviours, expectations, identities, and roles) significantly affect the course of inflammatory bowel disease (IBD) and the experience of living with IBD. Sex-influenced physiologic states, like puberty, the menstrual cycle, pregnancy, and andropause/menopause may also impact and be impacted by IBD.

While neither Crohn's disease nor ulcerative colitis are commonly considered sex-determined illnesses, the relative rates of new diagnoses of Crohn's disease and ulcerative colitis between males and females varies over the life cycle. In terms of gender, women tend to use healthcare resources at slightly higher rates than men and are more likely to have fragmented care. Women are more commonly prescribed opioid medications and are less likely than men to undergo colectomy. Women tend to report lower quality of life and have higher indirect costs due to higher rates of disability. Women are also more likely to take on caregiver roles for children with IBD. Women with IBD are more commonly burdened with adverse mental health concerns, and having poor mental health has a more profound impact on women than men.

Pregnant people with active IBD have higher rates of adverse outcomes in pregnancy, made worse in regions with poor access to IBD specialist care. The majority of individuals with IBD in Canada do not have access to a pregnancy-in-IBD specialist; access to this type of care has been shown to allay fears and increase knowledge among pregnant people with IBD.

Key Points

1. There is a clear impact of sex and gender on IBD and the disease experience. For example, Females who present with IBD symptoms can have those symptoms misattributed to ascribed sex/gender issues (e.g., menstrual cramping), and men are less likely to seek healthcare.

2. Research along sex and gender in IBD is lacking. Specifically, how conformity to masculine, feminine, or non-gender-normative roles impact IBD diagnosis and healthcare-seeking behaviour.

3. Females with IBD are about 50% more likely than males with IBD to report anxiety or depression.

4. Pregnancy is associated with greater risks in people with IBD. All individuals with IBD should have access to IBD specialists who focus on preconception counseling and management of IBD during pregnancy, and who collaborate with maternal-fetal medicine specialists and obstetricians who are experienced in obstetrical management of individuals with IBD.

5. It is important to deeply consider your disease before, during, and after pregnancy and engage your gastroenterologist as a member of your pregnancy team.

Introduction

Sex refers to the biological and physiological differences that occur between individuals as a result of the direct or indirect effects of their sex chromosomes. Gender refers to the identity of the individual and how they express themselves in the world.

In this chapter, we summarize the impacts of sex and gender on the disease course and experience of persons living with IBD. We provide a framework to understand the work that remains to be done in this area, and the role Crohn's and Colitis Canada and its membership can play in promoting research and mitigating gender-based inequities. We use the terms male/female when describing sex-related influences, and men/women when describing gender-related influences. When a study does not explicitly differentiate between sex and gender, or when it uses the terms interchangeably, we use sex (male/female) when the outcomes are related to the etiology, physiology, or objective measures of disease, and gender (men/women) when the outcome is primarily behavioural or related to the lived experience of having IBD. We recognize that there are more than two genders; currently, however, research extending to non-gender conforming individuals with IBD is lacking.

What Is the Impact of Sex and Gender on the Epidemiology of IBD?

Unlike in many autoimmune diseases, sex does not have a strong impact on the overall risk of developing IBD. In Canada, the ratio of Crohn's disease between females and males is approximately 1.3 to 1, and ulcerative colitis rates are roughly equal between the sexes.[1, 2] However, this ratio varies over the life cycle; males are more likely than females to be diagnosed with Crohn's disease prior to adolescence, and females being more commonly diagnosed in adulthood.[3] Rates of ulcerative colitis among males and females are similar until late adulthood, when more diagnoses in males begin to emerge.[3] Although these differences are relatively small, this observation may provide important insights in how age-related variations in sex hormone levels or other sex-related differences may impact the development of IBD. Data from animal studies have suggested that sex hormones, particularly estrogens, can promote certain inflammatory responses in the intestine. In humans, it is unclear if exposure to sex hormones, whether internally produced by reproductive organs, or in the form of medications or supplements, affect the course of IBD or impact inflammatory processes in a clinically significant way.[4-6]

Oral contraceptive use has been associated with an increased risk of being diagnosed with IBD,[7] though it is possible that the higher risk of IBD it is due to other factors or behaviours that are themselves associated with oral contraceptive use (e.g., higher socioeconomic status or more frequent physician visits and diagnostic testing).

Similarly, gender-related factors may also influence the epidemiology of IBD through the impact that differences in the likelihood of obtaining evaluations and testing have on the timeliness of diagnosis. While there is not yet any definitive evidence on the impact of gender on diagnostic delay,[8, 9] women are more likely to present with

abdominal pain that is presumed to be due to functional or being psychosomatic disease (i.e., conditions with symptoms but not observable cellular change; e.g., irritable bowel syndrome, chronic fatigue syndrome) rather than due to organic illness (i.e., diseases with cell changes or observable damage; e.g., IBD, rheumatoid arthritis).[10, 11] Conversely behavioural expectations around stoicism and toughness in men may prevent them from seeking healthcare for gastrointestinal symptoms that may prove to be IBD, though this has not been directly assessed.[12] Further research is required to understand how gender, and more specifically, how conformity to masculine or feminine gender roles impacts IBD diagnosis and healthcare-seeking behaviour. There is no clear or consistent evidence suggesting that sex or gender influence the rates of new diagnoses or the severity of any IBD specific complication, or that they are associated with any particular disease phenotype or characteristic.[13]

Sex hormones can affect gastrointestinal motility (i.e., how quickly substances pass through the digestive tract) and pain sensitivity. It has been observed that worsening of gastrointestinal symptoms in the premenstrual or menstrual cycle can occur in people with IBD, and this may affect the clinical assessment of IBD activity.[14-19]

The Impact of IBD in Lesbian, Gay, Bisexual, Transgender, Queer, Two Spirited Persons (LGBTQ2S+)

When discussing the LGBTQ2S+ community, it is important to differentiate between gender identity, sexual orientation, attraction, and sexual behaviour. As an example, a person assigned male at birth (sex), may see himself as a heterosexual man (sexual orientation and gender identity), be attracted primarily to women (heterosexual attraction), but participate in anal receptive intercourse (sexual behaviour). Each of gender identity, sexual orientation, attraction, and behaviour could conceivably have influences on all facets of IBD, from the risk of developing IBD, to how IBD care is accessed, to one's lived experience in managing and mitigating the effects of IBD.

People in the LGBTQ2S+ populations are more likely to be socioeconomically disadvantaged compared to the general population, which can affect their ability to access healthcare. These disadvantages are further compounded by negative experiences with the healthcare system and fears of further stigmatization, which often leads to delayed diagnosis and higher morbidity in LGBTQ2S+ persons than in the general population. These effects are even more pronounced among people with non-conforming gender identities and may be further compounded by race, ethnicity, and immigration status.[20-22]

A recent study using secondarily collected data suggested that men who reported practicing high-risk sexual behaviours with other men were more likely to develop Crohn's disease and ulcerative colitis than were men who practiced high-risk sexual behaviour with women (Crohn's disease, odds ratio [OR]: 1.64; 95% CI: 1.29, 2.09; ulcerative colitis, OR: 2.45; 95% CI: 2.35, 3.34).[23] This study, however, was criticized for conflating sexual behaviour with sexual identity, and was commonly misreported in the lay media as a link between being gay and developing IBD.[24] A more recent analysis using data

from the United States National Health Interview Survey showed no association in men or in women between sexual orientation and IBD prevalence (i.e., the total number of people with IBD) (Newman, K. & Targownik, L.E., unpublished data).

A qualitative study that gathered the experiences of gay and lesbian individuals with IBD identified a set of unique concerns of this population related to stigmatization of gay and lesbian identities, as well as the impact of sexual behaviors associated with same-sex attraction on IBD. Specifically, men who have sex with men commented on the impact of living with a stoma or having perianal disease on their ability to participate in anal receptive intercourse, as well as the impact on body image and dealing with misconceptions about the role their sexual behaviours had on developing IBD.[25]

The epidemiology and natural history of IBD in transgender and gender nonconforming (TG/NC) populations remains unreported. Studies on the lived experience of TG/NC persons with IBD is ongoing, and guidelines for the care of TG/NC adolescents have been proposed.[26] IBD-related concerns that may be specific to the TG/NC community include: The impact of gender-affirming hormonal therapy on IBD, the effect that perianal disease may have on the ability to undergo gender-affirming surgeries, and on the ability of their IBD care provider to provide culturally competent care in a welcoming and non-stigmatizing environment.[27]

The Impact of Sex and Gender on Healthcare Utilization

Dittrich *et al.* assessed individuals with Crohn's disease in Edmonton, Alberta showing both the annual likelihood of undergoing surgery among males and females was similar (approximately 5.8% per year in 1996; approximately 1.3% per year in 2013), and the change in surgeries in males (8.5% per year decline; 95% CI: 6.9%, 10.0%) and females (8.4% per year decline; 95% CI: 7/0%, 9.8%) from 1996–2013 were similar.[28] In a study using Ontario health administrative databases, females with IBD were less likely to receive high exposure of cumulative ionizing radiation (OR: 0.91; 95% CI: 0.87, 0.95); the authors concluded that this may reflect hesitancy to be exposed to radiation in those of childbearing age, rather than differences in access to care.[29]

Analyses performed on population-based data from Manitoba did not demonstrate any differences between males and females in the likelihood of being prescribed a biologic, or in persistence with biologic therapy once prescribed.[30, 31] However, in a different dataset, females were more likely than males to discontinue anti-TNF therapy due to subjective drug-related side effects (adjusted hazard ratio [aHR]: 4.05; 95% CI: 2.36, 6.98);[32] similar findings were also seen in a Swedish registry of vedolizumab users.[33] There have been few studies that have specifically sought to evaluate gender-based differences in treatment response to biologic therapies. Secondary analyses of individual studies have not generally shown consistent impacts of gender on treatment response.[34, 35] Two studies have suggested that men receiving golimumab or vedolizumab may have lower rates of response to induction therapy, but that this effect dissipates by the end of the maintenance phase.[36] Reasons for this difference in speed of response are not well understood.

Targownik *et al.* used a population-based IBD registry in Manitoba to assess direct costs attributable to caring for individuals with IBD between 2005–2015, as well as the inpatient, outpatient, and surgical visits associated with IBD.[37] In a that analysis, men were admitted to hospital at 20% less than women, and sought outpatient care for IBD 7% less frequently than women. However, men were admitted to hospital for surgical care 18% more often than women.[37] Direct costs for males were $762 per year more than women with IBD (95% CI: $440, $1,085). It is unclear whether this cost is driven by higher surgical costs, more frequent use of diagnostic testing, or greater use of costly biologic medications. The average Canadian male outweighs the average Canadian female by 15 kg,[38] resulting in higher costs for drugs with weight-based dosing (e.g., biologics). While there have been multiple other population-based studies detailing the direct costs of care associated with IBD in North America and Europe, none specifically describe gender-based differences in healthcare spending (see Chapter 4).

Shafer *et al.* reported that although higher levels of disability were associated with greater income loss, there was no analysis evaluating whether the impact of disability on income is different between women and men.[39] Better understanding the impact of disability on income is important as multiple European studies have suggested that women reported greater disability associated with IBD than men. In Sweden, women with IBD were shown to earn less than their age- and sex-matched siblings in the five years following diagnosis (income loss of €9,778 vs. €6,569).[40] In the same dataset, Swedish women reported a greater number of missed days of work than did men, especially in the time before treatment is started.[41] However, women did not appear to have higher rates of income loss in a Danish cohort.[42] Importantly, women who served as primary caregivers for dependents with IBD were more likely to perceive high levels of caregiver burden, which predicted higher rates of absenteeism and presenteeism (see Chapter 3).[43]

The Impact of Sex and Gender on Mental Health and Quality of Life in IBD

Mental health concerns are consistently identified by individuals with IBD as a priority. Health-related quality of life refers to the individual's subjective sense of well-being and is driven by the burden of disease-associated symptoms, a person's mental health, and the impact that physical and mental health has on a person's ability to socially and economically engage with their families and communities. International consensus panels and afflicted individuals agree that improving overall quality of life is a critical treatment goal in IBD,[44] and that care providers should be striving not only to improve symptoms and inflammation but working with individuals with IBD to optimize their overall sense of well-being.

There are limited data to support whether there are differences in the overall burden of symptoms associated with IBD, controlling for the underlying severity of IBD.[45] Women do tend to report more fatigue, which is a major driver of decreased quality of life in IBD and is associated with poorer mental health and decreased workplace engagement.[46] Different factors may be driving this, including the higher prevalence of iron deficiency among females, the impacts of hormones and hormonal fluctuations, or a higher prevalence of accompanying disorders of gut-brain interaction.[47]

Many women with IBD also report changes in IBD symptoms that occur at or before the time of menses, however there have not been any studies that have associated this change in symptoms to the level of inflammatory activity or directly to fluctuations in hormone levels.[16, 19] Gastrointestinal symptoms around the time of menstruation are frequently reported by people without IBD as well, and data about whether these symptoms are more severe for individuals with IBD are lacking.[15] With regards to the impact of comorbid disorders of gut-brain interaction (DGBI), Bryant *et al.* reported a higher rate of anxiety (78% vs 22%) and depression (89% vs 11%, both $p<0.001$) among women with DGBIs along with IBD, and female sex was reported as an independent predictor of having a DGBI in IBD (OR: 2.17; 95% CI: 1.02, 4.55).[48]

Women with IBD are about 50% more likely than men with IBD to report anxiety or depression.[49, 50] In 2019, Lewis *et al.* used the University of Manitoba Research Registry to identify people with currently active or previously active anxiety and depression.[51] Among 242 persons with IBD, 40% and 30% reported a history of depression and anxiety, respectively, of whom 11% and 17% reported their depression or anxiety being currently active. Men were more likely than women to state that they had not reported having depression to their physicians. These findings highlight the importance of a systematic approach to addressing mental health concerns among people with IBD, and not relying on individuals to self-report or relying on gender-influenced stereotypes to determine which individuals may have mental illness. An analysis of the population-based University of Manitoba IBD Epidemiologic Registry found that women with anxiety/depression had 1.23 additional ambulatory care visits when compared with men; however, they did not explore whether excess healthcare utilization in pepole with anxiety/depression was influenced by gender.[52]

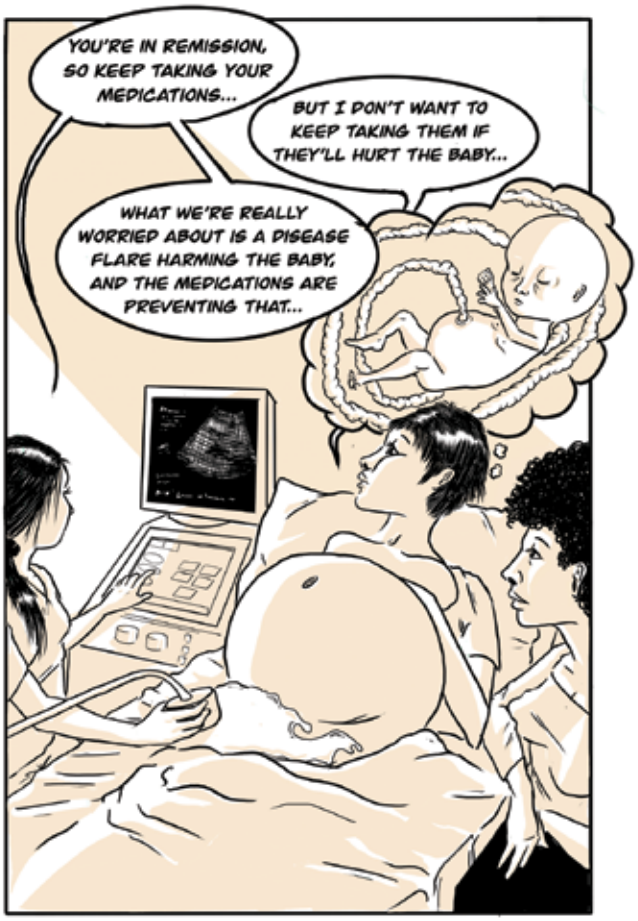
Narula *et al.* explored the relationship between elevated Hospital Anxiety and Depression Scores (HADS), a commonly used questionnaire to screen for anxiety and depression, on the subsequent course of IBD.[53] They determined that having an elevated HADS, particularly for anxiety, was associated with higher rates of a more severe IBD course. There was no difference based on gender in HADS, and sex/gender did not influence the likelihood of having a more severe disease course.

However, this study did not specifically assess whether sex/gender differences in individuals with adverse mental health impacted their likelihood of having adverse IBD outcomes.

The mental health of persons with IBD is addressed in more detail in Chapter 8.

Pregnancy and IBD

The majority of people with IBD are diagnosed during early adulthood and adolescence, meaning that they will be living with IBD during their prime reproductive years. People with IBD have concerns about the impact of the IBD diagnosis, IBD phenotype, and IBD disease activity on fertility and pregnancy outcomes, as well as delivery methods. They report concerns and lack of knowledge regarding uncertainty of the use of IBD medications during preconception and pregnancy.[54, 55] Therefore, it is recommended that individuals with IBD who are contemplating pregnancy or who are pregnant receive individualized education and counseling regarding the management of their IBD during this time.[56] They should have access to



clinicians (gastroenterologists and obstetricians) who are experienced and knowledgeable in the management of IBD during pregnancy.

Among the IBD population, there is a high rate of observed voluntary childlessness, and up to 17% of surveyed females report choosing to remain childless.[57] Factors associated with voluntary childlessness were poorer reproductive knowledge (as measured by the Crohn's Colitis Pregnancy Knowledge score), older age, unemployment, being single, and not seeking medical advice.[57] Lack of knowledge regarding reproductive health issues in IBD results in fears and uncertainty regarding having a diagnosis of IBD, taking IBD therapies, and pregnancy outcomes.[58] About one third of females considering pregnancy reported stopping their medications without discussing it with their physicians;[59] this seems to be a result of concerns about safety and uncertainty about the medications during pregnancy.[60] Dedicated clinical counselling and education can increase pregnancy-specific knowledge.[59, 61] Preconception counselling has demonstrated benefits, including reducing IBD flares in pregnancy by increasing adherence to medications and smoking cessation.[62] A subset of individuals with IBD who have had surgery may be at increased risk of miscarriage, requiring assisted reproductive therapies, caesarean section delivery, having a low birth weight infant, and possible infertility.[63] People with IBD, especially Crohn's disease, are less likely to become pregnant or carry a pregnancy to term when compared to age-matched controls, particularly around the time of diagnosis. Having a history of a pouch procedure may also reduce birth rates and pregnancies in people with ulcerative colitis by around 50%.[64, 65]

Females with IBD, especially those with active or complex disease, are at increased risk for adverse pregnancy outcomes, including pregnancy loss, preterm birth, small for gestational age (SGA) infants, low birthweight infants, and caesarean delivery, as well as complications such as venous thrombosis (blood clots in a vein). Predictors of disease activity in pregnancy include a history of disease activity in a prior pregnancy (OR: 4.21; 95% CI: 1.10, 16.58)[66] and active disease at conception (aOR: 7.66; 95% CI: 3.77, 15.54).[67] Individuals with these risk factors may benefit from specialized counselling and optimal management strategies in the preconception and pregnancy time. Specifically, pregnant individuals who have moderate or severe IBD who are at increased risk for adverse pregnancy outcomes may benefit from this model of care to attempt to reduce their increased risk for adverse outcomes to be comparable to those with milder IBD or the general population.[68] Females with IBD were also at increased risk of developing post-partum depression and anxiety.[69] Multidisciplinary shared care with gastroenterologists and obstetricians/maternal fetal medicine specialists who specialize in the care of pregnant people with IBD may benefit this population.

Many individuals with IBD do not have consistent access to IBD-specific preconception and pregnancy care and are not receiving frequent counselling about IBD and reproductive health issues.[59] A cross-sectional survey in the UK reported variation in the prenatal services provided by IBD units, where only 14% of IBD prenatal care was provided by a gastroenterologist with expertise in pregnancy, and only 14% of units offered combined clinics with obstetricians and gastroenterologists.[70] In an Ontario population-based cohort study, the highest rates of adverse outcomes (preterm delivery, aOR: 2.78; 95% CI: 1.03, 7.46; SGA infants, aOR: 5.66; 95% CI: 1.67, 19.14; Caesarean section aOR: 2.48; 95% CI: 1.11, 5.55) were observed in individuals in the most northern rural areas, with no differences observed in central urban health units.[71]

Recent international guidelines such as those from the British Society of Gastroenterology and British Maternal & Fetal Medicine Society recommend collaborative care between obstetrics and IBD units or coordinated communication to provide preconception counseling to all females with IBD and counselling to pregnant people on the safety of IBD medication during pregnancy and breastfeeding, the optimal mode of delivery, and the management of biologics and childhood vaccines.[72]

All individuals with IBD should have access to IBD specialists who focus on preconception counseling and management of IBD during pregnancy, and who collaborate with maternal-fetal medicine specialists and obstetricians who are experienced in obstetrical management of individuals with IBD. As there may not be a sufficient number of IBD specialists with this expertise, Canada should consider cross-provincial resources where consultants may offer support in other provinces.

Conclusion

Despite the centrality of sex and gender in our day-to-day experience, there has been relatively little research that is focused on the specific ways that sex or gender impact IBD. There is an increasing recognition on the importance of sex- and gender-related factors on health and disease, and many funding agencies (including the Canadian Institutes of Health Research and Crohn's and Colitis Canada) compel research applicants to describe how sex- and gender-related factors will be included as part of the research design. However, assessing sex- and gender-related influences are often not the primary question being studied. In addition, the interactions that sex- and gender-related factors have on known associations (e.g., adverse mental health or worse IBD outcomes) are rarely explored.

Due to the high number of people living with IBD in Canada, well-organized datasets, and a highly engaged patient/physician/researcher community, Canadians are well positioned to conduct, coordinate, and disseminate higher quality research in this area.

Knowledge Gaps & Future Research Directions

1. There is limited knowledge as to the experience and healthcare needs of transgender and gender diverse individuals living with IBD.

2. Further data confirming the value of comprehensive care clinics targeting females with high risk IBD who are or are seeking to become pregnant are required.

3. There are limited data on the impact of cyclical and lifetime hormonal changes on the etiology of IBD, symptom burden, and intestinal inflammation, which also needs to include cyclic hormones around menstruation and hormone replacement therapy.

Patient & Caregiver Partner Perspective

Due to a paucity of evidence presented in this chapter, patient partners consider it critical to continue promoting studies that understand how disease course, healthcare utilization, and experiences are affected by sex and gender, as well as research initiatives that identify strategies that could address existing gender inequities. For example, patient partners highlighted the need for evidence expanding our understanding of mental health differences by gender, experiences of transgender and gender-diverse individuals living with IBD, how masculine or feminine gender roles impact IBD diagnosis and healthcare-seeking behaviours, why certain gender groups face barriers of access to IBD care and sex and sexual health among individuals with IBD, among other topics. In addition, patient partners appreciated reading what is known about IBD and pregnancy but felt more research was needed. Understanding how this condition could affect their pregnancy, and vice versa, as well as learning about the use of medications for IBD during pregnancy is fundamental for persons living with IBD who are considering parenthood. Patient partners noted conversations surrounding gender issues, sexual health, and pregnancy planning rarely happen between persons living with IBD and gastroenterology care providers. The IBD community should advocate for access to preconception and prenatal counselling/education for individuals living with IBD and to the care of gastroenterologists and obstetricians with expertise in IBD during and after pregnancy, including cross-provincial models of healthcare that allow for sharing of expertise to more rural and remote areas.

Policy Implications & Key Advocacy Outcomes

1. Advocacy should aim to support research specifically addressing sex- and gender-related factors on the course of IBD, on the lived experience of IBD, and how to best minimize disparities based on sex and/or gender—including non-binary and other genders. A strong knowledge translation focus on this research will inform clinicians and may positively affect the quality of care they provide.

2. Research should aim to discover any correlations between sex (as reported in administrative healthcare databases) and gender (as identified by the individual).

3. Advocacy should continue to seek multidisciplinary care for those with IBD who are seeking to become pregnant and support mental and sexual health of Canadians living with IBD. This advocacy should include resources to match these individuals with OBGYN specialists who are knowledgeable in IBD care (e.g., databases, programs, inter-provincial collaboration).

4. Crohn's and Colitis Canada should advocate for a safe-space in hospitals and clinics and produce educational material (e.g., brochures, posters) for practitioners with resources/tips for creating a safe-space atmosphere, including information on differentiating common IBD symptoms from sex-specific symptoms (e.g., menstrual pains, endometriosis).

5. Crohn's and Colitis Canada should expand advocacy around washroom access to include advocacy for washroom access for transgendered individuals and those who do not identify as male or female.

THIS RESEARCH HIGHLIGHTS THE "TIP OF THE ICEBERG" STATUS WE CURRENTLY RESIDE AT WITH OUR KNOWLEDGE BASE--MORE RESEARCH IS NEEDED TO UNDERSTAND THE DIFFERENCES IN DISEASE COURSE AND EXPERIENCE BETWEEN THE SEXES/GENDERS.

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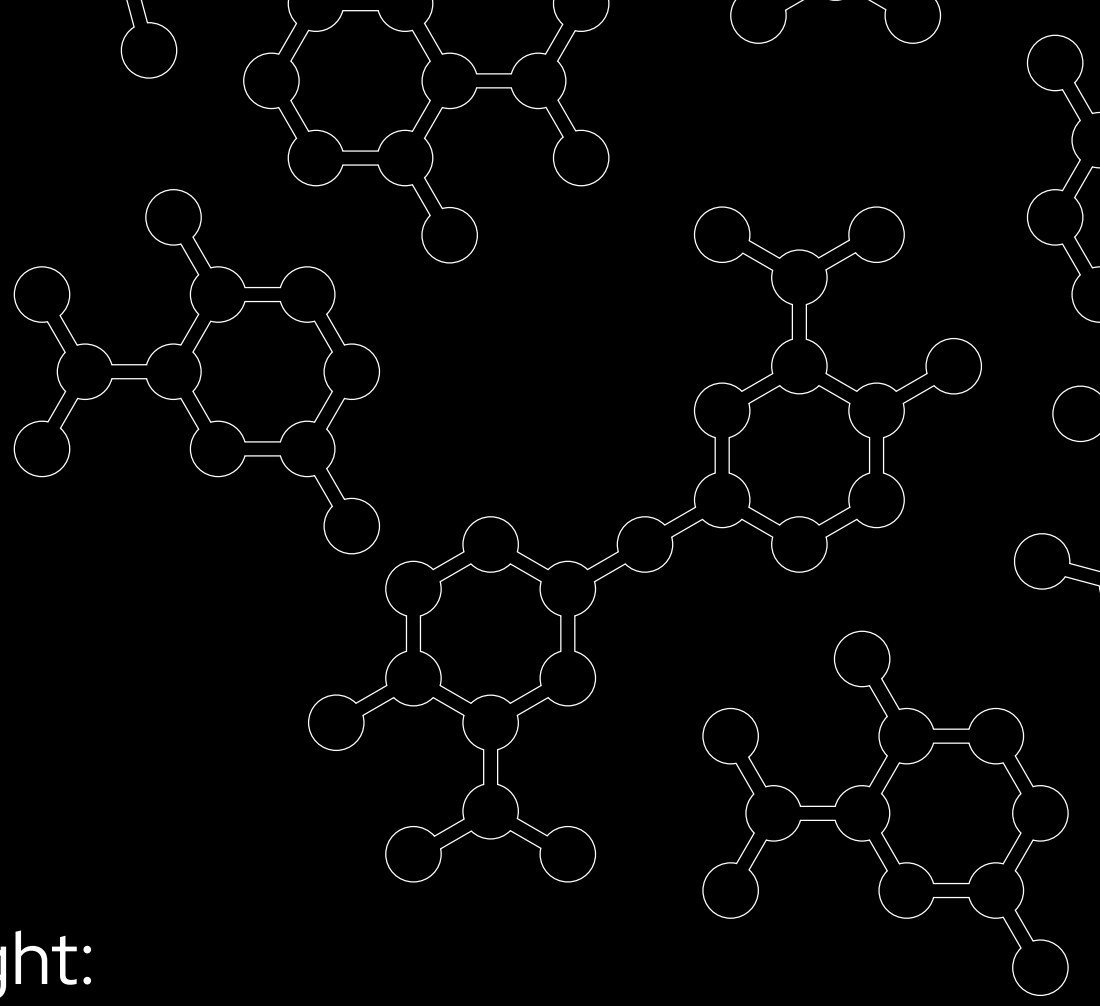


Section Eight:

Mental Health & IBD

Mental Health & IBD

Abstract

Psychiatric disorders—a broad range of ailments that affect a person's thoughts, feelings, behaviour, or mood—are 1.5–2 times more common in people with inflammatory bowel disease (IBD) than the general population. It is estimated that 21% of people with IBD are also diagnosed with clinical anxiety and 15% of people with IBD are diagnosed with depression. Rates are even higher when considering mental health symptoms, as nearly one third of people with IBD experience elevated anxiety symptoms and one quarter experience depression symptoms. Rates of these symptoms were much higher during periods of IBD disease activity, more common in women than men, and more common in people with Crohn's disease than people with ulcerative colitis. There is robust evidence of the detrimental effects of comorbid depression and anxiety on the disease course of IBD based on longitudinal studies tracking outcomes over time. Moreover, psychiatric disorders and IBD have bidirectional effects, with each affecting risk of the other. Elevated mental health concerns have been consistently associated with greater healthcare utilization and costs related to IBD. There is some evidence that low resilience in adolescence could be a risk factor for developing IBD and that enhancing resilience may improve mental health and intestinal disease outcomes in IBD. Psychological therapies used to treat anxiety and depression occurring in the context of IBD have been shown to significantly improve quality of life for people with IBD and reduce anxiety and depression. There is less evidence in regard to the impact of psychotropic medications on mental health or disease outcomes in people with IBD. There is consensus, however, that mental health must be addressed as part of comprehensive IBD care for children and adults.

Key Points

1. Psychiatric disorders are 1.5–2 times more common in people with IBD than the general population. It is estimated that 21% of people with IBD are also diagnosed with clinical anxiety and 15% of people with IBD are diagnosed with depression, and yet they can go undetected. Youth with IBD have nearly double the risk of a psychiatric diagnosis, and six-fold the risk of depression.

2. Nearly one third of people with IBD experience elevated anxiety symptoms and one quarter experience depression symptoms, with higher rates in women and people with Crohn's disease.

3. Depression and anxiety adversely affect the disease course of IBD and increase associated healthcare utilization; active IBD can adversely affect mental health.

4. Psychological therapies used to treat anxiety and depression in the context of IBD have been shown to significantly improve quality of life and reduce anxiety and depression for children and adults with IBD; there is less direct evidence in regard to the impact of antidepressant medication on mental health or disease outcomes in IBD.

5. High resilience is associated with improved mental health and IBD outcomes and is a promising target for intervention.

6. Strengthening autonomy in disease self management may be especially important for adolescents with IBD to facilitate transition from pediatric to adult care.

7. Clinical guidelines recommend screening people with IBD for mental health concerns as part of standard practice in IBD care, recognizing the prominent cooccurrence of these diseases and bidirectional effects, but also noting the importance of having clinical pathways for care if positive.

8. Multidisciplinary IBD clinics, which include mental health specialists, facilitate integrated medical and psychological care and are the recommended model for children and adults with IBD.

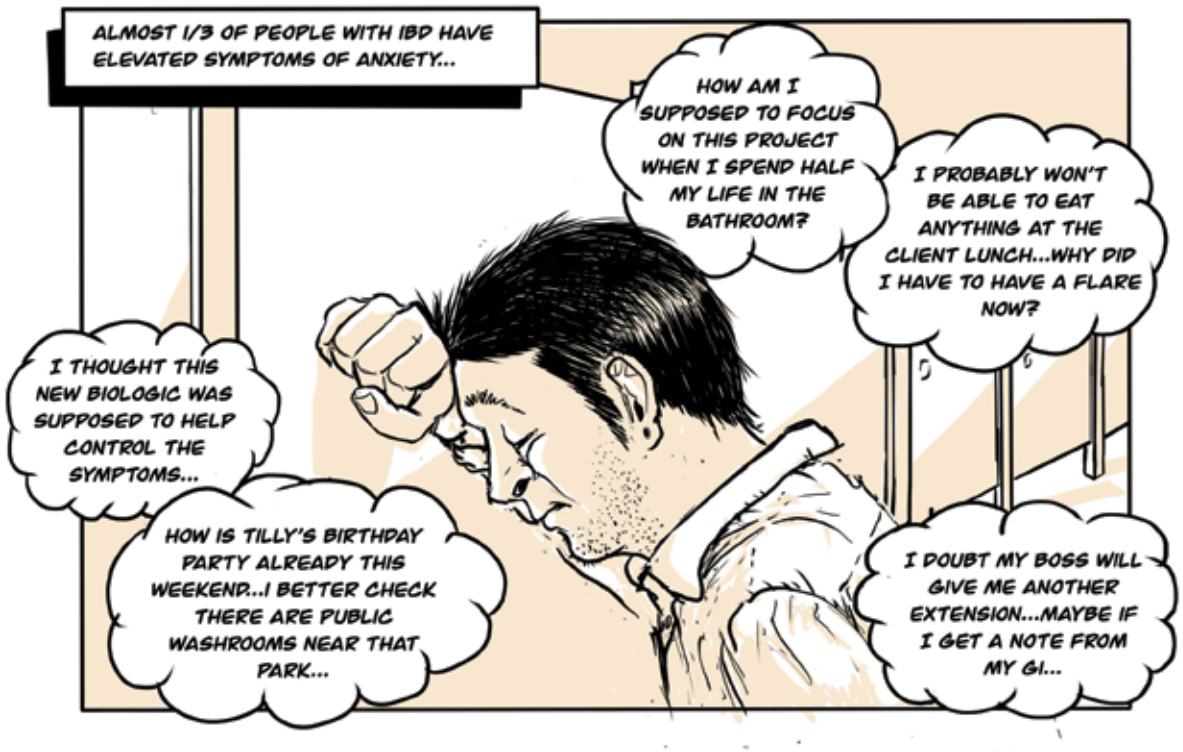
Summary of Crohn's and Colitis Canada's 2018 Impact of IBD Concerning Mental Health

In the 2018 report, mental health in relation to IBD was interwoven throughout several chapters. The 2018 report identified the broad reach of mental health on multiple aspects of IBD including symptoms, disease course, response to advanced therapies, and severe outcomes such as hospitalization and death. Psychological distress was reported to be elevated not just during periods of active IBD flares but also during periods of remission. Other psychosocial factors that were relevant for individuals with IBD included body image concerns, fear of sexual inadequacy, worry about dependency and stigmatization, social isolation, and concern about not reaching one's full potential. Mental illnesses were reported to be twice as common for those with IBD compared to the general population and thought to be more common than any other extraintestinal conditions associated with IBD. It was notable that not that many years ago, discussion of extraintestinal diseases of IBD would have only examined the musculoskeletal system, skin, eyes, and biliary tract. An important theme was the need for multidisciplinary care for those with IBD, integrating care from mental health specialists to address mental health concerns and overall disease management.

Risk of Mental Health Disorders and Symptoms in IBD

IBD is a complex, chronic condition with fluctuating and often unpredictable disease course. There are challenges not only in treating gastrointestinal and extraintestinal manifestations of disease, but also in addressing psychological distress and mental health concerns. This review focuses predominantly on comorbid anxiety and depression in IBD, as these are the most common mental health presentations. There are other mental illnesses emerging as potentially relevant for IBD such as disease-related post traumatic stress, substance misuse, and eating disorders, which are beyond the scope of this review, but may be addressed in a future impact report as further research becomes available.

One in five Canadians experience a mental illness in any given year;[1] this rate is even higher for adults with IBD. Epidemiologic studies have found that individuals with IBD have a higher incidence of diagnosed mental illnesses compared to people without IBD, inclusive of depression (IBD: 18.6 per 1,000 people; 95% CI: 14.2, 24.3 vs no IBD: 10.8 per 1,000; 95% CI: 9.26, 12.5), anxiety (IBD: 25.0 per 1,000; 95% CI: 19.6, 32.0 vs no IBD: 16.3 per 1,000; 95% CI: 14.3, 18.6), bipolar illness (IBD: 3.8 per 1,000; 95% CI: 2.29, 6.30 vs no IBD: 1.56 per 1,000; 95% CI: 1.09, 2.23), and schizophrenia (IBD: 4.62 per 1,000; 95% CI: 3.12, 6.84 vs no IBD: 3.15 per 1,000; 95% CI: 2.53, 3.92), as well as a higher total number of people living with these mental health conditions overall.[2, 3] The pooled prevalence (i.e., total number of people living with these conditions) of clinical anxiety was 20.5% (95% CI: 4.9%, 36.5%) and depression was 15% (95% CI: 9.9%, 20.5%) in a systematic review of 171 studies including over 158,000 participants with IBD.[4] The highest risk for a mental health concern has been seen in the first year after IBD diagnosis (hazard ratio [HR]: 1.4; 95% CI: 1.2, 1.6);[5] however, depression or anxiety can present at any time in the course of the illness. In addition, while still very uncommon, adults with IBD have a higher risk of suicide compared to the general community (HR: 1.2, 1.4).[5] Even with this



higher risk for these mental health concerns, depression may be undetected in one third, and anxiety undetected in two thirds of people with IBD.[6]

The pattern is similar when considering symptom rates of comorbid anxiety or depression in IBD. A recent systematic review and meta-analysis of 77 studies including over 30,000 individuals with IBD found that the total number of people with these comorbid conditions was almost twice as high as the general community, with close to one in three people with IBD experiencing elevated anxiety symptoms (32.1%; 95% CI: 28.3%, 36.0%), and one in four people with IBD experiencing depression (25.2%; 95% CI: 22.0%, 28.5%).[7] Further, rates were as high as 58% for anxiety symptoms and 39% for depression symptoms during periods of disease activity; symptoms of anxiety and depression were more common for women than men, and for those with Crohn's disease compared with those with ulcerative colitis.[7]

Childhood and adolescence are generally periods of risk for the development of psychiatric disorders, with prevalence estimates as high as 20%.[8] Children with chronic diseases have an increased prevalence and impact of mental health conditions,[9] and young people with psychiatric disorders, especially depression, can have impairments in social and educational functioning.[10] A systematic review of psychiatric disorders in people with IBD, which included pediatric (nine studies), adult (36 studies), and both adult and pediatric participants (24 studies), found higher rates of mental disorders for children with IBD as well as for adults—most commonly anxiety and depression.[11] A meta-analysis of studies comparing youth with IBD to those with other chronic illnesses reported similar rates of anxiety disorders (OR: 1.90; 95% CI: 0.47, 7.69; p=0.37), and higher risk of depressive disorders for youth with IBD (OR: 5.80; 95% CI: 1.60, 21.03; p=0.007).[12]

Mechanisms of Comorbid Mental Health Disorders and IBD

Reviews of depression and anxiety research suggest inflammation and gut microbiota play a role in the development of these disorders, which may explain why they are relevant in IBD.[13, 14] More specifically, a study of mice with induced colitis found that chronic stress was associated with a significant increase in inflammation-enhancing bacteria.[15] Interestingly, higher rates of mental disorders relative to matched controls have been found to pre-date an IBD diagnosis by up to five years, suggesting bidirectional vulnerability.[16] Corticosteroid medication used in the care of IBD, such as prednisone, has well known mood disturbing effects.[17] However, there has been surprisingly little examination of adverse psychiatric events with biologics, despite their increasingly widespread use for IBD over the past 20 years. A recent systematic review and meta-analysis found only 15 reported incidences of an adverse psychiatric event for over 2,600 individuals with IBD receiving any of the currently available biologics, based on eligible randomized controlled trials.[18] The study concluded that there was not sufficient evidence of any greater risk of depression, anxiety, psychosis, or suicide associated with the use of biologics, reporting a pooled risk difference of 0.01 (95% CI: 0.00, 0.02) comparing those with IBD on biologics to those not taking biologics.

The Bidirectional Influence of Mental Health and Disease Course in IBD

There is robust support for the detrimental effects of depression and anxiety on the subsequent course of IBD, based on longitudinal studies tracking outcomes over time.[19] The Swiss IBD Cohort Study with 1,973 participants evaluated depression annually and found that elevated depressive symptoms were strong risk factors for multiple adverse disease outcomes, including recurrence of active disease (adjusted hazard ratio [aHR]: 3.55; 95% CI: 2.34, 5.39), a new fistula (aHR: 1.81; 95% CI: 1.03, 3.17), having surgery (aHR: 2.16; 95% CI: 1.48, 3.17), experiencing primary nonresponse to therapy (aHR: 1.91; 95% CI: 1.10, 3.31), or having systemic corticosteroid therapy (aHR: 1.58; 95% CI: 1.06, 2.37), with a higher risk overall for clinical deterioration.[20] In addition, elevated depressive symptoms were associated with the onset of new extraintestinal manifestations, including peripheral arthritis/arthralgia (aHR: 1.42; 95% CI: 1.02, 1.98), primary sclerosing cholangitis (aHR: 3.97; 95% CI: 1.35, 11.68), and uveitis/iritis (aHR: 2.24; 95% CI: 1.17, 4.29).[20]

In a study from Manitoba, Canada, which followed an IBD cohort of 247 individuals over three years, the risk of subsequent active IBD was increased six-fold with elevated depressive symptoms (OR: 6.27; 95% CI: 1.39, 28.2), and elevated symptoms of anxiety doubled the risk for active IBD (OR: 2.17; 95% CI: 1.01, 4.66).[21] Further, a two-year follow up study of 228 individuals in the UK with established IBD remission at baseline had a significantly higher risk of disease flare and escalation of medical therapy if they had elevated psychological symptoms at baseline (HR: 3.18; 95% CI: 1.44, 7.02; HR: 2.48; 95% CI: 1.03, 5.93, respectively).[22]

While many of the disease outcomes reviewed in conjunction with mental health comorbidity are objective, such as medication use and fistula development, few studies have explored the relationship between mental health symptoms and specific markers of inflammation. In a Canadian cross-sectional study, participant-reported high stress was associated with increased disease symptoms but not with concurrent fecal calprotectin.[23] The association between gastrointestinal symptoms and fecal calprotectin is modest at best,[24, 25] and it may require closer longitudinal tracking.

Depression and anxiety have also been implicated in lower cognitive functioning for individuals with IBD. Higher rates of impairment in processing speed, verbal learning, and working memory using validated cognitive tests were found for those with IBD compared to the general population.[25] Higher levels of anxiety were significantly associated with reduced processing speed and verbal learning ($p<0.001$), and higher levels of depression symptoms were associated with slower processing speed ($p<0.01$) in the IBD sample of 247 participants,[25] suggesting that managing symptoms of anxiety and depression in IBD may also be important to mitigate their effect on cognitive functioning.

Overall, the presence of these mental health symptoms appears to have a role in a poorer disease course for IBD, and having IBD may in turn impact the risk of developing depression or anxiety. Among a cohort of 6,464 individuals with pediatric-onset IBD, researchers found a two-fold increased risk for any psychiatric disorder, inclusive of mood, anxiety, and eating disorders, over a nine-year period when compared to 323,200 matched controls; further, mental health disorders were more common for those with very early onset of IBD (onset younger than age six).[26] These findings were very similar to those observed in a study using the Taiwanese National Health Insurance Research Database, where 18.5% of people with IBD developed depression during the 11-year study compared to only 4.8% of siblings without IBD

(adjusted odds ratio [aOR]: 9.43; 95% CI: 6.43, 13.81) and 2.5% for matched controls (aOR: 1.82; 95% CI: 1.14, 2.91).[27] Another study of 405 people with IBD who were followed for over two years found an almost six-fold increase in risk for subsequent significant anxiety for those who had active Crohn's disease or ulcerative colitis at baseline (HR: 5.77; 95% CI: 1.89, 17.7).[28]

Mental Health Disorders and Healthcare Utilization in IBD

The high cost of mental health challenges in the context of IBD is not only reflected in the psychological distress experienced by the individual, and the impact on the course of the IBD, but also on health system utilization. That is, with the adverse impact of these mental health presentations on IBD, it is not surprising that there is also evidence of greater IBD-related healthcare needs for people with IBD who also have mental health comorbidities.

Both retrospective and prospective cohort studies, ranging in sample size from 400 to over 300,000, and following individuals with IBD who had elevated depression and anxiety found a significantly greater likelihood of disease relapse, hospitalization, emergency department (ED) visits, and higher healthcare costs (Table 1).[29-34] A study utilizing provincial administrative health databases also reported higher levels of physician visits and longer hospital length of stay for those with IBD and comorbid mental health disorders (anxiety, depression, bipolar disorder) relative to matched controls.[32] Similarly, a study of Canadian children with IBD found that mental health diagnosis was one of the strongest predictors of having high direct healthcare costs in the first year after IBD diagnosis.[35]

Table 1: Impact of mental health concerns on healthcare utilization in IBD

Study characteristics	Region	Type of study	Sample size	Outcomes
Anxiety and depression at baseline, adjusted for multiple variables including severity of disease at baseline and prior IBD related surgeries; followed four years.[29]	Canada	Prospective cohort two tertiary GI referral centres	414 (IBD)	Anxiety: risk factor for poorer IBD outcomes (defined as IBD-related ED visits, IBD-related hospitalization, or two or more courses of systemic steroids within one year (OR: 3.36; 95% CI: 1.51, 7.48) Depression: aOR not significant; however only 4% of the sample had elevated depressive symptoms at baseline, suggesting potential floor effects.
Depression at baseline adjusted for sex, disease status; followed two years.[30]	United States	Prospective cohort seven tertiary IBD referral centres	4,314 (IBD)	CD: increased risk for disease relapse (RR: 2.3; 95% CI: 1.9, 2.8), surgery or hospitalization (RR: 1.3; 95% CI: 1.1, 1.6); UC: increased risk for surgery or hospitalization (RR: 1.3; 95% CI: 1.1, 1.5).
Anxiety and depression at initial encounter; study period 20 months.[31]	United States	Retrospective cohort Tertiary IBD referral centre	432 (IBD)	Higher rates of utilization for comorbid anxiety, depression compared to IBD only: Imaging studies (53.6% vs 36.7%, $p < 0.05$), ED visits (30.7% vs 20.8%, $p < 0.05$) Hospitalized (31.7% vs 21.7%, $p < 0.05$), Prescribed corticosteroids (50.5% vs 36.7%, $p < 0.01$) Prescribed biologic medications (62.5% vs 51.3%, $p < 0.05$).
Comorbid anxiety, depression, bipolar disorder using validated case definitions.[32]	Canada	Retrospective cohort Provincial health administrative database	8,459 (IBD), 40,375 (matched controls)	Higher rates of utilization for those with IBD comorbid psychiatric disorders: Active psychiatric comorbidity was associated with>10 more physician visits, 3.1 more hospital days, used >6.3 more drugs. There was a synergistic effect of IBD (vs no IBD) and psychiatric comorbidity (vs no psychiatric comorbidity). Higher rates remained, after accounting for mental health related healthcare utilization
IBD hospitalization during six-month period; evaluated for comorbid anxiety, depression, bipolar disorder; followed for up to 10 months.[33]	United States	Retrospective cohort: Nationwide Readmissions Database	40,177 (IBD)	Higher utilization and costs for comorbid psychiatric disorders compared to IBD only: Hospital days (median seven days vs. five days, $p < 0.01$), Readmission rates—30-day (31.3 vs. 25.4%; $p < 0.01$); 90-day (42.6 vs. 35.3%; $p < 0.01$) Hospitalization-related costs (median $41,418 vs. $39,242, $p < 0.01$). Risk of readmission (HR: 1.16; 95% CI: 1.13, 1.20) Risk of severe IBD-related hospitalization (HR: 1.13; 95% CI: 1.08, 1.16).
Comorbid depression.[34]	United States	Retrospective cohort, National health administrative claims database	331,772 (IBD)	Higher utilization and costs for comorbid depression compared to IBD only: IBD-related healthcare costs (mean annual $17,706 (95% CI: $16,892, 18,521) ED visits (aIRR: 1.5; 95% CI: 1.5, 1.6) In the subset of IBD patients with ED visits or hospitalized, higher likelihood of: Repeated CT scans [1–4scans] (aOR: 1.6; 95% CI: 1.5, 1.7) IBD-related surgery (aOR: 1.2; 95% CI: 1.1, 1.2).LATED

Abbreviations: *IBD: Inflammatory Bowel Disease; ED: Emergency Department; CD: Crohn's Disease; UC: Ulcerative Colitis; RR: Relative Risk; OR: Odds Ratio; aOR: adjusted Odds Ratio; CI: Confidence Interval; aIRR: adjusted Incidence Rate Ratio.*

Resilience and Coping in IBD

Much of the work on mental health in IBD has focused on the illness end of the mental health continuum, with examination of elevated distress, depression, and anxiety. An emerging area of investigation in chronic disease more generally, and specifically in IBD, shifts the emphasis to wellness, with exploration of disease adaptation aspects such as resilience and self-efficacy for disease management. Resilience is described variously as an ability or process to maintain mental health despite experience with physical or psychological adversity.[36] Resilience research often considers protective mechanisms against stress-related disorders and chronic disease impact, with resiliency-based interventions aiming to prevent or mitigate mental disorders through enhancing resilience capacity.

Low resilience in adolescence could be a risk factor for developing IBD as an adult. A study of close to 240,000 young men (evaluated for resiliency through mandatory military conscription in Sweden and followed for an average of 25 years) found that those with low resilience in late adolescence were more likely to develop IBD (Crohn's disease, HR: 1.39; 95% CI: 1.13, 1.71; ulcerative colitis, HR: 1.19; 95% CI: 1.03, 1.37), adjusting for any early indicators of disease.[37] With the magnitude being relatively small, it is speculated that this factor may not be directly responsible for pathogenesis of IBD, but may influence a shift from subclinical potential to clinical disease. The generalizability of these findings to women is unknown.

Resilience has also been identified as a potential mediating variable in IBD. In a cross-sectional study, experiences of childhood trauma were associated with lower resilience, which in turn was related to higher depression and higher suicide risk in a sample of 172 adults with IBD.[38] Given the high prevalence of adverse childhood experiences overall,[39] and in people with IBD,[40] resilience, in addition to depression, may be an important target for intervention in those with IBD.

High resilience, as measured by the Connor-Davidson Resilience Scale, in a sample of 288 adults with IBD, was associated with significantly lower levels of anxiety (r: −0.47; 95% CI: −0.58, −0.34) and depression (r: −0.53; 95% CI: −0.62, −0.42).[41] Anxiety remained independently associated with resilience after controlling for depression (p=0.009), although the reverse was not supported for depression after controlling for anxiety. Individual differences in related aspects of psychological adjustment, examining self-efficacy (confidence in ability to manage) and sense of coherence (sense of personal resources to manage), were evaluated in a sample of 299 adults with IBD.[42] Lower self-efficacy and sense of coherence were significantly related to higher anxiety (p=0.001) and depression (p=0.02). In addition, higher resilience was found to be independently associated with lower disease activity and better quality of life for Crohn's disease (p<0.001; p=0.016) and ulcerative colitis (p=0.035; p=0.016), respectively.[43] Higher resilience was also independently associated with fewer surgeries for people with Crohn's disease (OR: 0.127; 95% CI: 0.03, 0.45).

Very few studies to date have evaluated resilience and self-efficacy over time in IBD, despite the value of this approach to establish directionality (does resiliency affect IBD outcomes, or do IBD outcomes affect resiliency, for example). Findings support a potential protective mechanism of psychological adaptation, with those with higher resilience experiencing fewer depressive symptoms.[44] Impact on IBD outcomes have also been promising. The Manitoba Living with IBD study monitored 154 individuals with IBD for a year through biweekly

validated measures completed online. After adjusting for demographic variables, higher self-efficacy was associated with lower likelihood of flare, both via self-report (OR: 0.80; 95% CI: 0.71, 0.91) and based on a validated clinical index, the Inflammatory Bowel Disease Symptom Inventory (OR: 0.89; 95% CI: 0.80, 0.99).[45]

Pediatric Considerations and Mental Health

Adolescence is a period of active growth and development. Onset of IBD in childhood or adolescence can impact physical and mental health as well as family relationships. Personality development in this period includes the evolution of a sense of self, personal identity, social comfort and relationships, and the further progression of independence and autonomy.[46] For the young individual with IBD, challenges in pain management and disease control can interfere with school attendance and participation in social activities, both of which are major environments for growth of academic and social skills.[47] A population-based Manitoba study found that children with IBD had similar Grade 12 education outcomes as matched controls comparing aspects such as standardized test scores for English and mathematics; however, poorer educational outcomes were independently predicted by lower socioeconomic status and diagnosis of mental health concerns six months prior to and six months after an IBD diagnosis.[48]

Natural efforts toward autonomy at this developmental stage can be undermined by the unpredictable nature of IBD and significant medical care needs such as surgery. Parents are faced with the challenge of helping their children develop autonomy and independence while at the same time supporting or leading difficult decisions associated with their child's medical care.

This issue is especially relevant during the period of transition around age 17 from pediatric to adult IBD care. Healthcare teams have become increasingly aware that this transition phase can result in increased anxiety, depression, and clinical symptoms, and they have identified program initiatives that may facilitate this transition period.[49] For example, transition to adult care may be smoother if autonomy was actively encouraged early in the course of illness through aspects such

as directly facilitating the adolescent's knowledge and responsibility for self-management. From an early point of care, this might involve the healthcare team adopting a strategy at each visit of speaking first to the individual (age 12 or older), and then to the parents and individual together. Similarly, more directly involving the individual in care decisions and disease management can engage them as an active member of the care team. Further, it may be helpful for the team to address with parents—as the primary caregivers—the challenges of autonomy faced by their child in the context of this chronic illness. Parents of a child with a complex chronic disease have a central role in shared disease management, gradually fostering more responsibility for knowledge and decision-making by their adolescent. This approach can enhance that individual's disease self-efficacy, confidence, coping, and autonomy.[50] The period of transition from pediatric to adult care is reviewed in more detail in Chapter 5.

Mental Health Interventions in IBD

There are well-established treatments for primary depression and anxiety in the general population. These treatments include psychological therapies, in particular, targeted cognitive behavioral therapy (CBT),[51-53] as well as antidepressant medication.52 Antidepressant medication, however, has had some recent controversy regarding strength of efficacy.[54-56] However, empirical evaluation is important to confirm applicability and effectiveness of these therapies for mental health concerns co-occurring in the context of IBD. This evaluation is necessary because, for example, depression phenotypes with differing symptom expression have been implicated through work with adolescents with IBD,[57] and gut inflammation may impact mental health and therapy response given the role of the brain-gut axis (the bidirectional nature of mental health and gastrointestinal concerns) in the pathobiology of IBD.[58]

Clinical guidelines recommend screening individuals with IBD for mental health concerns, recognizing the prominent comorbidity and disease influence, but also noting the importance of having clinical pathways for care if positive.[59, 60] Psychological therapies used to treat anxiety and depression occurring in the context of IBD (predominantly CBT, medical hypnotherapy, and more recently, mindfulness therapy) have been shown to significantly improve quality of life for people with IBD and reduce anxiety and depression.[61-63] CBT has demonstrated efficacy for improved mental health outcomes in IBD in both pre-post (significantly reduced anxiety, depression symptoms $p<0.001$),[64] and RCT studies, with the latter utilizing an IBD-tailored CBT protocol and finding significant benefit for moderate-to-severe mental health presentations (depression, d=0.48; anxiety, d=0.58).[65] A controlled mindfulness trial for people with IBD, using a group-based treatment protocol over eight sessions compared to treatment as usual, also found

IBD IS MORE THAN A PHYSICAL DISEASE. THE MENTAL HEALTH STATUS OF AN IBD PATIENT MATTERS AND SHOULD BE VALIDATED AND TREATED ACCORDINGLY. WITHOUT THE PROPER RECOGNITION AND TREATMENT OF CLINICAL AND SUBCLINICAL MENTAL HEALTH DISORDERS IN IBD PATIENTS, THEIR OVERALL WELL-BEING MAY DECLINE, RESULTING IN POOR DISEASE MANAGEMENT. THE PROCESS OF BEING DIAGNOSED AND TREATED FOR IBD CAN BE OVERWHELMING.

significant improvement on measures of anxiety, depression, and quality of life for those engaged in the mindfulness program. Immediate post-treatment effect sizes ranging from medium to large (d=0.56, 1.27), and durable effects at six months post treatment (d= 0.45, 1.38) were found.[66] While these therapies are usually delivered over multiple weekly sessions, results of a pilot study delivering a one-day behavioral intervention workshop, which included elements of CBT and mindfulness, showed evidence for improved anxiety and depression symptoms at three months post-treatment (p<0.01, p=0.06, respectively); although this study was hampered by a small sample size.[67]

Emerging data suggests that psychological therapies may have positive effects on IBD outcomes, prolonging remission for adults with ulcerative colitis,[68, 69] potentially through reducing inflammatory responses,[70] although other studies have not found improved disease outcomes after an extended time.[71] Virtual health technologies, including web-based delivery of psychological therapies, most commonly CBT, have also shown promise in IBD to improve disease outcomes[72] and address mental health concerns.[73] Importantly, they have the potential to broaden access to these behavioral interventions to facilitate disease self-management,[72] and participants have indicated receptivity to this approach.[74]

Up to 30% of adults with IBD have taken antidepressant medications, most commonly for pain or comorbid depression and/or anxiety.[75] Antidepressants were more likely to be initiated in the first year following IBD diagnosis,[76] which is not surprising in light of the higher risk of mental health concerns in that time period. However, up to two-thirds of those individuals on antidepressants discontinued the medication much earlier than the standard treatment duration, with many taking the medications less than a month. Young adults were most prone to discontinue antidepressants early.[76] In one of the only prospective studies of antidepressant use in IBD, individuals with Crohn's disease and depression who were using a selective serotonin receptor inhibitor (SSRI) or selective noradrenaline receptor inhibitor experienced

improvement in anxiety and depression symptoms at six months (p<0.001) as well as improved disease clinical index scores (p=0.01).[77] While antidepressant medications may have beneficial effects for depression and anxiety occurring in the context of IBD, there is a need for further evaluation as higher inflammation has been found to hamper response to antidepressant medication,[78] and there remains little data on efficacy directly in IBD.[56, 79]

Strengthening resilience may be another potential target of intervention to improve coping and IBD disease outcomes. This type of intervention is often utilized for pre-clinical or early clinical presentations such as mild depression or elevated stress, with encouragement to direct the individual to specific depression or anxiety treatment if there is a more significant clinical presentation.[80] A meta-analysis, based on 11 randomized controlled trials (RCTs) of resilience training approaches utilized more generally in community and IBD samples, reported moderate positive effects favoring resilience training (standard mean difference [SMD]: 0.44; 95% CI: 0.23, 0.64) to improve psychological resilience (SMD: 0.58; 95% CI: 0.27, 0.89), with durable effects at six-month follow up (SMD: 0.76; 95% CI: −0.04, 1.55).[81] Most of the studies used elements from CBT and mindfulness.

More specifically for IBD, Keefer *et al.* have developed a resilience analytic tool evaluating five areas (medical, nutritional, psychological, disease self-management skills, and health system access), and a resilience-based IBD care program, collectively referred to as the GRITT (Gaining Resilience Through Transition) method.[82] One hundred eighty four individuals with IBD scoring low on the GRITT resilience measure were offered a program tailored to the elements that needed strengthening, provided through an integrated care team, with outcomes compared pre/post intervention, and to 210 people with IBD who were nonparticipants. Participants had eight sessions on average, most commonly behavioral health (CBT, hypnotherapy) and nutrition. Only 13% discontinued the study before conclusion. There was significant improvement in resilience scores for GRITT participants (pre mean 46.3, post 73.6 p<0.001), with a large effect size (d=2.4, p<0.001), a significant decrease in ED visits compared to the year before (pre=138 visits, post=40 visits), and a significant decrease in hospitalizations (pre=72, post=4). Nonparticipants had no change in ED visits compared to the prior year and had an increase in hospitalizations, noting the limitation that the study used an uncontrolled comparator sample.

Acceptance and Commitment Therapy (ACT) is a third wave psychological therapy grounded in cognitive, behavioral, and mindfulness strategies, which aims to decrease stress, improve psychological flexibility, and strengthen values-based action in day-to-day life.[83] While ACT has shown some promise of improved stress and quality of life in people with chronic diseases and similar efficacy as standard CBT,[84, 85] there has been little application in IBD to date. An RCT in adults who had mild or inactive IBD demonstrated significant stress reduction compared to a treatment as usual control group,[86] and further feasibility studies are underway.[87, 88] However, efficacy for anxiety, depression, resilience, or IBD clinical outcomes has yet to be examined.

Mental Health Interventions in Pediatric IBD

Addressing mental health care in children and adolescents with IBD has been consistently identified as an integral part of IBD care.[89] Collaborative, integrated models of care for mental health in pediatrics may improve access to mental health support.[90] For the IBD team, where each provider is recognized as an expert who contributes to the overall treatment, mental health management may, to a large extent, be provided by members of the inter-professional, multidisciplinary care team. A first step is to screen for mental health and psychosocial concerns prior to or during the clinic visit. Issues for the individual may include family-related stress, emotional concerns, and stressors at school, in addition to the potential presence of a psychiatric disorder.

IBD care team meetings, which may include nurses, specialist physicians, nutrition consultants, and mental health professionals, can be utilized to identify and initiate a management plan that addresses co-occurring mental health needs of the individual with IBD and their family. This collaborative form of team management for mental health is an area of increasing clinical and academic interest and may help alleviate some of the resource allocation concerns inherent in the underfunding of the mental health care system.[91, 92] However, these care models are often lacking in pediatric centres and private practice clinics.[93]

If suspected, major psychiatric issues can be assessed in consultation with a psychologist or psychiatrist, and as noted previously, psychosocial management is often supported by several members of the team. This team may also include transition navigators with training in psychosocial support of individuals with chronic disease. However, even these supports can be unavailable to the healthcare team due to inadequate resources, and mental health aspects may need to be addressed directly by the clinic physicians and nurses with consultative support.

Treatment options for a child or adolescent with IBD who is diagnosed with anxiety or depression can include psychotherapy such as CBT and medications like SSRIs.[94] Psychological therapies for comorbid mental health concerns in IBD have been effective for adolescents in particular, demonstrating improved mental health outcomes. Szigethy *et al.* found that depression was significantly decreased following a course of CBT,[95] with treatment gains maintained at six months and one year.[96] A small pilot study evaluating CBT and clinical anxiety for adolescents with IBD reported that 50% of the participants no longer met criteria for the anxiety disorder following treatment.[97] CBT has also been a useful intervention more generally for children with IBD; this was shown in a large RCT that involved children and their parents in a CBT intervention demonstrating improved quality of life, decreased school absences, and more adaptive coping, as well as preliminary support for decreased flares.[98]

With regard to medication approaches, although approved for the treatment of mental health disorders in youth, the optimal dose and duration of SSRIs for depression and anxiety in IBD remains uncertain,[79] adherence to medication can be challenging,[76] and outcomes for mental health symptoms or IBD disease course have not yet been well-established.[56] The specific SSRI choice is based on the federal authority recommendations for treatment of mental health disorders in youth, and depends on the mental health condition being treated. Common therapeutic options include fluoxetine, sertraline, citalopram, and fluvoxamine,[99-102] with continued recommendation that suicidality should be monitored when these medications are used.[103] Common side effects

include nausea, vomiting, diarrhea, headache, insomnia, and agitation.[104] SSRI therapy has been reported to increase the risk of bleeding (platelet dysfunction related to the block of serotonin re-uptake), most frequently during initiation of treatment, and particularly while also taking aspirin or NSAIDs.[105] Therefore, clinicians should maintain awareness of the potential for unexplained bleeding, as well as the risk of prolonged QT interval (an irregular heart rhythm).[106]

Conclusions

In light of the higher incidence (new diagnoses) and prevalence (total number of people living with the disorder) of mental health disorders in individuals with IBD, the adverse impact on disease course, the heightened healthcare utilization for those with IBD, and comorbid mental health concerns, there have been multiple calls for better integration of psychological and medical care in IBD clinics.[80, 107] Integrated care models, including specific examples such as the IBD medical home, are well established as the most effective approach. This approach not only provides a whole-person response to the management of IBD, which is valued by individuals with IBD, but also demonstrates a direct benefit to health system through reduced IBD surgeries, hospital admissions, and IBD comorbidities.[107] The growing field of psychogastroenterology, which focuses on the brain-gut connection, the role of psychosocial factors, and the application of effective psychological approaches to gastrointestinal conditions, is well positioned to guide care models that optimize outcomes for individuals with IBD.[80]

Knowledge Gaps & Future Research Directions

1. Improving identification of those who are at risk for mental health concerns, especially during vulnerable periods around the IBD diagnosis and during transition from pediatric to adult care, will be important to ensure appropriate care is in place.

2. Little is known about the pathobiology of mental health disorders in IBD, however there is increased attention of whether mood disorders are inflammatory diseases, and whether aspects such as fatigue in both IBD and depression potentially signal a cytokine imbalance as a common base. Understanding the pathobiology of mental health disorders in persons with IBD may lead to unique treatment approaches, including optimizing anti-inflammatory mechanisms of antidepressant medications.

3. Further research is needed into effective therapies for mental health concerns in those with IBD, examining impact on both mental health and IBD outcomes. IBD-tailored CBT and gut-directed medical hypnotherapy have growing evidence of positive effects for psychological outcomes for people with IBD and potential benefit for IBD outcomes; this should be an area of focus for future studies.

4. Strengthening resilience to mitigate or even prevent stress-related disorders and improve outcomes for individuals with IBD is a promising line of inquiry, needing further longitudinal studies, ability to scale up interventions, and specific exploration for children and youth with IBD.

5. Virtual delivery of psychological therapies has been enabled by improved technological capabilities during the COVID-19 pandemic and has promise for broader accessibility to mental health care; these interventions need clinical assessment for efficacy and uptake among children and adults with IBD.

6. A better understanding of the potential mental health impact of caring for a person living with IBD of any age is needed to inform supportive resources for caregivers.

Patient & Caregiver Partner Perspective

Patient partners expressed feelings of validation after reviewing this chapter, especially related to the identification of the bidirectional nature of mental health and disease course in IBD and the recognition that mental health concerns are common in persons living with IBD. Patient partners highly recommend that the gold standard in IBD management should include ongoing assessment and treatment for mental health concerns. By intervening early, health system costs related to hospitalizations, ED visits, and surgeries can be reduced. Psychological interventions (i.e., cognitive behavioural therapy, mindfulness, hypnotherapy) offer great promise to enhancing the quality of life, mental wellness, and resilience of individuals living with IBD. However, it was noted that there were barriers to accessing mental health professionals and a lack of funding available to support access. Promising areas for future research noted by patient partners were on the topics of resilience, self-efficacy, and the links between gut and mental health.

Policy Implications & Key Advocacy Outcomes

1. Considering the detrimental effects of IBD on the mental health of children and adolescents with IBD and their families, and the risk of long-term mental illness in these vulnerable individuals, a multidisciplinary team including mental health specialists should be available to all children and adolescents with IBD, optimally for prevention and early intervention.

2. Integrated care models for adults with IBD, which incorporate mental health and medical services, are needed as the routine approach to care to benefit the individual and the health system.

3. Until integrated care models for IBD clinics are more readily available in jurisdictions across Canada, access to and funding for mental health care needs for children and adults with IBD should be prioritized.

4. Further research examining IBD outcomes for psychological and psychotropic medication therapies are needed to delineate the mechanisms and benefits of these mental health treatment approaches overall.

5. Enhanced physician education and resources to address mental health concerns are needed to facilitate more routine review and initiation of proper care pathways in the IBD clinic.

6. Enhancing mental health literacy for those with IBD, including children, adults, and their families, is important to facilitate identifying their care needs. Patient partners expressed that they knew how to describe their physical IBD symptoms, but sometimes lacked the language to raise or describe mental health concerns.

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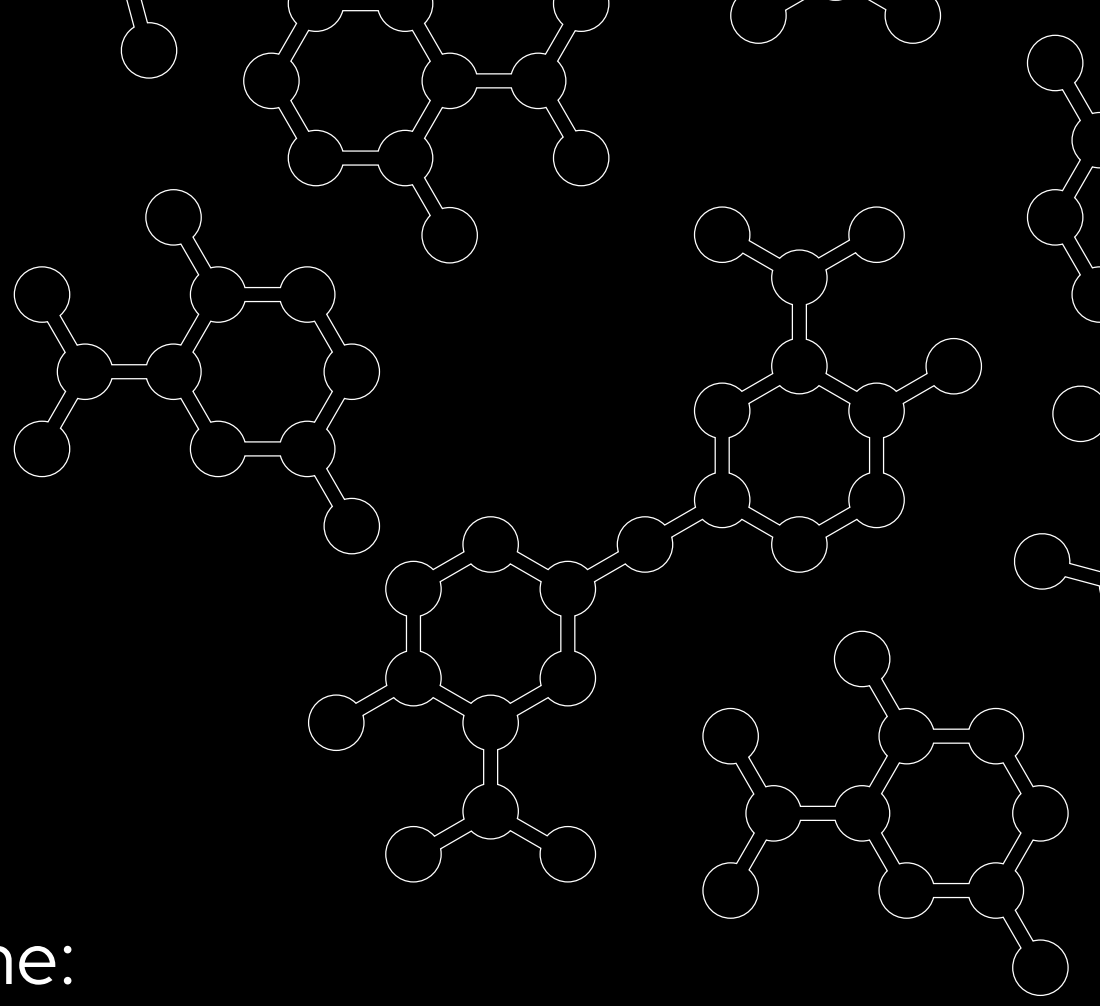


Section Nine:

COVID-19 & IBD

COVID-19 & IBD

Abstract

The COVID-19 pandemic had a monumental impact on the inflammatory bowel disease (IBD) community. At the beginning of the pandemic, knowledge on the effect of SARS-CoV-2 on IBD was lacking, especially in those with medication-suppressed immune systems. Throughout the pandemic, scientific literature exponentially expanded, resulting in clinical guidance and vaccine recommendations for individuals with IBD. Crohn's and Colitis Canada established the COVID-19 and IBD Taskforce to process and communicate rapidly transforming knowledge into guidance for individuals with IBD and their caregivers, healthcare providers, and policy makers. Recommendations at the onset of the pandemic were based on conjecture from experience of prior viruses, with a precautionary principle in mind. We now know that the risk of acquiring COVID-19 in those with IBD is the same as the general population. As with healthy populations, advanced age and comorbidities increase the risk for severe COVID-19. Individuals with IBD who are actively flaring and/or who require high doses of prednisone are susceptible to severe COVID-19 outcomes. Consequently, sustaining maintenance therapies (e.g., biologics) is recommended. A three-dose mRNA COVID-19 vaccine regimen in those with IBD produces a robust antibody response with a similar adverse event profile as the general population. Breakthrough infections following vaccine have been observed, particularly as the virus continues to evolve, which supports receiving a bivalent vaccine booster. Limited data exist on the impact of IBD and its therapies on long-term outcomes following COVID-19. Ongoing research is necessary to address new concerns manifesting in those with IBD throughout the evolving pandemic.

Key Points

1. Crohn's and Colitis Canada's COVID-19 and IBD Taskforce compiled knowledge and communicated with the IBD community through an expert-generated website and frequent webinars for a public audience. This work has set the stage for Crohn's and Colitis Canada to inform the IBD community in the event of any future public health emergencies.

2. Infection of SARS-CoV-2—the virus that causes COVID-19—for those with IBD is similar to the general population. Those with IBD are not at increased risk of acquiring COVID-19 or experiencing severe COVID-19 outcomes.

3. Individuals with IBD who require a high dose (>20mg per day) of corticosteroids are at higher risk of experiencing severe complications from COVID-19.

4. Those with IBD under the age of 50 who are actively flaring are at higher risk of severe COVID-19 outcomes.

5. Maintenance therapies (e.g., biologics) for IBD are not associated with more serious disease course following infection from SARS-CoV-2.

6. Vaccines for COVID-19 are safe and elicit robust immune responses to SARS-CoV-2 following three doses of vaccine in individuals with IBD, although immunity is less robust among those receiving prednisone to treat a flare or those on anti-TNF treatments.

7. As breakthrough infections following vaccination occur at an increasing rate for sub-variants of Omicron, a booster dose with a bivalent vaccine is recommended for those with IBD.

8. Guidance to the IBD community consistently recommended to continue IBD therapies during the pandemic to avoid flaring from lack of medication.

Summary of Crohn's and Colitis Canada's 2021 Impact of COVID-19 & IBD in Canada

In April 2021, Crohn's and Colitis Canada's COVID-19 and IBD Taskforce produced the 2021 Impact of COVID-19 & Inflammatory Bowel Disease in Canada. This report summarized the key learnings of the impact of COVID-19 on the IBD community at the one-year anniversary since the COVID-19 pandemic was declared by the World Health Organization. During the first year of the pandemic, and before the widespread dissemination of COVID-19 vaccines, the body of the scientific literature was synthesized and communicated to the IBD community through Crohn's and Colitis Canada's COVID-19 and IBD Taskforce using online resources and a webinar series. The scientific literature from that time suggested that those with IBD shared a similar risk of becoming infected by SARS-CoV-2—the virus that causes COVID-19—or experiencing severe outcomes as the general population with the primary exception being those flaring and/or requiring high doses of oral systemic corticosteroids. During the first year, lockdowns and shielding populations believed to be at high risk, like the IBD community, reduced the risk of transmission. However, mental health distress was prevalent due to isolation and uncertainty of risks, which was exacerbated in immunocompromised individuals with IBD. Major breakthroughs in novel SARS-CoV-2 vaccines and anti-viral medications, as well as adaptation to models of healthcare delivery (e.g., virtual care) offered hope that the second year of the pandemic would realize the easing of restrictions.

Introduction: Crohn's and Colitis Canada's COVID-19 & IBD Taskforce

Inflammatory bowel disease (IBD) affects more than 0.8% of the Canadian population in 2023, or roughly 322,600 Canadians.[1-4] When the World Health Organization declared COVID-19 a global pandemic on March 11, 2020, immunocompromised individuals with IBD were initially considered vulnerable to infection and complication by SARS-CoV-2, which is the virus that causes COVID-19.[5] As the SARS-CoV-2 virus was novel, direct clinical evidence was lacking to inform healthcare providers and policy makers on guidance for immunocompromised individuals. Consequently, Crohn's and Colitis Canada developed the COVID-19 and IBD Taskforce on March 12, 2020.[6] The Taskforce included adult and pediatric gastroenterologists from across the country with infectious disease specialists, nurses, and patient representatives. This team met regularly to review the emerging evidence on the impact of COVID-19 on those with IBD in order to establish recommendations for the IBD community.[6]

Expert reviews of population-level recommendations were tailored to the IBD community and communicated through website FAQs and infographics;[6] a public-oriented burden report[7] with foci on additional special populations (e.g., pregnant people,[8] pediatrics,[8] seniors[9]), IBD medications,[10] mental health,[11] and access to care;[12] and through a moderated, online webinar series. The one- to two-hour webinar recordings were then curated into three- to five-minute video clips to answer specific questions and uploaded to Crohn's and Colitis Canada's YouTube page.[6] As of October 2022, Crohn's and Colitis Canada's webpage on COVID-19 has been viewed over 800,000 times, and the thirty webinars produced on COVID-19 and IBD were viewed over 81,000 times.

Crohn's and Colitis Canada's 2021 Impact of COVID-19 and IBD report synthesized the knowledge learned by the COVID-19 and IBD Taskforce.[13] The purpose of this article is to provide up-to-date knowledge on the influence of COVID-19 on the IBD community.

Epidemiology: The Risk of COVID-19 among Those with IBD Is Similar to the General Population.

The global pandemic was in part driven by the high transmission of SARS-CoV-2. Earlier in the pandemic, concern was raised that those with IBD might be at higher risk of being infected by SARS-CoV-2. The Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) registry is an international cohort study that recruited over 6,000 individuals with IBD who were diagnosed with COVID-19.[14] Analyzing the waves of reporting into the SECURE-IBD registry showed similar patterns to the general population during the first year of the pandemic, which provided the first clues that having IBD or being immunosuppressed by therapies to treat IBD may not increase the risk of acquiring SARS-CoV-2.[15] Subsequently, a meta-analysis of seven observational studies showed that individuals with IBD had comparable rates of COVID-19 as the general population (pooled odds ratio [OR]: 0.47; 95% CI: 0.18, 1.26).[16] However, additional studies are necessary to assess whether the risk of SARS-CoV-2 was influenced by public health recommendations geared towards immunocompromised populations and adherence to those recommendations by those with IBD.[6]

General Risk: Those with IBD Had Similar Risk Factors for Severe COVID-19 with the General Population.

Overall, the accumulating data consistently demonstrated that the risk of severe COVID-19 in the general population was similar to those with Crohn's disease or ulcerative colitis.[16] Moreover, the risk factors associated with severe COVID-19, defined as hospitalization or death, were similar in those with IBD as compared to the general population: namely age and comorbidities.[16-19] Like the general population, seniors with IBD (particularly those with multiple comorbidities such as diabetes, cancer, or cardiovascular disease) were at the highest risk for hospitalization or death from SARS-CoV-2 infection.[16-18]

IBD Risk: Individuals on Prednisone Were at Risk for Severe COVID-19 Outcomes.

Numerous studies assessed the risk of severe COVID-19 in relation to the medications used to treat IBD. By July 2020, the first 500 cases reported in SECURE-IBD provided clues on the risk of drugs on severe COVID-19.[20] In 2022, the largest study—including 6,000 individuals with IBD from March 2020 to May 2021 (before widespread access to vaccines)—reported that those with IBD who were using anti-TNFs, vedolizumab, ustekinumab, or tofacitinib at the time of their infection with SARS-CoV-2, had a lower risk of hospitalization or death from COVID-19.[21] In contrast, those who experienced an active flare and required higher doses of oral prednisone (>20mg per day), were more likely to experience severe outcomes of from COVID-19.[20-22] The risk of severe COVID-19 was particularly observed among individuals under the age of 50 who were flaring with IBD.[22] Consequently, guidance to the IBD community consistently recommended to continue IBD therapies during the pandemic to avoid flaring from lack of medication adherence. Moreover, those with IBD who were flaring were recommended to isolate while on high doses of prednisone.[10] Unlike medications, the risk of severe COVID-19 is not specifically increased among those who had prior surgery for IBD.[23] Among those with IBD who are at increased risk for severe COVID-19, treatment with Paxlovid (nirmatrelvir and ritonavir) reduced the risk of hospitalization as compared to those not treated with antiviral therapy.[24]

Individuals with IBD Require Regular Booster Doses of SARS-CoV-2 Vaccines to Maintain Immunity

The approval of the first mRNA and non-replicating viral vector vaccines against SARS-CoV-2 occurred in December 2020.[25] Throughout 2021, numerous studies were conducted to evaluate the serological response to different dose regimens of the COVID-19 vaccines among immunocompromised individuals with IBD. The largest serological study in people with IBD is CLARITY-IBD, which initially showed that the antibody response following a two-dose vaccine regimen is superior for mRNA vaccines compared to adenovirus-vector vaccines, for those on vedolizumab compared to infliximab, and those on infliximab monotherapy versus those on concomitant immunomodulator therapy.[26] The VIP study demonstrated a lower antibody response after two vaccine doses among those using infliximab and tofacitinib, those who receive a vector adenovirus vaccine compared to an mRNA, and those of advanced age.[27] A meta-analysis of 46 studies in the IBD population confirmed high seroconversion (96%) after completing a two-dose vaccine series, with lower serological response those on anti-TNF therapies, and a subsequent decay of antibodies over time.[28] Adolescents with IBD mount a robust antibody response to a two-dose mRNA vaccine regimen.[29, 30]

A large prospective cohort study in Calgary, Alberta established the immunological efficacy of a three-dose mRNA vaccine series for those with IBD.[31] Following the third vaccine dose, the seroconversion rate was 99.6% with a high geometric mean titer within eight weeks of the third dose; however, after eight weeks, antibody levels fell by approximately 12% (95% CI: 8%, 15%) per week.[31] The independent factors associated with a reduced serological response were advanced age and use of oral prednisone at the time of the third vaccine dose (Figure 1).[31] Similarly, the CLARITY-IBD and VIP studies demonstrated robust serological

responses following a third SARS-CoV-2 vaccine, though anti-TNF therapy and tofacitinib were associated with lower antibody levels.[32,33] These data have led various jurisdictions to recommend a fourth vaccine dose, which has been associated with recapturing decaying antibody levels in those with IBD.[34] Despite booster doses of SARS-CoV-2 mRNA vaccines advocated by Crohn's and Colitis Canada,[35] data from Ontario indicated low uptake of a third vaccine dose in the IBD population in the pre-Omicron era (i.e., before December 2021).[36]

Bivalent Vaccines Are Recommended for Those with IBD Due to Breakthrough Infections.

Prior to the Omicron variant becoming the dominant strain, before December 2021, breakthrough infections following a complete vaccine series in those with IBD were not common. In a large cohort study in the US, completed before December 2021, only 1.7% of individuals with IBD reported COVID-19 more than one month after completing their vaccine series.[37] Moreover, individuals with a breakthrough infection had lower average (mean) antibody levels.[37] Similarly, a meta-analysis conducted on studies prior to the Omicron era showed the pooled risk of breakthrough infections after two vaccine doses was roughly 1%, and the risk of breakthrough

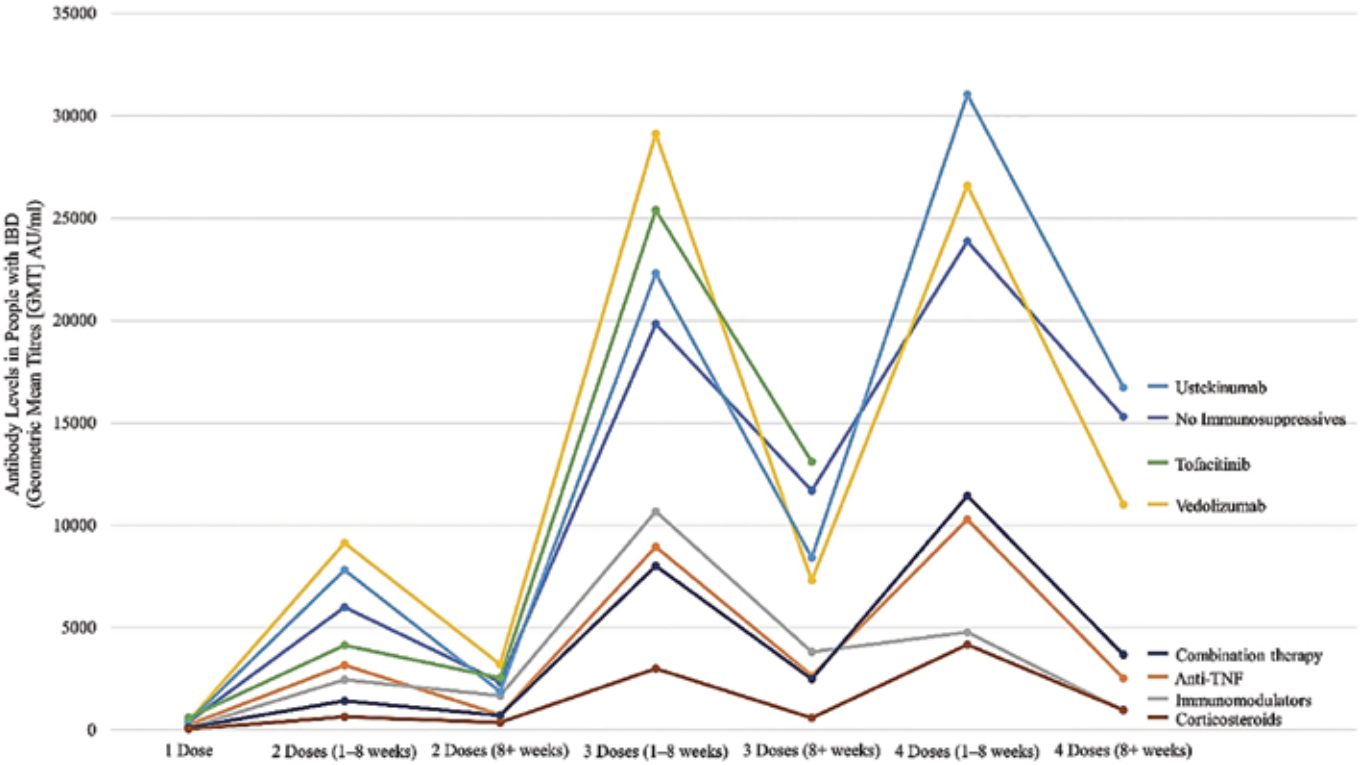


Figure 1: Average antibodies by medication class

Average antibodies by time period relative to vaccine doses in a cohort of 556 individuals with IBD from Calgary, Alberta, Canada, grouped by IBD medication class.

infections in those with IBD was similar to the general population (pooled relative risk [RR]: 0.60; 95% CI: 0.25, 1.42).[38]

Studies conducted during the Omicron wave (December 2021–present), however, have reported considerably higher breakthrough infection rates in those with IBD due to the highly infectious nature and vaccine evasive subvariants of Omicron. The CLARITY-IBD study demonstrated that, during the Omicron wave, 15% of individuals with IBD experienced a breakthrough infection after a three-dose SARS-CoV-2 vaccine regimen.[32] While breakthrough infection occurred more commonly in those on infliximab compared to vedolizumab, antibody levels alone were not associated with protection from infection.[32] These data suggest that those with IBD will likely benefit from bivalent vaccines (i.e., mRNA of the spike protein from the original virus along with that of subvariants: BA.1, BA.4, and/or BA.5). Moreover, a robust serological response to the bivalent vaccines has been shown in the IBD population,[39] though the durability over time will need to be confirmed in future studies.

SARS-CoV-2 Vaccines Are Safe in Those with IBD and Do Not Trigger a Flare of Disease Activity.

Overall, short-term adverse events to SARS-CoV-2 vaccines in those with IBD are similar to the general population. A cohort study from the US showed that the most commonly reported adverse events after receiving a vaccine were: injection site pain, fatigue, and malaise; the rate of reporting in those with IBD was not different than healthy controls.[40] Adverse events were classified as mild and short-lived (i.e., less than two days). After the third dose of a vaccine, approximately 41% of people with IBD reported an adverse event. Most adverse events decreased in severity from the second to the third dose.[39] The one exception was gastrointestinal symptoms, which were slightly worse after the third dose of the vaccine.[40] However, a Canadian study on adverse events within 30 days of each vaccine dose documented no objective risk of flaring IBD within 30 days of receiving either the first, second, or third vaccine dose.[41]

THIS RESEARCH IS ILLUMINATING FOR PERSONS LIVING WITH IBD, PARTNERS, PRACTITIONERS, AND POLICYMAKERS; AND WILL ALLOW FOR THE CREATION OF BETTER-INFORMED POLICIES TO PROTECT THE WELL-BEING OF IBD PATIENTS DURING CURRENT AND FUTURE PANDEMICS.

Complications of COVID-19 in Those with IBD Include Mental Health Concerns and Possible Long COVID.

Overall, the long-term complications of COVID-19 in those with IBD appear to be similar to the general population;[42] though, high quality, longitudinal studies in the IBD population are lacking. Post acute COVID-19 syndrome (also known as long COVID) is a consideration for those with IBD as SARS-CoV-2 antigens may persists in intestinal mucosa for months after clearing the infection.[43] Statistics Canada reported 14.8% of Canadians experience symptoms of long COVID three months after infection; population-based data from Ontario indicated increased health services utilization following COVID-19; and individuals with long COVID demonstrate physiological changes.[44, 45] However, studies in the IBD population are necessary to assess if the risk of post acute COVID-19 syndrome is elevated.[46] Irrespective of whether individuals with IBD are at additional risk of long COVID compared to the general population, overlapping long COVID and IBD places a significant burden on people living with IBD and the health systems.

Deterioration in mental health and elevated stress and anxiety impacted the IBD community as many feared worse outcomes from COVID-19.[11, 47] Depressive symptoms and distress were exacerbated in those who experienced isolation in an attempt to shield themselves from exposure to SARS-CoV-2.[11, 47] Furthermore, stress and anxiety were associated with worsening of gastrointestinal symptoms and disease activity (see also Chapter 8).[48] Consequently, many individuals with IBD struggled with low health-related quality of life during the pandemic,[49] which was also observed in children with IBD.[50]

Conclusion

Crohn's and Colitis Canada's COVID-19 and IBD Taskforce synthesized the medical literature during the pandemic to communicate timely and insightful guidance to the IBD community. Over the last three years, since the onset of the pandemic, the knowledge on the impact of COVID-19 on those with IBD has expanded dramatically. The risk of COVID-19 among those with IBD is similar to the general population. Individuals with IBD had similar risk factors for severe COVID-19 as the general population, namely age and comorbidities. Those with IBD who flared and received prednisone were at risk for severe COVID-19 outcomes. Vaccines served as the primary preventative health measure. Individuals with IBD require at least a three dose SARS-CoV-2 vaccine regimen. Additionally, bivalent vaccines are recommended due to breakthrough infections and immune-escaping variants of the virus. Importantly, SARS-CoV-2 vaccines are safe in those with IBD and do not trigger a flare of disease activity. Data on the long-term impact of COVID-19 in people with IBD are lacking. Despite actions to guide the IBD community through the pandemic, those with IBD struggled with mental health concerns and impaired quality of life during the pandemic.

Knowledge Gap & Future Research Directions

1. There is still work to be done to understand the impact of public health recommendations geared to immunocompromised populations on the risk of SARS-CoV-2 infection.

2. Determining the vaccine regimen that provides robust and durable serological response in those with IBD who are immunocompromised requires ongoing research.

3. Exploring the effect of bivalent vaccines in reducing breakthrough infections following vaccination will be important for future studies.

4. Determining the mental health impact and risk of long-term complications of COVID-19 (Long COVID) in those with IBD is necessary.

5. Lessons learned from the COVID-19 pandemic to prepare the IBD community for future viral outbreaks should be documented and incorporated into emergency planning measures.

Patient & Caregiver Partner Perspective

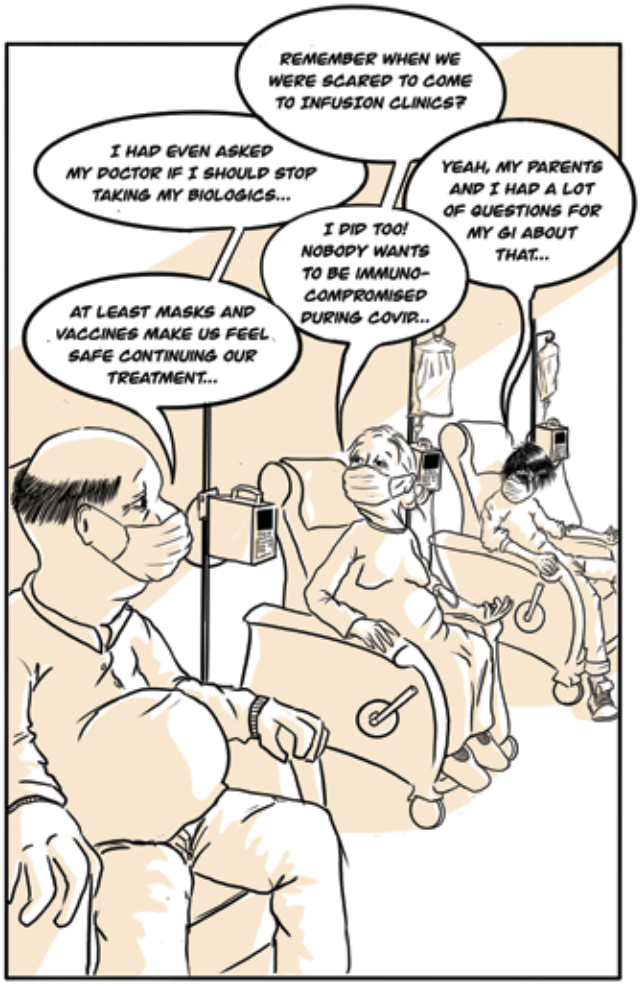
Patient partners emphasized that the risks of acquiring COVID-19 and the outcomes of COVID-19 are similar in individuals with IBD as they are for the general population. Preventing disease exacerbations and the need for high-dose steroid use are important to avoid more severe complications related to COVID-19. Partners stressed the importance of continuing with IBD-related medication therapies to prevent disease flares and the need for steroid use. COVID-19 vaccines were recognized as safe for individuals with IBD. Encouragement should be provided to individuals with IBD to receive bivalent vaccine boosters to allow for continued protection against COVID-19. Information provided in this chapter provides peace of mind and reassurance to patient partners, allowing them to make educated decisions about their physical and mental wellbeing. Patient partners encouraged greater access to mental health supports for pandemic-related isolation, stress, and anxiety that many individuals experienced. Partners recognized there were some individuals, such as those in active flares and/or on >20mg per day of prednisone, who remain clinically vulnerable or who may experience increased vulnerability to worse COVID-19 outcomes if they contract the virus. Ongoing protection and advocacy efforts need to center around these clinically vulnerable individuals. It was recommended that individuals perform their own risk assessment based on the scientific information available.

Policy Implications & Key Advocacy Outcomes

1. Crohn's and Colitis Canada's COVID-19 and IBD Taskforce served as an invaluable resource to synthesize rapidly evolving information on the pandemic and communicating this knowledge to the IBD community via their website and a webinar series. This approach should be used as a template for communication during future public health emergencies.

2. Crohn's and Colitis Canada can educate healthcare providers on the appropriate guidance of managing IBD throughout the pandemic, especially on the importance of receiving bivalent vaccines.

3. Crohn's and Colitis Canada should continue to advocate to policymakers and health authorities during the pandemic for vulnerable immunocompromised individuals with IBD.



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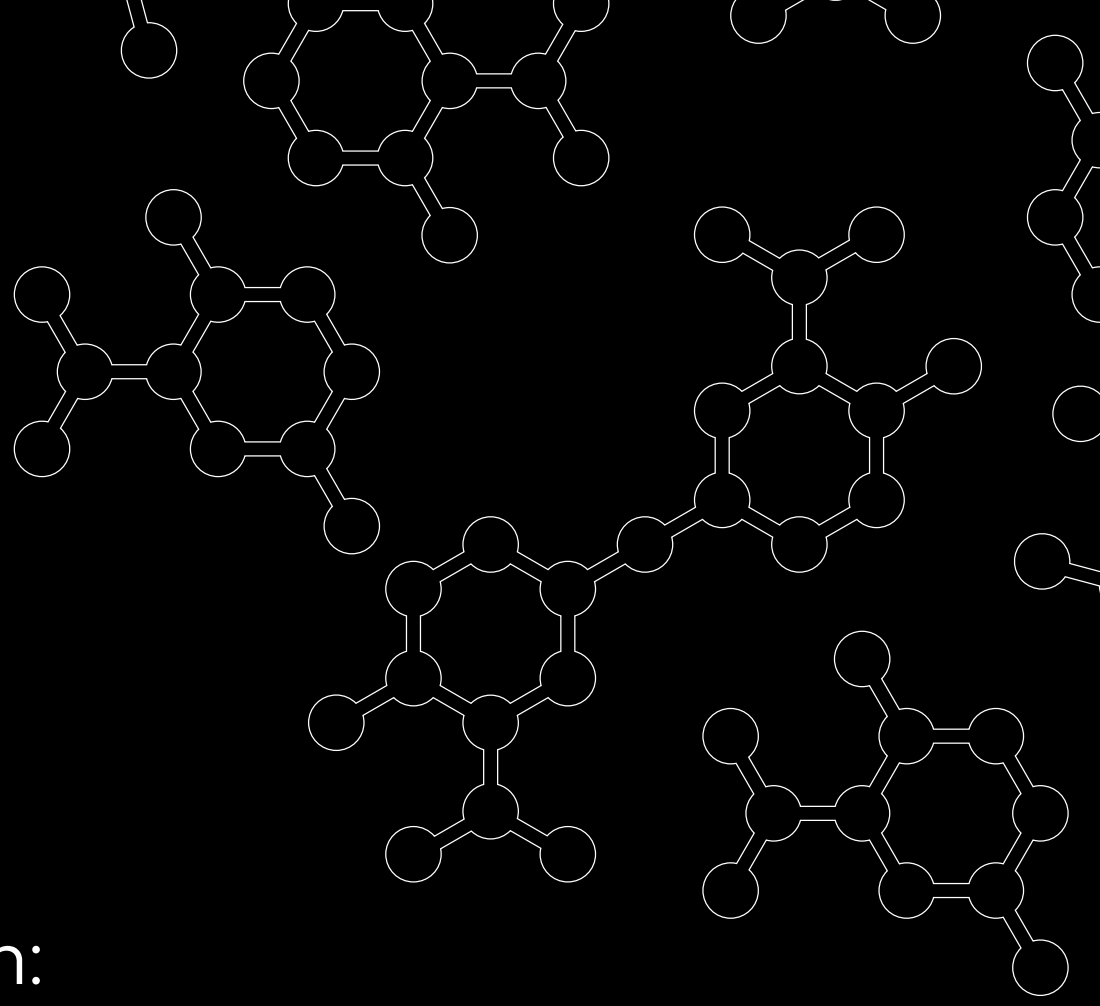


Section Ten:

Cancer & IBD

Cancer & IBD

Abstract

Certain cancers are more common among people with inflammatory bowel disease (IBD), and cancer is a substantial cause of premature death among people with IBD. Intestinal cancers may arise as a complication of IBD itself, while extra-intestinal cancers may arise due to some of the immunosuppressive medications used to treat IBD. Colorectal cancer (CRC) and small bowel cancer risks are elevated among people with IBD as compared to age-and sex-matched members of the general population, and the lifetime risk of these cancers is strongly correlated to cumulative intestinal inflammatory burden. However, the cumulative risk of cancer, even among those with IBD is still low. Some studies suggest that the frequency of CRC in people with IBD has declined over the years, possibly due to improved treatment standards and improved detection and management of early neoplastic lesions. Across studies of extra-intestinal cancers, there is generally higher frequency of melanoma, hepatobiliary cancer, and lung cancer, but no higher frequency of breast cancer, prostate cancer, or cervical cancer among people with IBD. While the relative risks of some extra-intestinal cancers are increased with treatment, the absolute risks of these cancers remain low, and the decision to forego treatment in light of these risks should be carefully weighed against the increased risks of intestinal cancers and other disease-related complications with undertreated inflammatory disease. Quality improvement efforts should focus on optimized surveillance of cancers for which surveillance strategies exist (colorectal cancer, hepatobiliary cancer, cervical cancers, and skin cancers) and developing cost-effective surveillance strategies for less common cancers associated with IBD.

Key Points

1. Colorectal cancer occurs 1.5–2 times more often in those with IBD than comparable members of the general population and is responsible for as much as 15% of IBD-related deaths.

2. Colorectal cancer risk is strongly associated with inflammation of the colorectal mucosa: IBD duration, extent of colorectal involvement, IBD severity, and frequency of active disease.

3. Extra-intestinal cancers may complicate IBD treatment with chronic immunosuppressive therapies, due to reduced immune surveillance and/or a direct effect of the medications.

4. Thiopurines have been associated with increased risks of lymphoma and non-melanoma skin cancers. The risks of melanoma and cervical cancer in association with immunosuppressive therapies remain uncertain.

5. Hepatobiliary cancer risk is significantly higher among those with IBD, particularly among people with comorbid primary sclerosing cholangitis. Emerging data also suggest a higher risk of lung cancer among those with IBD.

6. While the relative risks of certain cancers are increased in those with IBD, the absolute risk of those cancers remains low and should not be a deterrent to effective therapies to treat IBD.

7. Systematic cancer surveillance strategies currently exist for colorectal cancer, hepatobiliary cancers (in those who also have primary sclerosing cholangitis), cervical cancers, and skin cancers. Cost-effective surveillance strategies do not currently exist for less common cancers, such as small bowel cancers.

8. Endoscopic surveillance and management of colorectal neoplasia has evolved considerably over the past 10–15 years, leading to higher rates of endoscopic resection of neoplastic lesions and lower rates of surgery. Surgery is now reserved for very high-risk neoplasia.

9. Post-colonoscopy colorectal cancers (those arising within three years of a colonoscopy) account for up to 50% of colorectal cancers in people with IBD, which may be because of inadequate surveillance frequency, suboptimal colonoscopy quality, or altered tumour biology. Regular, high-quality surveillance colonoscopy is important for detecting and managing neoplastic lesions and reducing the risk of missed cancers.

10. As people with IBD are living longer, gastroenterologists will experience a higher volume of individuals who develop cancer; this may impact treatment decisions/options. As evidence accumulates, IBD care providers will need to revise their understanding of the implications of current IBD practice on cancer risk and accordingly modify preventive and treatment strategies across the spectrum of cancers observed in these individuals.

Introduction

Intestinal and extra-intestinal cancers can arise both as complications of inflammatory bowel disease (IBD) and treatments for IBD. Cancer is one of the most common causes of death in this population,[1, 2] and cancer prevention is one of the major goals of IBD management. To-date, the primary focus has been on preventing colorectal cancer (CRC). This focus may largely relate to the historical high rate of CRC (as compared to other cancers) in individuals with IBD, which may have resulted from the absence of highly effective treatments for IBD until the early 2000s. Over the past 20 years, multiple classes of effective biologic and targeted therapies that induce mucosal healing have been introduced,[3-17] and there have been paradigm shifts in how we use these therapies (see Chapter 11). Additionally, improved endoscopic techniques to detect and remove early neoplastic lesions (abnormal growths that may or may not be cancerous) have altered the relative potential for disease-related versus treatment-related cancers. The evidence for the effect of this shift on cancer related morbidity (cases of cancer) and mortality (deaths due to cancer) may take decades to realize. As evidence accumulates, gastroenterologists and other IBD care providers will need to revise their understanding of the implications of current IBD practice on cancer risk and accordingly modify preventive and treatment strategies across the spectrum of cancers observed in these individuals. This change will become increasingly important for shared decision-making between providers and individuals with IBD. In this chapter, we review the epidemiology of cancer in people with IBD, the impact of current treatments on cancer risk, and existing cancer preventive strategies in clinical practice.

Epidemiology of Cancer in IBD

The risk of some, but not all, cancers is increased among individuals with IBD. The most consistent evidence demonstrates increased risks of: (1) CRC among those with colonic involvement, varying with the extent, severity, and duration of colonic inflammation; (2) small bowel cancer among those with Crohn's disease; (3) lymphoma and non-melanoma skin cancer among those treated with thiopurines; and (4) to some extent, melanoma among those treated with anti-TNF biologics. Children diagnosed with IBD have also been reported to have increased cancer risk in their adult life.

No increase in cancer risk has been reported with vedolizumab, ustekinumab, or tofacitinib so far among individuals with IBD, although more data are required as these therapies are relatively recent additions to the IBD treatment landscape. In addition, no increased risk of cancer has been found with anti-TNF therapy after an initial cancer diagnosis, which suggests that lengthy post-cancer drug holidays are not likely necessary. Importantly, the absolute risk of cancers is small even for the cancers with higher risks due to medications, which is important information for shared decision making between providers and individuals with IBD.

In the following sections, we outline important studies that have influenced our understanding of the epidemiology of cancer in IBD, focusing on population-based studies (when available), and highlighting important Canadian studies on this topic. A summary of ranges of risk estimates across studies included in this article is listed in Table 1.

Intestinal Cancers

Intestinal cancers arise in people with IBD as a result of cumulative carcinogenic DNA damage from chronic or recurrent bouts of bowel inflammation.[35-38] Due to the high rate of colonic involvement in IBD (100% in ulcerative colitis, 70% in Crohn's disease), CRC accounts for more than 95% of gastrointestinal tract malignancies in IBD and up to 15% of IBD-related deaths.[2, 39] Recognized disease-specific risk factors for CRC in those with IBD include longer disease duration,[20, 40-44] more extensive colorectal involvement,[20, 45] more severe colorectal inflammation,[46-49] pseudopolyps,[47] and chronic mucosal scarring,[50] all of which are markers of cumulative colorectal inflammatory burden, which is now thought to be the most important factor overall.[51, 52] Other important CRC risk factors in individuals with IBD include personal history of colorectal neoplasia,[53, 54] family history of CRC in a first-degree relative (i.e., parent, sibling, or child),[55, 56] and co-morbid primary sclerosing cholangitis.[57] A normal colonoscopy (no inflammatory or neoplastic changes), particularly consecutive normal colonoscopies, is associated with a reduced risk of future advanced CRC.[50, 58]

Most population-based studies have reported CRC risk to be elevated among people with IBD as compared to age- and sex-similar people without IBD.[20, 59-62] A meta-analysis of population-based studies up to 2009 reported a standardized incidence ratio (SIR) of 1.7 (95% confidence interval [CI]: 1.2, 2.2) for CRC among people with IBD relative to the general population, which was similar across Crohn's disease and ulcerative colitis.[20] High-risk groups were individuals with extensive colitis (SIR: 6.4; 95% CI: 2.4, 17.5) and those diagnosed with IBD under 30 years old (SIR: 7.2; 95% CI: 2.9, 17.8). Cumulative risks of CRC in this study were 1% after 10 years and 2% after 20 years which is considerably lower than the earlier reported CRC incidence of 8% at 20 years across population-based and referral centre studies.[44]

Since then, multiple population-based studies of CRC risk in IBD have been published. A study from Northern California conducted between 1998–2010,

Table 1: Summary of recent studies comparing the risk of cancers in people with and without IBD.

When estimates from multiple studies are reported, data are presented as a range of effect estimates. When estimates come from a single study, they are reported as effect estimates with 95% confidence intervals (CI).

Cancer Type	Diagnosis at Any Age	Pediatric-Onset	Comments
Colorectal	**IBD,** IRRs: 1.1–1.8[18-20] OR: 1.78 (1.57, 2.02)[21] HR: 1.95 (1.65, 2.30)[22] **CD,** IRRs: 1.6–1.7[20, 23] **UC,** IRRs: 1.6–1.7[20, 23]	**IBD,** IRR: 20.29 (17.20, 25.90)[24]	Most studies show statistically significant increased risk among people with IBD.
Small intestine	**IBD,** IRR: 7.4 (5.6, 9.8)[19] OR: 6.6 (4.7, 9.4)[21] **CD,** HR: 19.7 (10.5, 36.7)	**IBD,** IRR: 16.2 (3.5, 74.7)[24]	Most studies show statistically significant increased risk among people with IBD.
Lymphoma	**IBD,** IRRs: 1.4–2.0[19] **CD,** IRR: 2.4 (1.8, 3.2)[25]	**IBD,** IRR: 3.1 (1.9, 5.1)[24]	Meta-analyses showed statistically significant increased risk among people with IBD, but many individual population-based studies were varied.
Melanoma	**IBD,** IRRs: 1.2–1.3[19, 26] OR: 0.9 (0.8, 1.1)[21] HR: 1.0 (0.7, 1.5)[27] **CD,** IRRs 1.4–1.8[28,29] ORs: 1.1–5.2[28] **UC,** IRRs: 1.1–1.2[28] OR: 0.9 (0.8, 1.1)[28]	**IBD,** IRR: 2.1 (1.3, 3.3)[24]	Studies show statistically significant increased risk among people with pediatric-onset IBD.
Non-Melanoma Skin Cancer	**IBD,** IRRs: 1.5–1.6[26, 30] OR: 1.03 (0.97, 1.10)[21] **CD,** IRR: 2.3 (1.4, 3.8)[25] UC, IRR: 1.4 (1.1, 1.7)[25]	**IBD,** IRR: 3.6 (2.0, 6.7)[24]	Most studies have shown a modest association of IBD with melanoma.
Cervical	**IBD,** OR: 0.7 (0.6, 0.8)[21] **CD,** IRRs: 1.3–1.6[19, 25, 31] **UC,** IRRs: 0.6–1.0[19, 25]		Inconsistent increased risk of cervical cancer.
Hepatobiliary	**IBD,** IRR: 2.5 (1.8, 3.5)[19] OR: 7.4 (5.6, 9.8)[21] **CD,** IRRs: 1.8–5.2[32] **UC,** IRRs: 0.7–5.6[32-34]	**IBD,** IRR: 55.5 (19.6, 157.0)[24]	Most studies show statistically significant increased risk among people with IBD.
Lung	**IBD,** OR: 4.0 (3.5, 4.6)[21] **CD,** IRRs: 1.5–1.8[19, 25, 33] **UC,** IRR: 0.4 (0.2, 0.7)[33]		Studies generally show statistically significant increased risk among people with Crohn's disease but not ulcerative colitis.
Breast	**IBD,** IRR: 1.0 (0.9, 1.2)[19] OR: 0.7 (0.6, 0.8)[21]		Studies generally show no association between IBD and breast cancer.
Prostate	**IBD,** IRR: 1.0 (0.9, 1.2)[19] OR: 0.6 (0.6, 0.7)[21]		Studies generally show no association between IBD and risk of prostate cancer.

Abbreviations: *CD = Crohn's disease; HR = hazard ratio; IRR = incidence rate ratio; OR = odds ratio; UC = ulcerative colitis*

based on the Kaiser Permanente database, reported SIRs for CRC among people with Crohn's disease and ulcerative colitis of 1.6 (Crohn's disease, 95% CI: 1.2, 2.0; ulcerative colitis, 95% CI: 1.3, 3.0).[59] Conversely, adjusting for age, sex, and calendar time, a nationwide study from Denmark examining the years 1978–2008 did not find an increased CRC risk in their IBD population as compared to non-IBD members from the general population (SIR: 1.07; 95% CI: 0.95, 1.21). That study actually reported a lower CRC risk in their IBD population by 1999–2008 (SIR: 0.57; 95% CI: 0.41, 0.80).[42] Unique characteristics of their cohort, including a high propensity for early colectomy, may have influenced their findings. Recent population-based studies from Canada have reported similarly increased risk for CRC among people with IBD, as compared to age- and sex-matched controls without IBD (Ontario 2017–2020, SIR: 1.78; 95% CI: 1.64, 1.95;[61] Alberta 2002–2018, OR: 1.78; 95% CI: 1.57, 2.02;[62] Manitoba 1987–2012 [cases also matched to controls by area of residence, and analysis adjusted for prior history of lower gastrointestinal endoscopy, frequency of healthcare visits, and socio-economic status], adjusted hazard ratio (aHR): 1.95; 95% CI: 1.65, 2.30).[63] A meta-analysis of three population-based studies reported a pooled rate ratio (RR) of 20.29 for CRC (95% CI: 15.90, 25.90) among people with pediatric-onset IBD as compared to similar people without IBD; the higher relative risk in this study may relate to a low baseline CRC risk in a younger population as well as longer IBD duration in many individuals (due to developing IBD early in life).[64]

Several population-based studies have further reported a significant decline in CRC frequency over time among people with IBD,[42, 61] although others have not.[40, 59, 63] A recent population-based study from Ontario reported that CRC incidence steadily declined between 1994–2020 among persons with ulcerative colitis (average annual percentage change [AAPC]: −1.95; 95% CI: −2.59, −1.30) but not among persons with Crohn's disease (AAPC: −1.04; 95 % CI: −2.91, −0.87).[61] Notably, CRC incidence similarly declined among persons without IBD during this period, and the relative risk of CRC in individuals with IBD as compared to age- and sex-matched people without IBD during the 2017–2020 period was similar to what has been reported in earlier studies, suggesting that factors unrelated to IBD treatment may have led to the observed decline.

CRC-related mortality has also been reported to be higher among people with IBD across studies. The aHR for mortality among people with IBD in a population-based study from Manitoba was 2.15 (95% CI: 1.60, 2.89).[63] Similarly, a study from Northern California between 1998–2008 reported standardized mortality ratios for CRC of 2.3 (95% CI: 1.6, 3.0) in individuals with Crohn's disease and 2.0 (95% CI: 1.3, 2.7) among individuals with ulcerative colitis.[59] A Danish medical registry study reported five-year adjusted mortality risk ratios for people with Crohn's disease of 1.26 (95% CI: 1.07, 1.49) and ulcerative colitis of 1.14 (95% CI: 1.03, 1.27).[65] IBD was an independent risk factor for death after CRC diagnosis in studies from Japan[66] and Manitoba.[67] CRC-related mortality was reported to have declined several-fold among people with IBD between 1960–2004 in a population-based study from Sweden.[40] Conversely, the study from Manitoba reported no decline in the aHR for CRC-related death between 1987–1993 and 2002–2012 periods in people with IBD as compared to people without IBD, matched by age, sex, and area of residence.[63]

Small bowel carcinomas account for 1–5% of all gastrointestinal tract cancers in people with Crohn's disease and have been historically reported to occur at a 20–30-fold higher rate as compared

to people without IBD.[68, 69] A recent population-based study from Manitoba reported a hazard ratio (HR) for small bowel cancer of 19.7 (95% CI: 10.5, 36.7) among people with Crohn's disease, which was lower for those above 65 years of age (HR: 8.41; 95% CI: 3.05, 23.2) than among younger individuals (age <50, HR: 44.5; 95% CI: 9.88, 200; age 50–64, HR: 30.3; 95% CI:10.0, 91.7), and highest for ileal adenocarcinoma (HR: 125.7; 95% CI: 16.6, 950.7). Estimates from Ontario (2017–2020)[61] and Alberta (2002–2018)[62] have reported risk ratios for small bowel cancer among people with IBD of 7.39 (95% CI: 5.58, 9.79) and 6.59 (95% CI: 4.65, 9.35), respectively, as compared to matched controls. Among individuals with pediatric-onset IBD, a meta-analysis of population-based studies reported a pooled risk ratio of 16.20 (95% CI: 3.52, 74.66) for small bowel cancers. Importantly, the high relative rate for small bowel cancers may largely be due to the low baseline rate of small bowel cancers in the general population: Similar to other cancers observed more frequently among people with IBD, the absolute incidence of these cancers remains low.

Summary of Intestinal Cancer Epidemiology

CRC incidence continues to be 1.5–2 times higher among people with IBD as compared to age- and sex-matched members of the general population; a risk ratio that has not appreciably changed over time. This ratio suggests that the observed downward trend in absolute CRC incidence in people with IBD over the past three decades in several studies may be more related to changing genetic and/or environmental risk factors as opposed to changes in IBD treatment. Increased uptake of colonoscopy screening in society may have played a role in declining CRC risk over time. CRC-related mortality also remains roughly two times higher among people with IBD as compared to pepole without IBD who develop CRC suggesting either more aggressive tumour biology; a higher rate of advanced, incurable cancers at diagnosis among people with IBD; or a direct effect of increased CRC incidence. People with IBD remain at substantially higher risk of developing small bowel cancer as compared to their non-IBD counterparts, likely due to greater difficulty in managing small bowel inflammation and the absence of screening strategies for detecting early small bowel neoplasms. However, the absolute risk of small bowel cancer remains exceedingly low. Overall, intestinal cancer risk is likely to always be dominated by CRC risk. Strategies aimed at reducing the CRC potential of IBD, and at improving identification of individuals at higher risk of developing CRC to prioritize colonoscopy or surgery will be required to reduce the difference in CRC risk between people with and without IBD.

Extra-Intestinal Cancers

Extra-intestinal cancers in individuals with IBD may arise as a result of immunosuppression due to medications or as a direct effect of such therapies. Thiopurines, for example, are photosensitizers and lead to developing mutagenic reactive oxygen species.[70] The most commonly reported extra-intestinal cancers in those with IBD are lymphoma, melanoma, non-melanoma skin cancers (NMSC), cervical cancer, and hepatobiliary cancers.[71] In a recent meta-analysis of 15 studies, the overall risk of extra-intestinal cancers was found to be increased in individuals with Crohn's disease (incidence rate ratio [IRR]: 1.43; 95% CI: 1.26, 1.63) and ulcerative colitis (IRR: 1.15; 95% CI: 1.02,1.31).[25]

Lymphoma

Several population-based studies have not found an overall association between IBD and lymphoma risk.[72-74] However, a recent meta-analysis of 15 population-based studies reported an increased risk of hematologic malignancies among people

with Crohn's disease (IRR, 2.40; 95% CI: 1.81, 3.18). A meta-analysis of three population-based studies further reported an increased risk for lymphoid cancer among people with pediatric-onset IBD (pooled RR: 3.10; 95% CI: 1.88, 5.10).[64]

Thiopurine use (azathioprine and 6-mercaptopurine) in people with IBD has been consistently associated with an increased risk of lymphoma.[75-77] In a recent meta-analysis of studies comparing people with IBD receiving thiopurines to members of the general population, the SIR for lymphoma was 4.92 (95% CI: 3.10, 7.78), ranging from 2.80 (95% CI: 1.82, 4.32) in eight population studies to 9.24 (95% CI: 4.69, 18.2) in 10 referral studies.[75] Population-based studies demonstrated an increased risk among current thiopurine users (SIR: 5.71; 95% CI: 3.72, 10.1) but no increased risk among former thiopurine users (SIR: 1.42; 95% CI: 0.86, 2.34). The magnitude of risk only became significant after one year of cumulative exposure. Individuals younger than 30 years of age had the highest relative risk (SIR: 6.99; 95% CI: 2.99, 16.4), whereas the absolute risk was highest in individuals older than 50 years (28.24 cases per 10,000 person-years, with a relative risk of 4.78). Males carried a greater lymphoma risk than females (males, SIR: 4.50; 95% CI: 3.71, 5.40; females, SIR: 2.29; 95% CI: 1.69, 3.05).

A more recent French nationwide study of 189,289 adults with IBD followed for a median of 6.7 years reported a 2–3 times higher risk of lymphoma with thiopurine monotherapy (aHR: 2.60; 95% CI: 1.96, 3.44) and anti-TNF monotherapy (aHR: 2.41; 95% CI: 1.60, 3.64), and a synergistic effect with combination therapy (aHR: 6.11; 95% CI: 3.46, 10.8). The aHR among those receiving combination therapy was 2.35 (95% CI: 1.31, 4.22) compared to thiopurine monotherapy and 2.53 (aHR: 2.53; 95% CI: 1.35, 4.77) compared to anti-TNF monotherapy.[78] Notably, other studies have not found an independent association between anti-TNF therapy and lymphoma risk.[79-81] To-date, there is no data supporting an increased lymphoma risk with other classes of biologic therapy.

Across Ontario (2017–2020), the SIR for non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma among people with IBD, relative to age- and sex-matched controls, was found to be 1.43 (95% CI: 1.23, 1.65) and 1.95 (95% CI: 1.00, 3.81), respectively.[61] For NHL, this risk increased over a 25-year period (average annual percent change [AAPC]: 2.26; 95% CI: 0.924, 3.62), whereas it remained unchanged in the general population (AAPC: −0.071; 95% CI: −0.486, 0.346). Across Alberta (2002–2018), the odds ratio (OR) for hematologic malignancies was 1.37 (95% CI: 1.21, 1.56) for people with IBD relative to age-and sex-matched controls.[62] To what extent the higher rates of lymphoma in these populations were driven by immunosuppressive therapies is being actively investigated.

Furthermore, research with the DEVELOP registry has demonstrated a clear association between thiopurine use (but not biologic monotherapy) and lymphoma risk in children with IBD.[82] While most thiopurine-related lymphomas are Epstein-Barr virus associated B-cell lymphomas,[76] young males have also been reported to develop fatal early post-mononucleosis B-cell lymphomas (if they are sero-negative for Epstein-Barr virus prior to initiating thiopurine therapy)[76] and hepatosplenic T-cell lymphomas (γδ variant) following exposure to thiopurines.[83]

Melanoma

Multiple studies have demonstrated a modest association between IBD and melanoma, although the impact of medical therapies on melanoma risk remains uncertain. A meta-analysis of 12 cohort studies between 1940–2009, comprising 172,837

individuals with IBD, reported an increased risk of melanoma among people with Crohn's disease (seven studies, IRR: 1.80; 95% CI: 1.17, 2.75) and ulcerative colitis (seven studies, IRR: 1.23; 95% CI: 1.01, 1.50).[28] The pooled incidence rate of melanoma was 27.5 per 100,000 person-years (95% CI: 19.9, 37.0). A meta-analysis of four population-based cohorts reported a pooled IRR of 1.14 (95% CI: 0.92, 1.42) among people with ulcerative colitis and 1.52 (95% C: 1.03, 2.23) among persons with Crohn's disease.[25] A meta-analysis of three population-based studies among individualss with pediatric-onset IBD reported a pooled rate ratio of melanoma of 2.05 (95% CI: 1.27, 3.29).[64]

A US administrative claims database study comparing 108,579 people with IBD to matched controls without IBD between 1997–2009, similarly reported an IRR of 1.29 for melanoma among those with IBD (95% CI: 1.09, 1.53).[26] A nationwide Danish cohort registry study further reported an increased risk of melanoma among 13,756 people with Crohn's disease between 1978–2010 (SIR: 1.4; 95% CI: 1.0, 1.9).[29] Notably, more recent Canadian population-based studies have not reported an increased risk of melanoma among people with IBD as compared to age- and sex-matched controls (Ontario [2017–2020], SIR: 1.23; 95% CI: 0.857, 1.77;[61] Alberta [2008–2018], OR: 0.89; 95% CI: 0.75, 1.07;[62] Manitoba [1986–2018], HR: 1.04; 95% CI: 0.71, 1.53).[27]

Most studies have not found an increased risk of melanoma in association with thiopurine therapy.[26, 84, 85] A meta-analysis of 13 studies in 149,198 people with IBD reported a non-significant rate ratio of 1.22 (95% CI: 0.90, 1.65) for melanoma in association with thiopurine use. However, several studies have demonstrated a slightly higher risk of melanoma in association with anti-TNF biologic therapy.[26, 27, 86] A nested case-control study

IT'S IMPORTANT FOR PATIENTS, CAREGIVERS, AND HEALTHCARE PROVIDERS TO HAVE INFORMED CONVERSATIONS ABOUT THE RISKS OF CANCER WHEN IT COMES TO IBD AND IBD TREATMENTS. THIS CHAPTER PROVIDES DETAILED INFORMATION THAT I HOPE CAN GIVE PATIENTS AND CAREGIVERS A BETTER UNDERSTANDING OF THE RISKS SO THEY CAN MAKE INFORMED DECISIONS ABOUT THEIR HEALTH WITH THE MOST ACCURATE AND UP TO DATE INFORMATION AVAILABLE. RATHER THAN RELY ON GOOGLE SEARCHING THAT CAN CAUSE MORE ANXIETY AND FEAR.

of a large IBD cohort based on US claims data reported an increased odds of melanoma in users of biologic therapy of 1.88 (95% CI: 1.08, 3.29). However, a meta-analysis of eight cohort studies among 51,231 people with IBD did not find a significant association between anti-TNF therapies and melanoma risk.[87] A population-based study from Quebec also did not find an association between anti-TNF therapy and melanoma risk.[88] What contributes to these differing results is not well understood at this point.

Non-Melanoma Skin Cancer (NMSC)

NMSCs, mainly basal cell carcinomas (BCC) and squamous cell carcinomas (SCC), are typically non-fatal cancers that are strongly linked to sun exposure. Studies using US administrative health insurance claims data have reported a higher incidence of NMSC among people with IBD compared with matched controls (IRR: 1.64; 95% CI: 1.51, 1.78;[89] IRR: 1.46; 95% CI: 1.40, 1.53[26]). A recent population-based study from Manitoba also reported that the risks of BCC (HR: 1.53; 95% CI: 1.37, 1.70) and SCC (HR: 1.61; 95% CI: 1.29, 2.01) were significantly increased in individuals with IBD, but not for SCC in those with ulcerative colitis.[27] However, this study also reported an increased risk of BCC predating ulcerative colitis diagnosis (OR: 1.32; 95% CI: 1.08, 1.60). A meta-analysis of 15 population-based studies reported IRR of 1.36 (95% CI: 1.05, 1.71) in people with ulcerative colitis and 2.28 (95% CI: 1.36, 3.81) in people Crohn's disease.[25] A meta-analysis of three population-based studies in people with pediatric-onset IBD reported a pooled rate ratio of NMSC of 3.62 (95% CI: 1.97, 6.66).[64]

Most studies have reported an increased risk of NMSC in association with thiopurine therapies.[26, 27, 85, 88, 89] A meta-analysis of 13 studies comprising 149,198 individuals with IBD reported an excess risk of NMSC associated with thiopurine use (RR: 1.88; 95% CI: 1.48, 2.38). Deaths due to NMSC predominantly occur among individuals who continue thiopurines after NMSC diagnosis.[90] The risk of NMSC with anti-TNF therapies remains unclear: Some studies have reported a marginally increased risk,[27, 86, 89] while other studies have not.[26, 88]

Cervical Cancer

Studies describing the risk of cervical neoplasia in people with IBD have shown conflicting results, with some reporting increased risk,[91-95] some reporting lower risk,[60, 62, 96-98] and others reporting no association.[61, 99] A Danish nationwide cohort study of 19,691 women diagnosed with ulcerative colitis and 8,717 women diagnosed with Crohn's disease between 1979–2011, matched to 1,508,334 women from the general population reported increased risks. This study found that women with ulcerative colitis had increased risks of low-grade (IRR: 1.15; 95% CI: 1.00, 1.32) and high-grade (IRR: 1.12; 95% CI: 1.01, 1.25) squamous intraepithelial lesions (SILs), and women with Crohn's disease had increased risks of low-grade SIL (IRR: 1.26; 95% CI: 1.07, 1.48), high-grade SIL (IRR: 1.28; 95% CI: 1.13, 1.45), and cervical cancer (IRR: 1.53; 95% CI: 1.04, 2.27), compared with controls.[95] However, a meta-analysis of three population-based studies reported no higher risk of cervical cancer among women with ulcerative colitis (IRR: 0.95; 95% CI: 0.60, 1.51) or Crohn's disease (IRR: 1.58; 95% CI: 0.90, 2.77).[25] Notably, most studies have not adjusted for differences in cervical cancer screening rates.

A population-based study from Ontario (2017–2020) reported no increased risk of cervical cancer among people with Crohn's disease (SIR: 1.25; 95% CI: 0.829, 1.87) and a decreased risk of cervical cancer among people with ulcerative colitis (SIR: 0.62; 95% CI: 0.38, 0.99).[61] A population-based study from Alberta (2002–2018) showed a decreased odds of cervical cancer among those with IBD (OR:

0.68; 95% CI: 0.61, 0.77).[62] An earlier population-based study from Manitoba reported no association between cervical abnormalities and ulcerative colitis (OR: 1.03; 95% CI: 0.77, 1.38), and only showed an increase in risk for women with Crohn's disease if they were exposed to 10 or more prescriptions of oral contraceptives (OR: 1.66; 95% CI: 1.08, 2.54); this study adjusted for cervical cancer screening in the preceding five years.[99]

In the Manitoba study, combined exposure to corticosteroids and immunosuppressants was associated with increased risk of cervical abnormalities (OR: 1.41; 95% CI: 1.09, 1.81).[99] A meta-analysis of eight studies comprising 77,116 individuals with IBD receiving immunosuppression further reported 1.3 times higher risk of cervical high-grade dysplasia among women with IBD as compared to healthy controls (OR: 1.34; 95% CI: 1.23, 1.46).[100] Furthermore, a Danish cohort study of 341,758 individuals with autoimmune diseases reported an increased risk of cervical cancer among those who had received a high cumulative dose of azathioprine (HR: 2.2; 95% CI: 1.2, 3.9).[101] The association between biologics and cervical neoplasia in people with IBD has not been extensively studied. One small study did not observe any cervical cancer cases among people exposed to anti-TNF therapy.[98] Further research is required in this area.

Hepatobiliary Cancers

Hepatobiliary cancers in people with IBD are more likely to occur as a complication of comorbid liver or biliary disease—particularly primary sclerosing cholangitis—than as a complication of IBD itself or its treatments. A population-based study from Manitoba reported a higher incidence of hepatobiliary cancers in both Crohn's disease (IRR: 5.22; 95% CI: 0.96, 28.5) and ulcerative colitis (IRR: 3.96; 95% CI: 1.05, 14.9).[60] However, a subsequent meta-analysis of eight population-based cohort studies comprising 17,052 individuals with IBD reported an increased risk of hepatobiliary cancers only among individuals with ulcerative colitis (SIR: 2.58; 95% CI: 1.58, 4.22).[33] A Swedish national study also reported strong associations between bile duct cancers and ulcerative colitis (SIR: 5.6; 95% CI: 3.6, 8.4).[34]

A more recent meta-analysis of population-based studies reported pooled rate ratios of close to three times higher for biliary tract cancers across three studies (ulcerative colitis, IRR: 2.93; 95% CI: 1.73, 4.96; Crohn's disease, IRR: 2.93; 95% CI: 1.16, 7.41), but no increased risk of liver cancer across six studies (ulcerative colitis, IRR: 1.41; 95% CI: 0.99, 2.01; Crohn's disease, IRR: 1.81; 95% CI: 0.88, 3.75). Strikingly, a meta-analysis of three population-based cohort studies in people with pediatric-onset IBD reported a pooled rate ratio of 55.45 (95% CI: 19.59, 156.99) for biliary tract cancers. Again, this heightened risk may largely relate to a lower baseline risk of biliary tract cancers in a younger population.

A recent population-based study from Ontario (2017–2020) reported a 2.5 times increased risk of hepatobiliary cancers (SIR: 2.53; 95% CI: 1.84, 3.47),[61] which was similar in Crohn's disease and ulcerative colitis, while a population-based study from Alberta reported a 7.4 times increased risk (OR: 7.41; 95% CI: 5.58, 9.84).[62] There are no data on the risk of hepatobiliary cancers with biologic or other therapies in IBD.

Other Cancers

An earlier meta-analysis of population-based studies reported a higher incidence of lung cancer (SIR: 1.82; 95% CI: 1.18, 2.81) and bladder cancer (SIR: 2.03; 95% CI: 1.14, 3.63) among people with Crohn's disease, and a lower incidence of lung

cancer (SIR: 0.39; 95% CI: 0.20, 0.74) among people with ulcerative colitis—as compared to people without IBD.[33] A more recent meta-analysis of 15 population-based studies reported a slightly higher risk of lung cancer in people with Crohn's disease (IRR: 1.53; 95 % CI: 1.23, 1.91), but otherwise no increased risks of lung cancer in people with ulcerative colitis. That study also found no increased risk of breast, prostate, or urogenital cancers in people with Crohn's disease or ulcerative colitis.

In a recent population-based study from Ontario, a weak association was observed between Crohn's disease and lung cancer (SIR: 1.64; 95% CI: 1.37, 1.96), but no association was observed between IBD and either breast cancer (SIR: 1.04; 95% CI: 0.93, 1.15) or prostate cancer (SIR: 1.02; 95% CI: 0.88, 1.19).[61] Across Alberta, people with IBD showed a four times higher odds of lung cancer (OR: 4.01; 95% CI: 3.46, 4.64), but slightly lower odds of breast cancer (OR: 0.72; 95% CI: 0.64, 0.81) and prostate cancer (OR: 0.64; 95% CI; 0.57, 0.73), relative to age- and sex-matched controls.[62] They also reported substantially higher odds of pancreas (OR: 7.79; 95% CI: 5.53, 10.97), kidney (OR: 2.05; 95% CI: 1.66, 2.52), and neurologic (OR: 4.58; 95% CI: 2.97, 7.04) cancers, but lower odds of bladder (OR: 0.68; 95% CI: 0.54, 0.87) and endometrial (OR: 0.48; 95% CI: 0.34, 0.66) cancers.

Summary of Extra-Intestinal Cancer Epidemiology

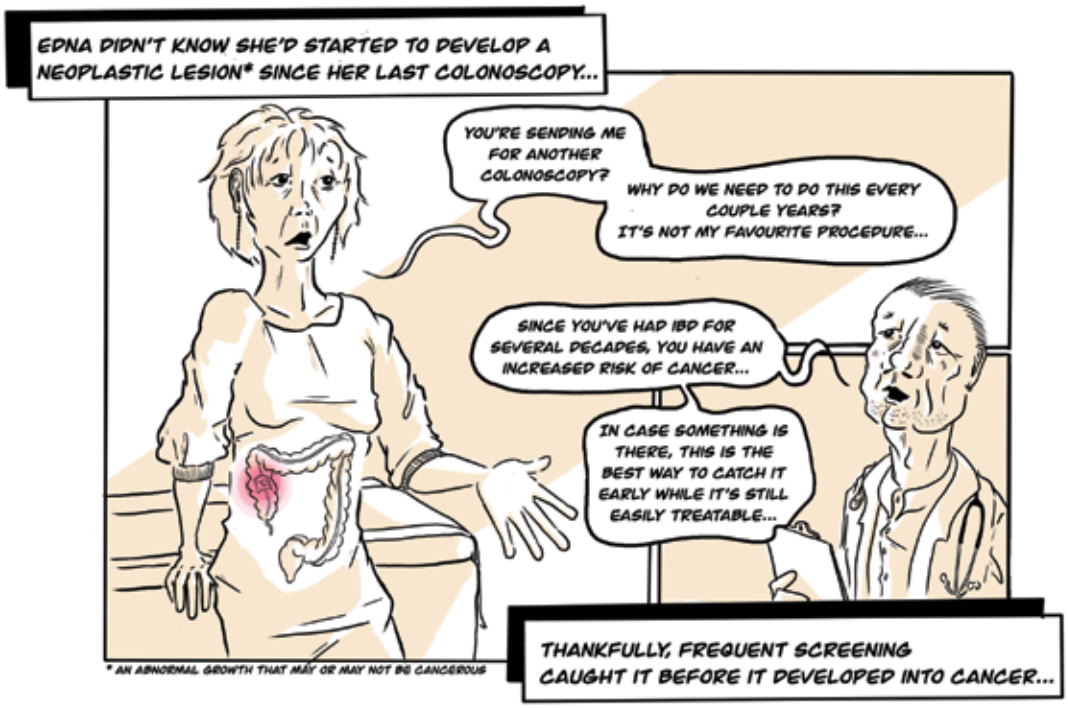
Overall, the risks of extra-intestinal cancers appear to be higher among individuals with IBD as compared to individuals without IBD, which may be partly driven by chronic systemic inflammation and/or by the immunosuppressive therapies used to treat IBD. Whether individuals with IBD also have increased genetic susceptibility to these cancers remains unknown. Clear evidence for increased cancer risks among individuals with IBD exist for lymphoma and non-melanoma skin cancers (primarily in association with thiopurine therapy), hepatobiliary cancers (mainly in association with comorbid primary sclerosing cholangitis), and lung cancer. However, the risks of other extra-intestinal cancers have been variable across studies and require further research. A multi-provincial Canadian population-based study aims to investigate the association between anti-TNF and thiopurine therapies and cancer risks in the IBD population. Of particular concern is the potential risk of fatal lymphomas in association with thiopurine therapies in young males. Until more data are available, practitioners should limit excess thiopurine exposure for people with IBD, particularly the elderly and young males, and maintain vigilance in minimizing risk of extra-intestinal cancers, such as through following appropriate screening measures and monitoring for early signs of cancer occurrence.

Cancer Prevention in IBD

Screening for CRC

Prevention of CRC and CRC-related death have long been important goals in the management of IBD. Historical reports of widespread DNA damage in chronically inflamed colorectal mucosa (i.e., field cancerization),[35-37] a propensity towards irregular and indistinct growth patterns of colorectal neoplasia that could evade detection during colonoscopy,[102-104] and high rates of missed CRC during colonoscopy,[105-114] in conjunction with epidemiologic evidence of increased CRC incidence above the background risk beyond the first decade after diagnosis among people with colonic IBD,[20, 43, 44] have led to societal recommendations for lifelong intensive colonoscopy surveillance in individuals with IBD affecting the colorectum, beginning at 8–10 years following disease diagnosis.[115-119] Surveillance intervals of 1–5 years are now recommended for most people with colorectal IBD, guided by established CRC risk factors.[120] A detailed summary of colonoscopy surveillance recommendations across multiple societies is provided in a review by Shah & Itzkowitz.[121] While there is limited direct evidence of the utility of colonoscopy surveillance, the observed reduction in CRC incidence among people with IBD over time in some studies could, at least partly, be attributed to improved surveillance standards, with increased recognition and treatment of early colorectal neoplasia.

Updated guidance favours endoscopic management of all colorectal neoplasia with clearly delineated borders and without advanced features suggestive of invasive cancer or submucosal fibrosis, as well as continued endoscopic surveillance, as opposed to surgery, for individuals without high-risk neoplastic findings (multi-focal invisible dysplasia, invisible high-grade dysplasia, unresectable colorectal neoplasia) or difficult to surveille colons.[120, 122]



Referral to an advanced endoscopist or a specialized centre for advanced endoscopic approaches is recommended for individuals with poorly delineated, invisible, or difficult to resect lesions prior to considering surgery.[120] Dye-spray chromoendoscopy and virtual chromoendoscopy techniques are being increasingly advocated as primary screening and surveillance support to high-definition colonscopy.[120, 123, 124] While taking extensive non-targeted biopsies has been a support method to colonoscopy surveillance in IBD for many years, its utility for routine screening and surveillance is being increasingly questioned due to its low yield for detecting neoplasia and increasing evidence that most colorectal neoplasia are visible with modern endoscope technology.[120, 122, 125]

Importantly, several studies have demonstrated high rates of post-colonoscopy CRC (CRC diagnosed within three years following a colonoscopy) among people with IBD, ranging between 25% and 50% of all CRC diagnosed in this population across studies.[67, 126-128] To what extent these findings are due to altered biology of CRC in people with IBD versus missed colorectal neoplasms during colonoscopy is unknown. These findings highlight the importance of careful inspection during colonoscopy under optimized conditions for neoplasia detection and of appropriate management of identified neoplastic lesions by specialists who are trained to do so.[120] It further highlights the importance of intensive colonoscopy surveillance in those with higher risk, and the need for non-invasive tests to detect CRC and CRC precursors in people with IBD.

There are inconsistent data regarding the chemopreventive benefits of IBD therapies, including 5-ASA therapies[129-131] and thiopurines.[132-135] Thus, no firm recommendations exist for the use of these treatments solely for the purposes of CRC prevention.

Screening for Small Bowel Cancer

There are no screening or surveillance recommendations for small bowel cancers in IBD due to the lower rate of new cases as compared to CRC and perceived cost-ineffectiveness of routine screening.[2, 68] Fortunately, most small bowel cancer in Crohn's disease occurs in the distal terminal ileum, which should be routinely inspected during colonoscopy performed for any reason in those with Crohn's disease, offering some opportunity for small bowel surveillance.[136]

Screening for Hepatobiliary Cancer

The American College of Gastroenterology (ACG) recommends screening for biliary tract and gall bladder cancers with ultrasound or magnetic resonance cholangiopancreatography along with CA19-9 measurement every six months if an individual has comorbid primary sclerosing cholangitis and IBD.[137] Prophylactic cholecystectomy is further recommended for gallbladder polyps larger than eight mm to prevent the development of gallbladder cancer.[137] The impact of these strategies on hepatobiliary cancer-associated mortality remains unknown.

Screening for Cervical Cancer

While it is unclear whether IBD or its treatments are truly associated with an increased risk of cervical cancer, the American College of Obstetricians and Gynecologists,[138] ACG,[139] and an expert panel[140] have recommended annual cervical cancer screening with Papanicolaou (Pap) tests for females with IBD receiving chronic immunosuppressive therapy. At a minimum, females with IBD should remain up to date with cervical cancer screening recommended for females in the general population. Traditionally, rates of Pap testing have been lower among females with IBD on immunosuppressants.[141] Being vaccinated against HPV (human papilloma virus) is recommended as per general population guidelines.[139]

Screening for Skin Cancer

The ACG recommends that all individuals with IBD undergo regular skin surveillance for NMSC if they are receiving thiopurine therapy, particularly if they are over the age of 50, as well as regular skin surveillance for melanoma, irrespective of their use of immunosuppressive therapy.[139] They further recommend that all individuals initiating or already taking chronic immunosuppressive therapy be evaluated by a dermatologist to tailor further evaluations based on individual risk, in addition to performing regular self-examinations, and also use sunscreen that is protective against UVA and UVB light and wear sun protective clothing.[139]

Summary of Cancer Screening Recommendations in IBD

At present, cancer screening recommendations for people with IBD are best established for CRC and for biliary cancers in those with comorbid CRC, whereas guidance for other cancer screening is limited. It is reasonable for individuals with IBD, particularly those receiving chronic immunosuppressive therapy, to undergo regular skin exams and Pap testing with their family physician. The role of routine screening for small bowel cancers and lung cancers, as well as for other internal cancers, must weigh the benefits of screening against the risks and costs, and it should be individualized. Formal screening recommendations for these and other rare cancers in individuals with IBD need to be developed. A summary of existing screening recommendations for IBD-relevant cancers is provided in Table 2.

Table 2: Summary of available surveillance strategies for intestinal and extra-intestinal cancers in persons with IBD

Cancer Type	Survweillance Method	Surveillance Frequency
Colorectal	Colonoscopy	1–5 years, based on risk factors[120, 121]
Skin Cancers	Skin exam	Annual if receiving thiopurine therapy[139]
Hepatobiliary	Ultrasound or MRCP, along with CA19-9 measurement	Every six months[137]
Cervical	Papanicolaou test	Annual if receiving immunosuppressive therapy; otherwise maintain up to date with general population screening[138-140]

Biologic/Immunomodulator Use after Cancer Diagnosis.

Data are limited on the use of immunosuppressive therapies after a cancer diagnosis. Immunomodulators are currently not recommended within 2–5 years after a cancer diagnosis.[142] Mounting evidence from large retrospective studies shows no increased risk of relapse (or new cancer) with anti-TNF therapies or thiopurines,[142-146] nor with vedolizumab or ustekinumab.[147-149] Ongoing use of biologics and/or immunomodulators after cancer should be individualized based on the type of cancer and type of immunosuppression and should be a shared decision in consultation with the treating oncologist and/or surgeon.

Knowledge Gaps & Future Research Directions

1. Research in large cohorts with long-term follow-up is required to better understand cancer risks faced by those with IBD, particularly in relation to different classes of existing and emerging medications. Individual risk factors for treatment-related cancers need to be elucidated. Additionally, cancer risk from IBD itself needs to be distinguished from that related to IBD treatments.

2. A clearer understanding of the importance and optimal methods of cancer screening and prevention is needed. Better defined and more widely available screening and surveillance methods are required for extra-intestinal cancers. Cost-effective screening and surveillance methods are also needed for cancers that are not as easily identifiable in their early stages.

3. Better risk stratification tools to optimize colonoscopy delivery are also required to improve colorectal neoplasia detection in high-risk individuals and defer unnecessary colonoscopy in low-risk individuals.

4. A better understanding of the reasons underlying the high rate of post-colonoscopy colorectal cancers and methods to reduce this occurrence is required.

Patient & Caregiver Partner Perspective

While the risk of developing cancer in persons living with IBD is small, there is still an increased risk of certain cancers that individuals with IBD need to be aware of. The risk of cancer can be associated with the disease itself or the medications used to treat IBD. Even though the prospect of being at a greater risk for cancer development can be worrying for some, patient partners welcome conversations with multidisciplinary providers regarding risk factors and recommended screening for cancers. Receiving this information can facilitate self-advocacy and informed, shared decision making about treatment options and disease management. Patient partners stressed the importance of cancer screening and surveillance to decrease the risk of cancer development or discover the cancer in its early stages.

Policy Implications & Key Advocacy Outcomes

1. Individuals with IBD receiving immunosuppressive therapies (especially thiopurines and anti-TNF therapies) should receive regular screening and surveillance for potential treatment-related cancers where screening protocols exist.

2. Life-long excellent control of bowel inflammation is important to reduce colorectal cancer risk; physicians should have access to the best treatment to control inflammatory burden as required.

3. Beyond treating the underlying IBD, careful high quality colonoscopy examinations remain the best strategy for colorectal cancer prevention and should be available to all individuals with colorectal IBD.

4. Research should be encouraged and funded to develop non-invasive markers of neoplasia in IBD.

5. Shared decision-making should inform treatment choices and cancer risks for IBD, weighing the risks of untreated inflammatory disease against the small, but potentially serious, risks of extra-intestinal cancers with immunosuppressive therapies. The difference between the absolute risks and relative risks of various cancers should be highlighted during these discussions.

6. For individuals with IBD who develop cancer, regular communication between gastroenterologists and oncologists should be encouraged to optimize management.

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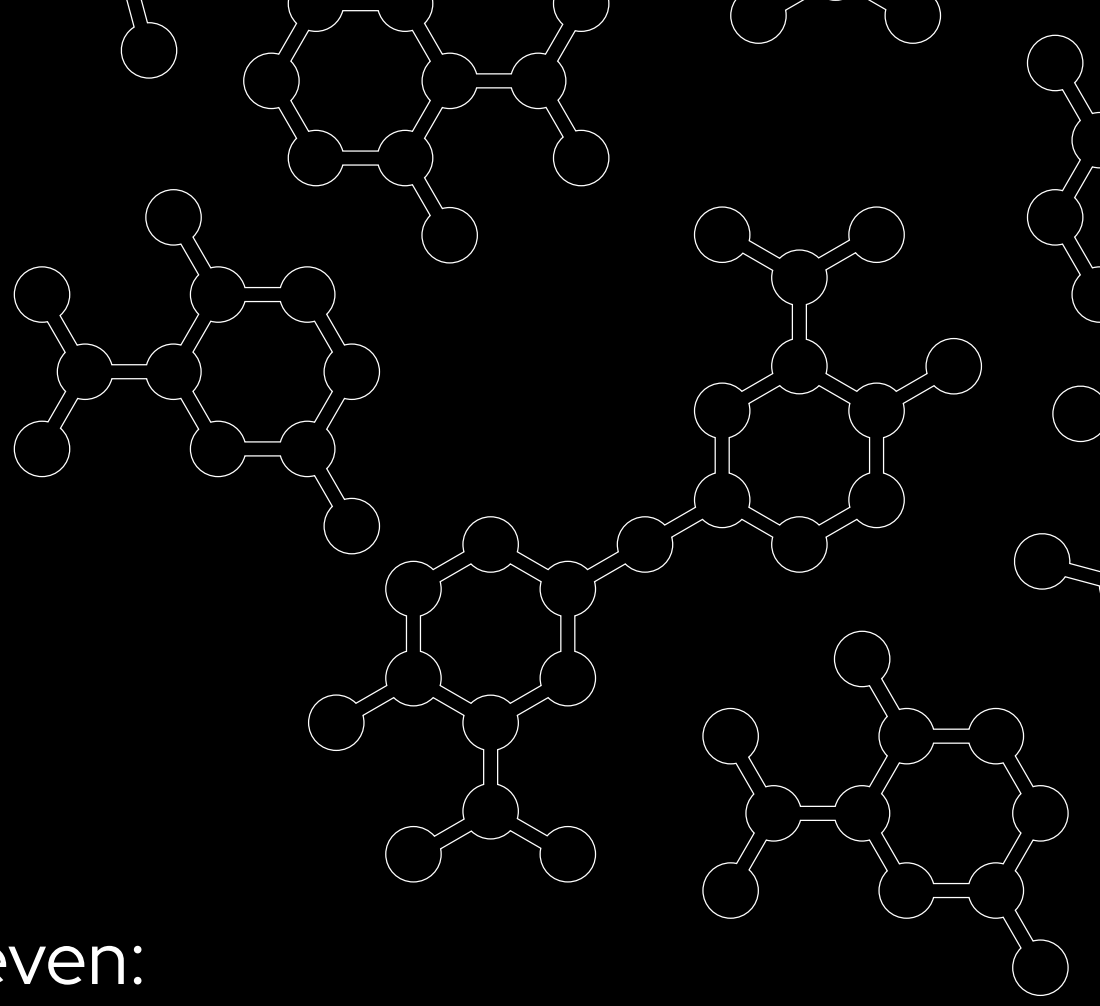


Section Eleven:

Treatment Landscape

Treatment Landscape

Abstract

The treatments available for inflammatory bowel disease (IBD) have changed considerably over the past two decades due to the development and widespread usage of targeted therapies, including biologics and small molecules. While some conventional treatments continue to have an important role in managing IBD, we are increasingly moving towards targeted therapies that have greater efficacy and safety in comparison to conventional medications. Early use of these therapies—particularly in people with Crohn's disease—combining targeted therapies with traditional immunomodulators and targeting objective markers of disease activity (in addition to symptoms), has been shown to improve health outcomes and will be increasingly adopted over time. The substantially increased costs associated with targeted therapies has led to a ballooning of healthcare expenditure to treat IBD over the past 15 years. The introduction of less expensive biosimilar anti-TNF therapies may bend this cost curve downwards, potentially allowing for more widespread access to these medications. Newer therapies targeting different inflammatory pathways and complementary and alternative therapies (including novel diets) will continue to shape the IBD treatment landscape. More precise use of a growing number of targeted therapies in the right individuals at the right time will help minimize the development of expensive and disabling complications, which has the potential to further reduce costs and improve outcomes for the individual.

Key Points

1. Over the past two decades, targeted therapies—such as biologics and small molecules—have dramatically changed the treatment landscape and improved quality of life for people with IBD.

2. Strategies to optimize the effectiveness of available therapies, such as introducing biologic therapy early in the course of Crohn's disease, targeting normalization of objective markers of disease remission, and using therapeutic drug monitoring to guide treatment decisions have the potential to improve long-term prognosis and longevity of current medical treatment options.

3. Randomized controlled trials and real-world studies have demonstrated that biologic therapies are effective and safe for treating IBD. However, proactive use of these therapies early in the disease course and optimizing these therapies based on treatment response and therapeutic drug monitoring may further improve their effectiveness in clinical practice. Increasing knowledge on how to identify the right therapy for the right person at the right time should further improve long-term outcomes and cost-effectiveness of treatment strategies for individuals with IBD.

4. The latest targeted therapies introduced into clinical practice, including selective anti-IL-23 inhibitors, sphingosine-1-phosphate agonists, and Janus kinase-1 (JAK-1) inhibitors, have shown promising results in randomized controlled trials and may further improve treatment outcomes for people with IBD.

5. Biosimilar anti-TNF agents have shown similar treatment response rates and safety as their bio-originator counterparts. Biosimilars typically have a substantially lower cost, which may favourably bend the cost curve and promote more widespread access to targeted therapies in clinical practice.

6. Surgery continues to play an important role in IBD management, particularly for stricturing and penetrating complications of Crohn's disease, perianal fistulizing Crohn's disease, IBD that does not respond to medication, and intestinal cancers.

7. Evolving therapies directed at modifying gut bacterial flora (e.g., modified diets, probiotics, and fecal microbiota transplant) have shown promise as potential therapies for IBD, although further research is required in these areas before they can be widely recommended.

Introduction

The goals of inflammatory bowel disease (IBD) treatment are to induce and maintain disease remission, reduce disease-related complications, prevent permanent bowel damage, and improve quality of life.[1] Medical IBD treatment is largely focused on moderating the body's abnormal immune response to normal gut bacteria using immunosuppressive therapies. Dietary and alternative medicine treatment strategies, which help modulate inflammation by modifying the gut microbiome, hold promise as supports to medical therapy. Additionally, updated goals for IBD treatment and monitoring, including treating to a combined target of sustained bowel healing and elimination of clinical symptoms, may help to improve the long-term disease course. Despite advances in medical management, surgery continues to play an important role in managing bowel strictures, penetrating complications, perianal disease, and medically-refractory intestinal inflammation (inflammation that cannot be managed by medication).

Compared to older, non-targeted immunosuppressive therapies, newer classes of IBD treatments—such as biologics and small molecules—have shown greater potential to positively alter the disease trajectory. Newer agents on the horizon will hopefully continue to improve efficacy, safety, and tolerability of IBD treatments. The emergence of biosimilar therapies, which have similar effectiveness and safety to bio-originator medications but typically at a substantially lower cost, may help bend the overall cost curve of biologic therapies downward and improve access to targeted treatments in the future.

In this chapter, we review current IBD treatments, strategies to optimize available treatments, emerging therapies, and key data supporting current treatment decisions, with a focus on Canadian data where available.

What Are the Available Medical Treatment Options for People with IBD?

The IBD treatment landscape has evolved rapidly over the last several decades, and the pace of this evolution is increasing.[2] Prior to the 1960s, corticosteroids were the only medical therapy available to treat IBD. Five-aminosalicylic acid (5-ASA/mesalamine) and immunomodulators were introduced in the 1960s and 1970s. The first anti-tumour necrosis factor alpha (anti-TNFα) biologic therapy (infliximab) was approved for use in Canada in 2001, followed by a second (adalimumab) in 2004. Since then, several additional biologic therapies and small molecules that target specific inflammatory pathways have been introduced.[3] A summary of medications to treat IBD that are approved for use in Canada, their routes of administration, primary indications, and major adverse events is provided in Table 1. In general, biologic and other targeted therapies have demonstrated greater efficacy and improved safety as compared to non-targeted immunosuppressive agents. In particular, approved anti-integrin and anti-IL 12/23/anti-IL 23 agents have achieved a very high standard for safety.

What Do Large Canadian Studies Tell Us about the Impact of Newer Anti-TNF Therapies on IBD Outcomes?

Most,[4-9] but not all,[10] Canadian real-world studies have demonstrated declining trends in IBD-related hospitalizations and/or intestinal surgeries in parallel with the introduction of biologic therapies into the marketplace. However, a recent population-based study in Ontario that corrected for secular trends was not able to demonstrate a significant change in the rates of IBD-specific hospitalizations or intestinal

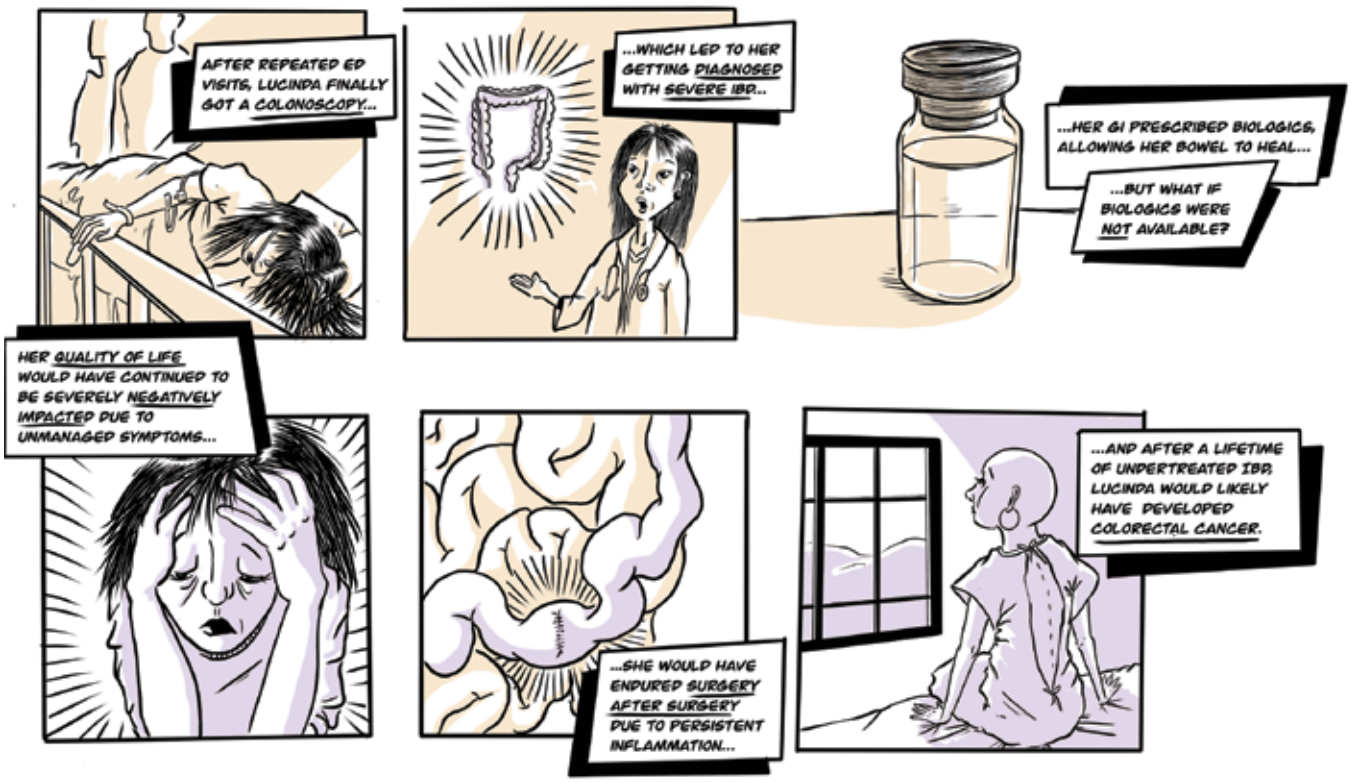


Table 1: Currently available treatments for IBD in Canada

Drug	Route of Administration	Standard Maintenance Dose Schedule	Treatment Phase	Type of IBD	Common side effects and Serious adverse reactions (Selected)
Topical Anti-Inflammatory Therapies					
5-Aminosalicylates (5-ASA), mesalamine: Older generation (oral) • Sulfasalazine (SSZ) Newer generation (oral) • Pentasa • Salofalk • Mezavant • Octasa • Teva 5-ASA Enemas • Salofalk • Pentasa • Mezera Suppositories • Salofalk • Pentasa	Oral, rectal (suppositories, foams, and enemas)	Oral: Daily Rectal: Daily, though twice weekly has been shown to be beneficial for maintenance of remission	Induction, maintenance	Mild-to-moderate ulcerative colitis (oral); rectal therapy may be used in distal ulcerative colitis. May be beneficial in mild colonic Crohn's disease, but this is controversial.	**Common Side Effects:** • nausea/vomiting, • paradoxical diarrhea • allergic hypersensitivity reactions (causing skin rash and mild fever) • male infertility (SSZ) **Serious adverse reactions (rare):** • serositis (pericarditis, serositis, mesenteritis) • allergic interstitial nephritis • cytopenias • pancreatitis • hepatitis
Topical corticosteroids: Budesonide (Entocort, Cortiment)	Oral, rectal	Oral: Daily Rectal: Daily	Induction	Mild-to-moderate Crohn's disease (Entocort) or ulcerative colitis (Cortiment)	See below for corticosteroids N.B. Risk of steroid-related side effects markedly lower than prednisone or solumedrol
Non-Targeted Immunosuppressive Therapies					
Corticosteroids (prednisone, prednisolone, methylprednisolone)	Oral (prednisone) or intravenous (prednisolone, methylprednisolone)	Daily	Induction	Crohn's disease, ulcerative colitis	**Common Side Effects:** • Sleep disturbance • Irritability, mood swings • Mild anxiety or depression • Fluid retention • Increased appetite • Weight gain • Acne • Linear growth delay (children) • Myalgias, arthralgias **Serious Adverse Reactions:** • Opportunistic infections • Osteonecrosis • Osteoporosis • Diabetes mellitus • Hypertension • Cataracts • Muscle atrophy • Body fat redistribution (Cushingoid)
Cyclosporine	Oral or intravenous	Daily	Induction	Ulcerative colitis	**Common Side Effects:** • Hirsutism • Tremor • GI upset • Headache **Serious Adverse Reactions:** • Opportunistic infections • Seizures • Renal toxicity • Hypertension

Table 1: Currently available treatments for IBD in Canada *(continued)*

Drug	Route of Administration	Standard Maintenance Dose Schedule	Treatment Phase	Type of IBD	Common side effects and Serious adverse reactions (Selected)
Non-Targeted Immunosuppressive Therapies *(continued)*					
Thiopurines (azathioprine, 6-mercaptopurine)	Oral	Daily	Maintenance	Crohn's disease, ulcerative colitis	**Common Side Effects:** • GI upset • Hypersensitivity skin and joint reactions **Serious Adverse Reactions:** • Opportunistic infections • Pancreatitis • Bone marrow toxicity • Hepatotoxicity • Lymphoma • Non-melanoma skin cancer
Methotrexate	Oral, subcutaneous	Weekly	Maintenance	Crohn's disease	**Common Side Effects:** • Flu-like symptoms • GI upset • Nausea, vomiting • Mucositis **Serious Adverse Reactions:** • Bone marrow toxicity • Hepatotoxicity, hepatic fibrosis • Pneumonitis, lung fibrosis
Targeted Immuno-active Therapies					
Biologics					
Anti-TNFs					
Adalimumab (Humira, Abrilada, Adalimumab injection, Amgevita, Hadlima, Hadlima Pushtouch, Hyrimoz, Hulio, Idacio, Simlandi, Hadlima, Yuflyma)	Subcutaneous	Every two weeks	Induction, maintenance	Crohn's disease, ulcerative colitis	**Common Side Effects:** • Injection site reactions • GI upset • Hypersensitivity reactions (skin, joints) • Upper respiratory tract infections • Headache • Nausea **Serious Adverse Reactions:** • Opportunistic infections • Drug-induced lupus • Cardiomyopathy • Demyelinating neuropathy • Lymphoma • Melanoma
Golimumab (Simponi)	Subcutaneous	Every four weeks	Induction, maintenance	Ulcerative colitis	As per Adalimumab
Infliximab (Remicade Inflectra, Ixifi, Renflexis, Remsima, Remsima SC, Avsola)	Intravenous	Every eight weeks	Induction, maintenance	Crohn's disease, ulcerative colitis	As per Adalimumab Acute infusion reactions (including anaphylaxis)

Drug	Route of Administration	Standard Maintenance Dose Schedule	Treatment Phase	Type of IBD	Common side effects and Serious adverse reactions (Selected)
Anti-Integrins					
Vedolizumab (Entyvio)	Intravenous	Every eight weeks	Induction, maintenance	Crohn's disease, ulcerative colitis	**Common Side Effects:** • Acute infusion reactions (IV) • Injection site reactions (SC) • GI upset • Hypersensitivity reactions (skin, joints) • Upper respiratory tract infections • Headache
Anti-IL-12/23s; Anti-IL-23s					
Ustekinumab (Stelara) (Anti-IL-12/23)	Intravenous induction followed by subcutaneous maintenance	Every eight weeks	Induction, maintenance	Crohn's disease, ulcerative colitis	**Common Side Effects:** • Injection site reactions • Upper respiratory tract infections • Headache
Risankizumab (Skyrizi) (Anti-IL-23)	Intravenous induction followed by subcutaneous maintenance	Every eight weeks	Induction, maintenance	Crohn's disease	**Common Side Effects:** • Injection site reactions • Upper respiratory tract infections • Headache
Small Molecules					
Janus kinase (JAK) inhibitors					
Tofacitinib (Xeljanz) (JAK-1/2/3, TYK-2)	Oral	Twice daily	Induction, maintenance	Ulcerative colitis	**Common Side Effects:** • GI upset • Hypersensitivity reactions • Upper respiratory tract infections • Headache • Elevated liver enzymes • Hypercholesterolemia **Serious Adverse Reactions:** • Opportunistic infections • Herpes Zoster (shingles) • Venous thromboembolism* • Major cardiovascular events* • Cancers*
S1P Receptor Modulators					
Ozanimod (Zeposia)	Oral	Daily	Induction, maintenance	Ulcerative colitis	**Common Side Effects:** • GI upset • Upper respiratory tract infections • Pyrexia • Headache • Elevated liver enzymes **Serious Adverse Reactions:**** • Opportunistic infections • Hypertension • Bradycardia (rare) • Progressive multifocal leukoencephalopathy (rare)

**Only demonstrated in studies in rheumatoid arthritis patients*

***Until more data available, extrapolated from studies in tofacitinib*

surgeries corresponding to the period following marketplace introduction of infliximab among people with Crohn's disease over a 10-year period or among people with ulcerative colitis over five-year period; this suggests that factors other than anti-TNF therapy may have also contributed to the observed trends in earlier studies.[7] Data from Ontario and Manitoba have also shown increasing use of anti-TNF therapy in people with Crohn's disease over the first decade following market introduction, but very little uptake in individuals with ulcerative colitis; this suggests that underuse of biologic therapies may limit the population-level impact on ulcerative colitis disease course.[11, 12] An ongoing multi-provincial study by the Canadian Gasto-Intestinal Epidemiology Consortium (CanGIEC) with longer follow-up aims to further evaluate the impact of more widespread uptake of biologic and other targeted therapies on IBD outcomes across Canada.

A population-based study from Manitoba further showed that receiving anti-TNF treatment in the first two years following a diagnosis of Crohn's disease was associated with 4.5 fewer hospitalizations due to IBD (95% CI: 2.1, 7.0) and 10.4 fewer hospitalizations for any reason (95% CI: 3.7, 17.0) per 100 person-years, over the five years following the start of therapy.[13] The decrease in IBD-specific and all-cause hospitalizations was most prominent in the latter half of the five-year follow-up period. The adjusted cumulative surgery rate over the five years after beginning anti-TNF therapy was not significantly different between those who began the therapy early or late in the follow-up period (5.7 vs 7.3 operations per 100 person-years; risk difference, −1.6 [95% CI, −4.5, 1.3]). However, when the first year of follow-up after starting anti-TNF therapy is excluded, early anti-TNF therapy was associated with 3.6 fewer surgeries per 100 person-years (95% CI, 1.9, 5.3). Similarly, data from a multicenter study in 552 people younger than age 17 diagnosed with inflammatory (nonpenetrating, nonstricturing) Crohn's disease between 2008–2012 at 28 pediatric gastroenterology centers in North America found that treatment with anti-TNFα therapy within three months of diagnosis was superior to early treatment with an immunomodulator alone in achieving clinical remission at one year (85.3% vs 60.3% in remission; relative risk: 1.41; 95% CI: 1.14, 1.75; p=0.002).[14] A landmark pragmatic randomized controlled trial conducted in Belgian and Canadian non-academic centers showed that early introduction of combined immunosuppression with an anti-TNF agent and an anti-metabolite immunomodulator in persons with Crohn's disease reduced the risk of surgery, hospital admission, and/or serious disease-related complications at 24 months as compared to conventional step-up therapy (27.7% and 35.1%, absolute difference: 7.3%, hazard ratio: 0.73; 95% CI: 0.62, 0.86; p<0.001).[15]

A population-based study from Manitoba further showed an annual reduction in corticosteroid use of 3.8% over the past two decades in people with Crohn's disease (most marked after 2007) and of 2.5% in people with ulcerative colitis, which could relate to increasing usage of biologic therapies and greater recognition of the potential adverse events associated with of long-term corticosteroid use.[16] Similar findings were observed in a population-based study from Alberta, with an average annual decline in corticosteroid use of more than 18% among people with IBD between 2010–2015, coinciding with increasing penetration of anti-TNF therapy.[17]

Given the relatively recent introduction of other classes of biologic and targeted therapies, limited real-world Canadian data exist for these therapies. Such studies will hopefully inform a future review of the IBD treatment landscape.

How Do We Optimally Use IBD Treatments to Improve Long-Term Disease Outcomes?

Several strategies have emerged over the past 10–15 years that have improved our ability to optimize the effectiveness of targeted therapies used to treat IBD.

Treat-to-Target

Selecting Therapeutic Targets in Inflammatory Bowel Disease-II (STRIDE-II) was a landmark paper guiding treatment targets in adults and children with IBD.[18] In those with IBD experiencing a flare of disease activity, the short-to-intermediate-term goal is to achieve rapid symptom reduction followed by clinical remission and normalization of C-reactive protein (CRP) and fecal calprotectin (proteins the body produces that can be measured to determine active inflammation). The longer-term targets include endoscopic healing, normalization of growth (in children), normal quality of life, and absence of disability (Figure 1). Specific timelines for meeting these targets were not provided in the STRIDE-II document as they may vary across disease phenotypes and medications used. In general, short term may be considered as four to six weeks, intermediate term as three to six months, and longer term as six to 12 months and beyond. When these targets are not met, a new strategy of managing IBD is required, such as optimizing the dose of therapy, using support therapies, changing medications, or surgery.

Achieving treat-to-target (T2T) goals requires regular disease activity monitoring that evaluates a combination of: symptoms, blood work, fecal calprotectin, bowel imaging, and endoscopy. The most notable innovation has been targeting objective markers of disease remission, particularly fecal calprotectin and endoscopic and radiographic healing, in combination with reducing symptoms.[19-22] Importantly, gastrointestinal symptoms that persist despite achieving objective disease remission are common and may relate to chronic bowel damage or superimposed irritable bowel syndrome that does not require treatments that target IBD.[23]

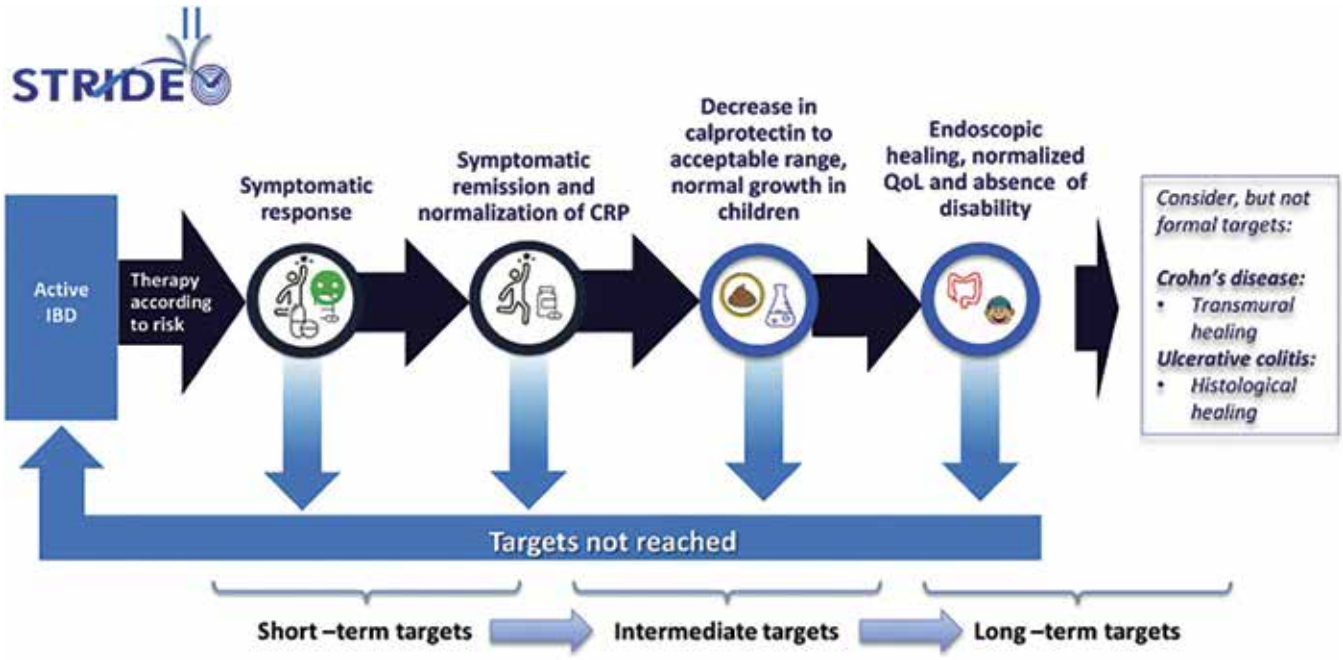


Figure 1: *STRIDE-II*

Multiple studies have demonstrated the value of endoscopic healing on long-term IBD prognosis.[24-27] A T2T strategy has further been shown to increase the probability of endoscopic healing.[19, 22] A randomized controlled trial, the effect of tight control management on Crohn's disease (CALM), demonstrated that adjusting medications based on regular disease activity monitoring using symptoms and biomarkers, such as CRP and fecal calprotectin, improves clinical and endoscopic outcomes out to three years.[22] A follow-up Canadian study further demonstrated that this treatment approach is cost effective relative to symptom-based management.[28]

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) of biologics has permitted a more scientific method to guide treatment decisions. Such monitoring is most relevant for the anti-TNF class of biologics, as the chimeric nature of the molecules leads to greater potential for the development of anti-drug antibodies and permanent loss of efficacy.[29] In the case of on-going or recurrent disease activity during treatment with a biologic agent, the presence of high drug or anti-drug antibody levels in the blood indicate either a mechanistic switch of disease activity (to another phenotype) or the person has mounted a resistance to the drug; this is associated with markedly reduced drug effectiveness and the need to switch to another medication.[30, 31] Conversely, the presence of low circulating levels of drug or of anti-drug antibodies during a disease flare may be managed, at least in the short-term, through optimizing drug dosage.[30, 31] An expert international panel unanimously voted that a reactive TDM strategy should be used for all biologics to help manage both primary non-response and secondary loss of response;[31] this approach has been demonstrated to be cost-effective relative to an older strategy of empiric drug optimization (optimization based on medical guidelines and physician experience).[32] Furthermore, it was recommended that discontinuing treatment with infliximab or adalimumab should not be considered until a drug concentration of at least 10–15 μg/mL (micrograms per millilitre) is achieved.[31] Importantly, the target drug concentration to affect disease activity may vary depending on the disease phenotype, the assay used to measure levels, and the desired therapeutic outcome; thus, treatment decisions based on TDM should be individualized.[31] Some individuals may require higher-than-established drug concentrations to establish optimal long-term disease control, such as individuals with perianal fistulizing Crohn's disease or small bowel Crohn's disease.[33]

Proactive TDM, a strategy in which biologic treatment escalation or de-escalation is guided purely by drug and/or anti-drug antibody concentrations in the blood, in the absence of objective disease activity, has not demonstrated convincing evidence of benefit with respect to health outcomes and is associated with a substantially higher cost than conventional management.[34] However, a large randomized controlled trial demonstrated that proactive dose adjustment of adalimumab when treating pediatric Crohn's disease was associated with a higher rate of corticosteroid-free clinical remission, a higher rate of composite sustained corticosteroid-free clinical remission, normal CRP, and normal fecal calprotectin at all visits from 8–72 weeks when compared to reactive TDM.[35] The personalized anti-TNF therapy in Crohn's disease study (PANTS), a large prospective UK study in anti-TNF-naïve people aged six years of age or older with active luminal Crohn's disease at first exposure to infliximab (955 participants) or adalimumab (655 participants), found that week 14 drug concentration was independently associated with the probability of week 14 primary non-response (infliximab, OR: 0.35; 95% CI: 0.20, 0.62; adalimumab, OR: 0.13; 95% CI: 0.06, 0.28); week 54 non-remission (infliximab, OR: 0.29; 95% CI: 0.16, 0.52; adalimumab,

OR: 0.03; 95% CI: 0.01, 0.12); and the development of anti-drug antibodies (infliximab: 62.8%; 95% CI: 59.0, 66.3; adalimumab: 28.5%; 95% CI: 24.0, 32.7).[36] This study further reported that the optimal week 14 drug concentrations associated with remission at both week 14 and week 54 were 7 mg/L (milligrams per litre) for infliximab and 12 mg/L for adalimumab. In light of these data, an international panel voted strongly in favour of proactive TDM once after anti-TNF treatment has begun, at least once during maintenance therapy, after any reactive TDM-based treatment change, and before and after any dose escalation or de-escalation to guide drug dosing; the panel noted the need for more data to support proactive TDM for other biologic agents.[31]

Step-Up vs. Top-Down Approaches to Therapy with anti-TNFs

Multiple randomized controlled studies have demonstrated that early combined immunosuppression of an anti-TNF and a thiopurine early in the disease course can improve disease outcomes compared with a conventional step-up treatment strategy or anti-TNF monotherapy.[15, 37-39] Population-level data from Manitoba and other Canadian provinces have similarly demonstrated a positive impact of early combined immunosuppression on the risk of future IBD-related complications,[40, 41] as well as earlier introduction of anti-TNF therapy on healthcare utilization in people with Crohn's disease.[13] The long-term impact on colectomy from early medical intervention for individuals with ulcerative colitis is less clear. At present, the considerably higher costs of targeted therapies as compared to conventional medications limits access to early combined immunosuppression for individuals dependent on public drug coverage. Fortunately, some provinces have recently approved access to biosimilar anti-TNF agents and vedolizumab without the requirement for loss of effectiveness of an immunomodulator.

Choosing the Right Therapy for the Right Person at the Right Time

Given the increasing variety of drugs available to treat IBD, there is great interest in understanding how to choose the right drug for the right person at the right time. To date, only two randomized controlled trials have directly compared approved targeted therapies for IBD. In the VARSITY trial, vedolizumab was superior to adalimumab at standard dosing for achieving clinical remission (although not steroid-free remission) in individuals with moderate-to-severe ulcerative colitis.[42] In the SEAVUE trial, ustekinumab was equivalent to

adalimumab in attaining symptomatic and endoscopic remission in individuals with Crohn's disease. While there are other head-to-head trials ongoing, these will only assess a fraction of the possible comparisons that can potentially be made between drugs. Network meta-analyses (NMA) have tried to fill in some of these data gaps through indirect comparisons. Recent NMAs have suggested that anti-TNFs and anti-IL-23 therapies may be superior to other therapies for Crohn's disease, and anti-TNF (infliximab), anti-IL-23, and JAK inhibitor therapies (tofacitinib) may be most effective for ulcerative colitis, while anti-integrin therapy (vedolizumab) ranks highest for safety.[43-45] Importantly, differences in the design and populations of studies included in NMAs may account for some of the apparent differences. Further research will be required to identify which specific sequence or combination of available drugs, possibly in conjunction with other strategies of medical treatment (such as modulating gut bacteria), optimally impacts long-term disease prognosis in individuals.

How Will Biosimilar Agents Impact Treatment Options for Canadians with IBD?

A biosimilar medication must show a high degree of similarity to the original biologic product and have no clinically meaningful differences in safety, purity, or potency.[46] As several anti-TNF bio-originator (biologic) drugs have now exhausted their patent, multiple biosimilar anti-TNF drugs have been developed and are now available, often at lower prices than their biologic originators. Given that spending on biologic medications is currently responsible for the majority of direct healthcare spending in IBD (see Chapter 4), the availability of less expensive alternatives could yield substantial cost savings. As a result, many provinces and insurers have been instituting policies that favor the use of biosimilar formulations of infliximab and adalimumab in place of their bio-originator forms (Remicade® and Humira®, respectively). In addition, six Canadian provinces have either instituted or have imminent plans to institute a mandatory switch policy, whereby the majority of current users of Remicade® and Humira® will be required to switch to a corresponding biosimilar in order to maintain insurance coverage.

Most studies comparing bio-originator to biosimilar anti-TNF therapies for anti-TNF-naïve individuals have not shown any meaningful differences in objective IBD-related or safety outcomes.[47-49] A systematic review of clinical trials that investigated biosimilar infliximab in anti-TNF-naïve people with IBD and in people with IBD who switched from originator infliximab also did not show any significant differences in efficacy or safety between the originator infliximab and its biosimilar. However, a recent systematic review and position statement released by the Canadian Association of Gastroenterology and Crohn's and Colitis Canada reported very low quality evidence, according to GRADE criteria, does not support nonmedical switching to biosimilar infliximab in individuals who have stable IBD and are doing well on the originator

biologic due to an increased risk of worsening disease, requiring dose escalation, and/or needing to switch to an alternative medication.[46] This position is shared by some, but not all, national societies. Nonetheless, given the potential cost savings and minimal risk of disease recurrence associated with non-medical switching, most North American and European societies, concur that this is an acceptable approach if agreed upon by both the physician and the individual.[46, 50-54] Conversely, the overwhelming majority of societies do not support mandatory substitution of a biosimilar agent for the originator agent in all individuals due to a lack of evidence for the efficacy and safety of this approach.[46, 50] Crohn's and Colitis Canada has suggested the use of a risk matrix (https://crohnsandcolitis.ca/Get-Involved/Advocating-for-change/Non-Medical-Switch-Biosimilars) to guide biosimilar switching in individuals with IBD. The position statement by the Canadian Association of Gastroenterology and Crohn's and Colitis Canada did provide a weak recommendation that an infliximab biosimilar could be started in people with active Crohn's disease who are naïve to anti-TNF therapy, for cost reasons, but noted that there were insufficient data to recommend the use of biosimilars in people with active ulcerative colitis naïve to infliximab.

Importantly, it has been reported that 10–20% of individuals may experience a nocebo effect with biosimilar switching (an increase in symptoms that follow a perception of a change in therapy),[55, 56] particularly those who have high levels of anxiety and a tendency toward catastrophization.[57] The impact of nocebo effects can be mitigated by involving the individual in the decision-making process, setting expectations of a positive outcome, and identifying individuals in who may be at higher risks for nocebo effects.[55]

While more data are needed, in the absence of a significant observable deterioration in individual health outcomes in most studies to date evaluating biosimilar start or switch, biosimilar drugs offer an attractive solution to the ballooning costs associated with IBD therapies. What is less clear is to what extent these cost savings will be reinvested to improve IBD care and research. At a minimum, the lower costs associated with biosimilar agents, alongside the parallel lowering costs of their bio-originator counterparts, should allow for improved access to these medications. Several provincial drug formularies have now agreed to fund biosimilar anti-TNF therapies for individuals with IBD irrespective of prior failure of conventional antimetabolite immunomodulating drugs, which is not the case for most bio-originator drugs.

AS SOMEONE WHO HAS THE UNIQUE VIEWPOINT OF WORKING IN HEALTHCARE WHILE SIMULTANEOUSLY LIVING WITH IBD, THIS REPORT AND CHAPTER DOES A TREMENDOUS JOB OUTLINING THE CURRENT STATE OF AFFAIRS SURROUNDING IBD TREATMENT OPTIONS IN CANADA.

What's on the Horizon for IBD Treatment?

In the last year, two new drugs were approved by Health Canada for the treatment of IBD. Risankizumab (Skyrizi®) was approved for the treatment of moderate-to-severe Crohn's disease, and ozanimod (Zeposia®) was approved for the treatment of moderate-to-severe ulcerative colitis. Upadacitinib (Rinvoq®) is also being considered for approval in Canada.

Risankizumab is the first drug that specifically targets interleukin-23 (IL-23) that is approved for Crohn's disease.[58, 59] It has been approved in Canada since 2019 for psoriatic arthritis and plaque psoriasis, and, thus far, has not demonstrated any increased risk of serious complications in comparison to other medications.[60] A head-to-head trial comparing risankizumab to ustekinumab in Crohn's disease is underway.[61] A head-to-head trial of these drugs in people with plaque psoriasis has demonstrated superiority of risankizumab over ustekinumab.[62]

Ozanimod is an oral sphingosine-1-phosphate (S1P) inhibitor, and is the first drug in its class approved in Canada for moderate-to-severe ulcerative colitis.[63] It has been approved in Canada since 2017 for multiple sclerosis and has been shown to have an excellent safety profile over the long-term in that condition.[64, 65]

Upadacitinib is a Janus kinase (JAK)-1 specific inhibitor that, in its initial trials, has yielded remission and response rates higher than those seen with other drugs.[66] Though there have not been head-to-head comparisons, indirect comparisons with other drugs suggest that upadacitinib may be one of the more effective therapies for ulcerative colitis.[67] Concerns have been raised about JAK inhibitor users being at higher risk of heart complications, cancer, and blood clots based on studies evaluating another JAK-inhibitor (tofacitinib) in elderly people with rheumatoid arthritis.[68] The only serious adverse event that has been consistently associated with this class of medications in people with ulcerative colitis is herpes zoster (i.e., shingles), typically with higher dose, long-term usage.[69] However, this risk is also elevated in people using anti-TNFs and may be reduced through vaccines against shingles, as suggested for all adults with IBD on immunosuppression by clinical practice guidelines from the Canadian Association of Gastroenterology.[70]

Medications that currently have active research programs in IBD and may become available in coming years include other selective JAK inhibitors (filgotinib for ulcerative colitis and Crohn's disease,[71, 72] upadacitinib for Crohn's disease[73]), other selective IL-23 inhibitors (mirikizumab and guselkumab for Crohn's disease and ulcerative colitis[74, 75]), other S1P receptor modulators (ozanimod for Crohn's disease, etrasimod for ulcerative colitis[76]), and mesenchymal stem cell treatment for perianal fistulizing Crohn's disease.[77] Health Canada approval of these drugs will depend on their efficacy and safety in ongoing clinical trials. Public drug coverage will depend on the ability to demonstrate that these drugs will achieve meaningful improvements in the quality of life for Canadians with IBD at a reasonable cost. Most likely, these agents will initially be funded as second or third-line treatments in public drug benefit programs across Canada. Crohn's and Colitis Canada will continue to advocate for Canadians living with IBD to receive the best available treatments when they are required.

What Is the Role of Alternative and Microbiome-Altering Therapies in IBD Care?

The application of treatments that are neither Health Canada approved immune-modulating medications nor surgery in the management of IBD, known as complementary and alternative medicine (CAM), are common among individuals with IBD. The prevalence of CAM use has been estimated to be as high as 50% in some studies.[78-81] There are many potential contributors to the use of CAM in these individuals, including lack of efficacy of conventional therapies, safety concerns with conventional therapies, and improved sense of control over the disease.[80] Despite the high prevalence of CAM use, there is limited data demonstrating its efficacy in treating IBD. In recent years, however, there has been emerging data evaluating microbiome altering therapies such as fecal microbiota transplantation (FMT) and probiotics.

The composition of the gut microbiome has been shown to have a significant influence on the body's immune response, and changes in the microbiome have been implicated in the development of IBD and flares of disease activity.[82] As a result, there is great interest in emerging therapies that seek to restore a healthy microbiome, such as FMT and probiotics, in the hopes that this will decrease intestinal inflammation and reduce symptom burden. In FMT, fecal material from a healthy individual is introduced via enema, colonoscopy, or nasogastric tube into the intestine of someone with IBD; the aim is to supplant the microbiome of the recipient with that of the healthy donor. A recent meta-analysis of six randomized controlled trials found that FMT was associated with a higher odds of clinical and endoscopic remission as compared to placebo in people with ulcerative colitis (OR: 4.11; 95% CI: 2.19, 7.72), with no difference in the risk of side effects.[83] A more recent study of 66 people with ulcerative colitis in clinical remission who were randomized to either the combination of FMT and an anti-inflammatory diet or standard medical therapy noted higher rates of clinical and endoscopic remission at 48 weeks (25% vs 0%, p=0.007) in the portion receiving FMT.[84] There is less evidence supporting the role of FMT in maintaining remission in ulcerative colitis or in the treatment of Crohn's disease. Two randomized controlled trials evaluating the role of FMT in Crohn's disease have shown improvements in short-term clinical remission rates.[85, 86] Most other studies evaluating the role of FMT in Crohn's disease are limited by small study size, discrepancies in results, and publication bias (the fact that frequently, only significant results or successful tests are published). Though the FMT data is promising in ulcerative colitis, it is still not available as a therapeutic strategy for IBD outside of clinical trials.

Probiotics, defined as products containing specific strains of live microorganisms that can be taken orally, are also commonly used by individuals with IBD, despite a lack of convincing evidence on effectiveness or safety. The American Gastroenterology Association recently issued Clinical Practice Guidelines stating that there is no evidence of benefit to any probiotic for either inducing or maintaining remission and suggested that probiotics should only be used in the context of clinical trials. This document did make a conditional recommendation for a specific 8-strain probiotic combination for treating individuals with pouchitis based on a review of seven studies,[87] four of which supported a role of this probiotic in preventing pouchitis flares.[88-91] The quality of evidence was rated as very low.

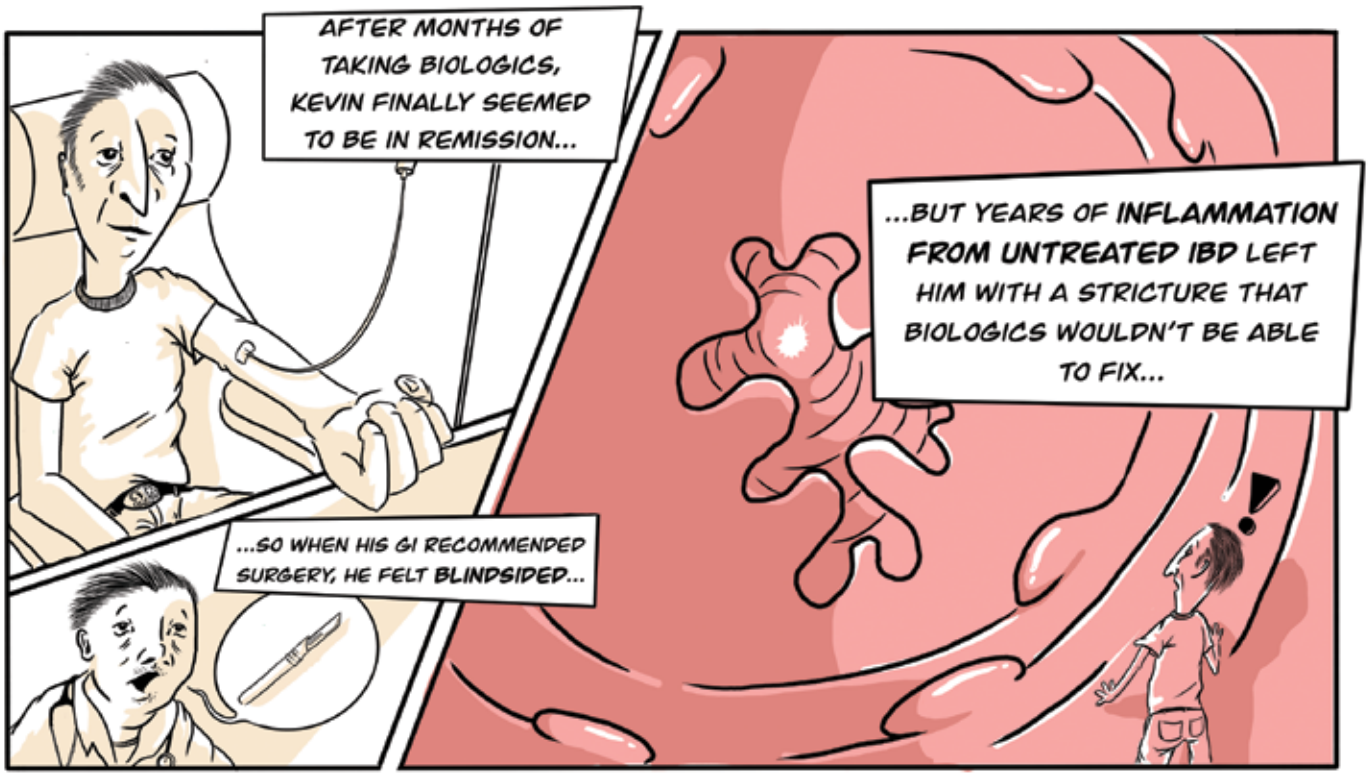
What Is the Role of Diet in IBD?

Many people look to dietary therapy as either an alternative or a supplementary treatment to conventional IBD management. To date, the strongest evidence to support dietary therapy is in pediatric IBD. Exclusive enteral nutrition (EEN), whereby individuals receive all nutritional intake through a formula for up to 12 weeks delivered orally, via nasogastric tube, or a gastrostomy tube, has been shown to be effective in inducing remission in Crohn's disease.[92, 93] While this treatment requires a significant commitment from both the individual and their caregivers and adherence can be a challenge, some guidelines favour it over corticosteroids, particularly in children with a history of delayed growth.[94, 95] Partial enteral nutrition is another nutritional therapy that may be better tolerated than EEN. A 2019 study evaluated a combination of partial enteral nutrition with a specific whole foods-based exclusion diet (the Crohn's disease exclusion diet [CDED]).[96] Participants were randomized to receive partial enteral nutrition and the CDED for 12 weeks or EEN for six weeks, then transition to partial enteral nutrition and a free diet. The CDED consists of a diet that avoided or reduced exposure to foods containing animal/dairy fat, high fat from other sources, wheat, red or processed meat and protein sources rich in taurine, emulsifiers, artificial sweeteners, carrageenans, and sulfites. The second phase stepdown diet involves higher exposure to fruits, vegetables, and legumes along with some foods that are reintroduced with restrictions to increase food flexibility and relieve monotony. Among 74 participants at week six, 75% of children given CDED plus partial enteral nutrition were in corticosteroid-free remission vs. 59% given EEN. At week 12, 75.6% of children given CDED plus partial enteral nutrition were in corticosteroid-free remission vs. 45.1% given EEN. Partial enteral nutrition and CDED was also better tolerated than EEN.

The data to support of the use of dietary therapy in adults with IBD is not as strong. A Cochrane systematic review on diet for inducing remission in Crohn's disease concluded that all studies provided low or very low-quality evidence.[97] One of the most common therapeutic diets used by adults is the Specific Carbohydrate Diet (SCD).[98] The Mediterranean diet has also become increasingly popular and several studies have identified a lower risk of Crohn's disease among populations consuming this diet, which consists of fruits, vegetables, nuts, fish, whole grains, and use of olive oil as the predominant fat source.[99] A recent study compared these two diets.[100] Adults with Crohn's disease were randomly assigned 1:1 to consume the Mediterranean or SCD for 12 weeks. The primary outcome was symptomatic remission at week six. Among the 194 participants, SCD was not superior to Mediterranean diet to achieve symptomatic remission, fecal calprotectin response, or CRP response. The authors concluded that the greater ease of following the Mediterranean diet and its other health benefits make it preferred to the SCD for most individuals with Crohn's disease.

What Is the Role of Surgery in IBD Management?

Surgery, once the mainstay of IBD treatment, continues to play an important role in the management of IBD due to failure or inadequate usage of medical therapy or the development of disease-related complications. Often, surgery complements medical therapy, particularly for perianal fistulizing disease and fibrostenotic small bowel disease. Common reasons for IBD surgery include perianal abscesses or persistently draining fistula tracts, fibrotic intestinal strictures resulting in bowel obstruction, penetrating intestinal complications (such as intra-abdominal abscess or enteric fistulae), treatment-refractory disease resulting in persistent and/or rapidly escalating disease activity (sometimes associated with complications such as toxic megacolon or bowel perforation), and intestinal cancer. A multicenter randomized controlled trial from the Netherlands and the UK examined individuals with non-stricturing ileocecal Crohn's disease affecting less than 40 cm of small bowel, in whom conventional therapy had failed. That study demonstrated that surgical resection was associated with similar health outcomes and quality of life as infliximab treatment and was more cost effective in people with limited small bowel Crohn's disease.[101, 102] Close collaboration between medical and surgical IBD specialists is important for managing complex IBD phenotypes.



Conclusion

The IBD therapeutic landscape and treatment goals have changed dramatically over the past two decades, and we can anticipate further changes in the years to come as more drugs with different mechanisms of action and a greater number of biosimilar drugs gain Health Canada approval. An improved understanding of matching drugs and treatment strategies to individuals may lead to better health outcomes, prevent complications, and improve quality of life.

Knowledge Gaps & Future Research Directions

1. Understanding the factors that may predict individual-level response to drugs with specific mechanisms of action will allow physicians to choose the right therapies for the right individual at the right time.

2. Understanding the changes in the immune system that lead to a loss of response to a previously effective medication may help mitigate loss of effectiveness or change the choice of individual therapy.

3. Randomized controlled studies and real-world evidence to understand the comparative effectiveness of different types and combinations of medical therapies in people with specific IBD subtypes, as well as pragmatic trials and real-world evidence to better understand how to optimize the usage and sequencing of medical therapies in clinical practice will better enable treat-to-target and personalized treatment strategies.

4. Real-world evidence is required to inform the effectiveness and safety of newer biosimilar drugs that are entering the marketplace.

5. Future clinical trials and observational studies of IBD therapies should aim to include under-represented populations, such as Indigenous peoples, pregnant people, children and adolescents, seniors, and immigrants.

Patient & Caregiver Partner Perspective

This chapter provided patient partners with hope and peace of mind particularly related to the ongoing research towards developing new medication options to treat IBD. Partners were also reassured from the research related to the safety and efficacy of biosimilars as more provinces enforce a non-medical switch from biologics. The availability of biosimilars can enhance access to life-changing medications for persons with IBD. Patient partners encouraged greater education for patients and caregivers related to the safety and efficacy of switching from biologic to biosimilar medications to decrease anxiety related to non-medical switching. Partners encouraged individuals with IBD who are non-medically switching to biosimilar medications to maintain positive thoughts about the switch to prevent nocebo effects. Selecting the right therapy for the right person at the right time was seen as an important strategy to adopt. Also, combination therapies for certain individuals could result in better outcomes. Partners recognized that complementary therapies have potential roles as treatment adjuncts, particularly in individuals living with ulcerative colitis.

Policy Implications & Key Advocacy Outcomes

1. All Health Canada approved therapies to treat IBD should be accessible to individuals when deemed necessary to control their disease by prescribing physicians. Advocacy should target barriers to accessing the safest and most effective medications as part of shared decision making between the individual and the physician.

2. Increasing acceptance of biosimilar drugs by individuals with IBD and their physicians should be encouraged to help control the rate of rising drug costs to treat IBD, enhance competitive pricing of biotherapies, and improve access to biotherapies.

3. Non-medical switch policies should consider the individual experience and integrate both the risk of increased disease activity and the impact of disease on the individual and family. Use of the Crohn's and Colitis Canada Risk Matrix to help guide non-medical switch policies implemented by provincial health ministries is encouraged. Vigilance should be maintained to ensure that new biosimilar drugs that enter the marketplace are held to the same standards for efficacy and safety as their bio-originator counterparts.

4. Healthcare practitioners and afflicted individuals should be informed of the nocebo effect and tools (including mental health support) should be introduced to help mitigate it in those forced to switch.

5. The cost savings realized from increasing use of biosimilar drugs should be redirected towards improving access to targeted therapies and diagnostic testing for people with IBD and increasing research funding for IBD.

6. Tools required to monitor individuals according to a treat-to-target approach, including, but not limited to endoscopy, cross-sectional imaging, and fecal calprotectin should be readily available to practitioners to assist with IBD management.

7. Scientific literature on the evidence for IBD treatment options should be free and accessible to all Canadians to better inform individuals and healthcare providers as to the options and modifiable behaviours for disease control.

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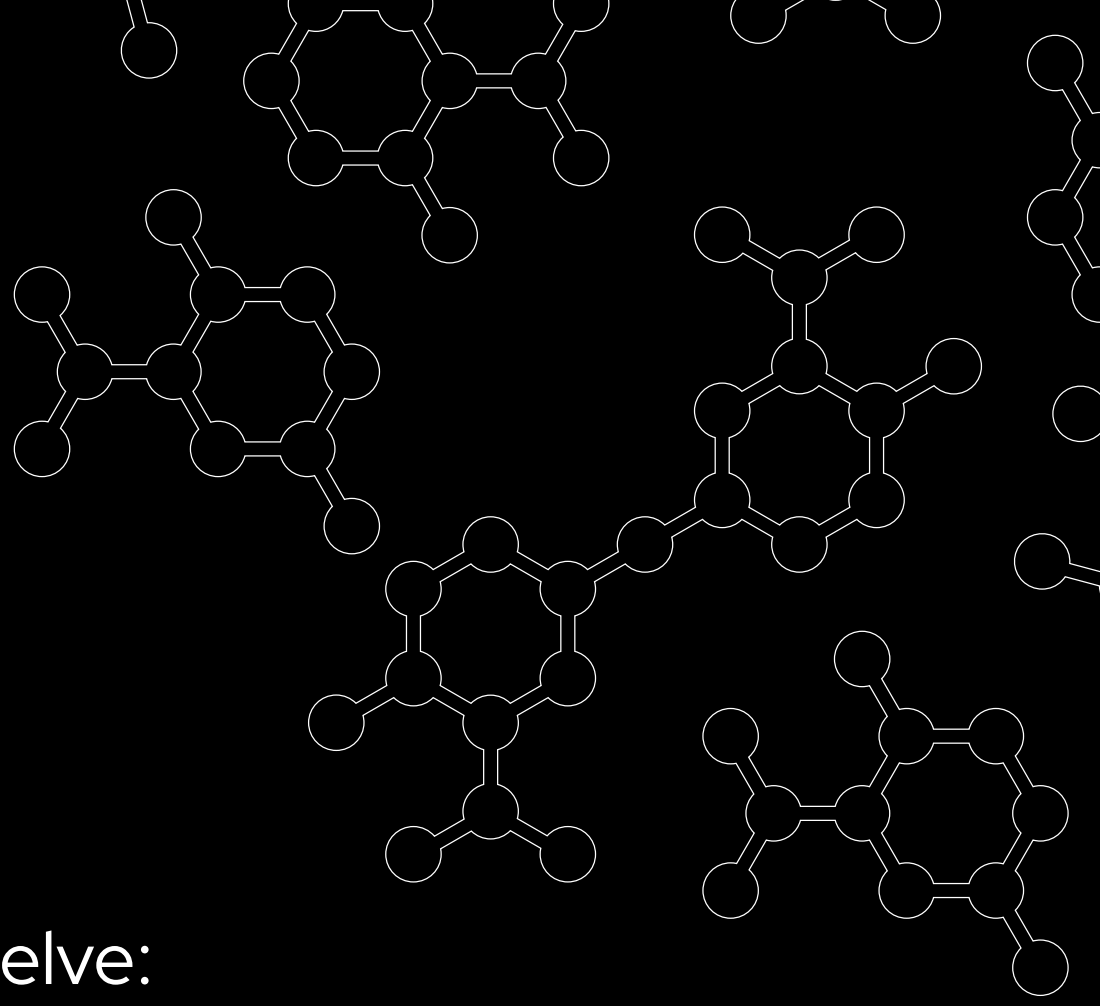


Section Twelve:

Access to & Models of Care

Access to & Models of Care

Abstract

The compounding prevalence[1] of inflammatory bowel disease (IBD)—the exponential rise in the total number of people living with IBD—and pandemic-exacerbated health system resource limitations resulted in significant variability in access to high-quality, evidence-based, person-centered specialty care for Canadians living with IBD. Individuals with IBD have identified long wait times, gaps in biopsychosocial care, treatment and travel expenses, and geographic and provider variation in IBD specialty care and knowledge as some of the key barriers to access. Care delivered within integrated models of care (IMC) has shown promise related to impact on disease-related outcomes and quality of life. However, access to these models is limited within the Canadian healthcare systems and much remains to be learned about the most appropriate IMC team composition and roles. Although eHealth technologies have been leveraged to overcome some access challenges since COVID-19, more research is needed to understand how best to integrate eHealth modalities (i.e., video or telephone visits) into routine IBD care. Many individuals with IBD are satisfied with these eHealth modalities. However, not all disease assessment and monitoring can be achieved through virtual modalities. The need for access to person-centered, objective disease monitoring strategies, including of point of care intestinal ultrasound, is more pressing than ever given pandemic-exacerbated restrictions in access to endoscopy and cross-sectional imaging. Supporting learning healthcare systems for IBD and research relating to the strategic use of innovative and integrative implementation strategies for evidence-based IBD care interventions are greatly needed. Data derived from this research will be essential to appropriately allocating scarce resources aimed at improving person-centred access to cost-effective IBD care.

Key Points

1. Quality of IBD care varies across Canada. Crohn's and Colitis Canada's Promoting Access & Care through Centres of Excellence (PACE) is a quality improvement initiative that may help standardize quality of care.

2. Patient-identified barriers to accessing care include long wait times, gaps in psychosocial care, treatment and travel expenses, and geographic variation in available specialty care.

3. Many individuals with IBD utilize emergency departments when access to care is limited. However, IBD care in this setting can be inadequate.

4. Several communities, including Indigenous and immigrant communities, and those of lower socio-economic status experience barriers to care.

5. Integrated models of care, including multidisciplinary care teams, may facilitate access to high-quality biopsychosocial care.

6. Multiple timely and appropriate approaches to disease monitoring, including point of care intestinal ultrasound, can support individual-reported outcomes and quality of life. Monitoring strategies should be guided by individual preference and experience.

7. Adapting virtual healthcare has changed the way IBD care is provided by improving access, provider communication, tracking individual outcomes, and timely management of disease and flares, while reducing costs and maintaining individual and clinician satisfaction.

Introduction

Over 320,000 Canadians currently live with inflammatory bowel disease (IBD), and this number is expected to rise to 470,000 Canadians by 2035.[2] (See Chapter 2.) Variation in the availability and structure of IBD care across Canada has been observed.[3, 4] This variation has highlighted the need for standardized quality care in IBD.[5-8]

Quality in healthcare is defined by the World Health Organization (2022) as "the degree to which health services for individuals and populations increases the likelihood of desired health outcomes."[9] Quality of IBD care is assessed through structures, processes, and outcomes according to an analytic model, called the Donabedian Framework.[10] Providing high quality IBD care can reduce geographical variation in care, healthcare services utilization, and costs to the health systems, while improving individual health outcomes.[7, 10-12] To standardize quality of IBD care, several countries have developed and implemented standardized clinical guidelines and care pathways, including the Promoting Access & Care through Centres of Excellence (PACE) pathways in Canada.[13-18]

Access to healthcare has historically been defined as "the fit between the individual and the healthcare system" and is an important aspect of quality IBD care.[13] More recently, access has been reconceptualized as a multifaceted experience that moves away from geographic availability of services to include patient-centered considerations such as cultural appropriateness.[19] This multifaceted access framework emphasizes the importance of patient-

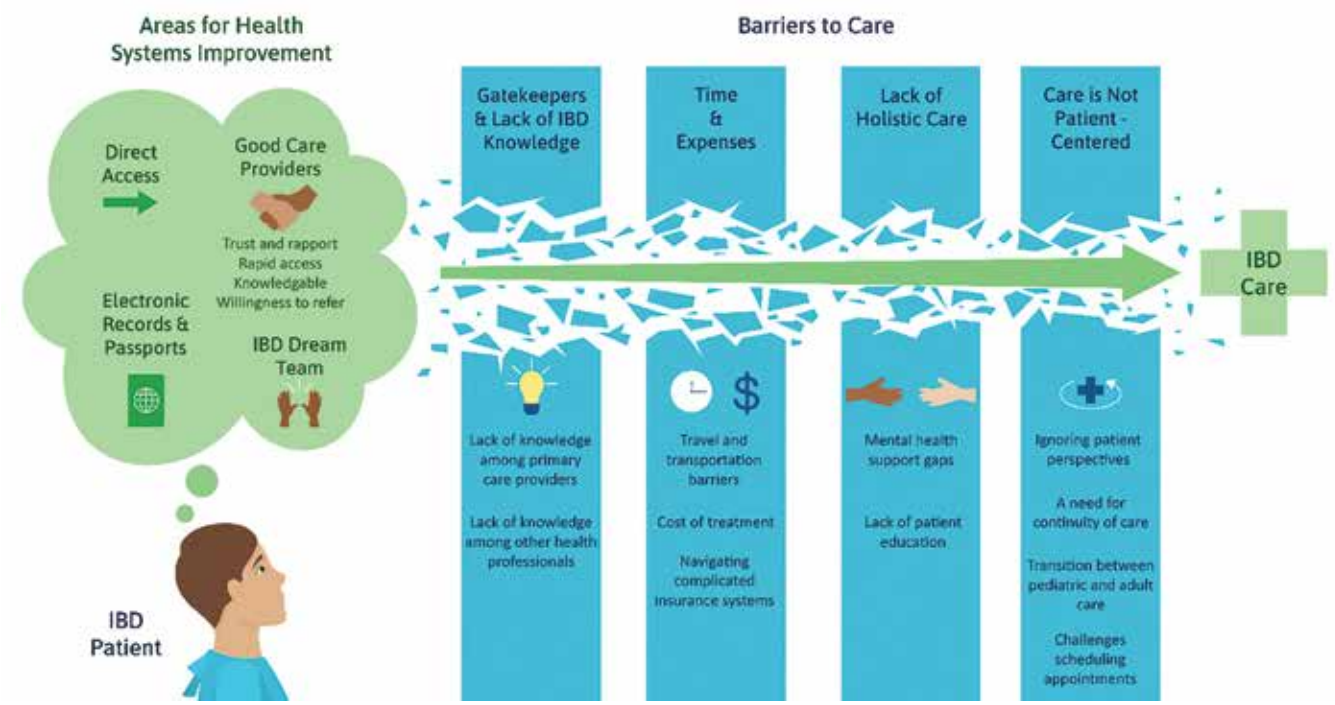


Figure 1. *Patient-identified barriers to IBD care in Canada*

centeredness—a principle that has been at the forefront of IBD health services research in Canada.[20-23] Patient-oriented research has established that individuals with IBD and other stakeholders are dissatisfied with existing access to specialty IBD care and to allied health professionals (Figure 1). Key barriers to access include wait times, limited access to mental health care that is responsive to the needs of the individual, limited coordination of care, costs, and geographic variation in access to specialty care.[21, 24-26] Specific subpopulations, such as pediatric and elderly populations and those residing in rural areas, may face additional barriers to access.[5, 6, 23, 27, 28] When access to specialty care is limited, many individuals with IBD access the emergency department (ED); however, the appropriateness of care received in the ED can be inadequate.[29, 30] ED utilization is also costly to healthcare systems and efforts have been made to direct people with IBD to other points of care using clinical care pathways.[30]

Addressing access to high quality care is important. Improving quality of care also requires addressing barriers that prohibit the uptake of evidence-based practices and guidelines, including geographic variation in care, limited time and resources, limited data collection, and provider knowledge.[12, 31, 32] Some programs have developed and implemented interventions, including novel technology,[17, 33-36] IBD nursing roles,[17, 37] clinic certifications,[33] and open access clinics.[38] Further development and adaptation of these patient-oriented, healthcare delivery models in Canadian and regional contexts may support improvements in the quality of care provided to individuals living with IBD. Improving access to patient-centered, integrated interprofessional care delivery models as well as comprehensive and consistent disease monitoring and treatment strategies is critical; they can be achieved, in part, by leveraging innovations in models of care delivery and eHealth.

Integrated Collaborative Models of Care

Inter-professional and integrated care delivery models that facilitate high-quality care addressing the biopsychosocial needs of people living with IBD are needed. Integrated models of care (IMC) offer a solution to the fragmented and single-system focus of traditional healthcare delivery.[39-41] Globally, IMCs have been implemented for the care of individuals with IBD.[42-45]

Integrated care brings together "inputs, delivery, management, and organization of services related to diagnosis, treatment, care, rehabilitation, and health promotion to improve access, quality, user satisfaction, and efficiency."[46] Approaches to developing IMCs are supported by multiple guidelines, quality standards, and expert opinion,[43, 47-49] as well as mounting evidence of the positive impact of IMCs on individuals and health systems.[44, 45, 50-52]

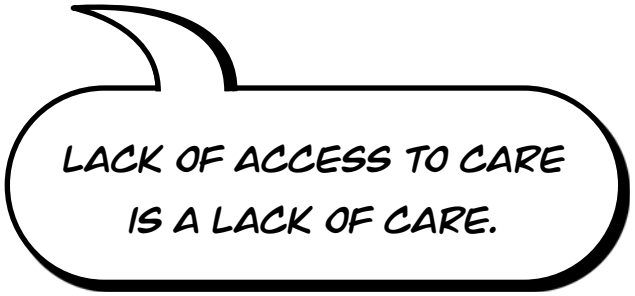
An IMC involves a multidisciplinary team (MDT) of healthcare professionals working together to deliver comprehensive care to individuals. Gastroenterologist-led MDTs are more effective than the traditional patient-specialist model of care.[45, 52-54] Although robust evidence is lacking in defining MDT membership in the context of IBD, guidelines provide some framework including identifying core and ancillary members.[13, 16, 47, 55, 56] Core individuals for IBD-specific IMCs include nurses,[13-15, 37, 44, 45, 47, 55-78] mental health care providers such as psychologists and psychiatrists,[36, 44, 56-58, 60, 65, 66, 69-71, 73, 77, 79-83] dietitians,[15, 37, 44, 47, 55, 56, 58, 60, 62, 69-71, 73, 75, 77, 78] and social workers.[56, 58, 60, 65, 69, 70, 73] Pathologists, radiologists, and pharmacists with a special interest in IBD have also been suggested as core members of an IMC.[47] Ancillary members may also include a rheumatologist, ophthalmologist, hepatologist, dermatologist, pediatric IBD care team, obstetrician, and physiotherapist.[36, 47, 55, 56] At minimum, an IMC team should involve a gastroenterologist lead, a colorectal surgeon, an

IBD nurse specialist, a dietitian, and a psychologist or a mental health counsellor. There is little research on best practices for the delivery of IMC, outside of the importance of an MDT; however, one literature review suggests that delivery through standard IBD specialty clinics and virtual care are most common.[84]

IMCs are focused on person-centered care, timely access to care, disease education, interprofessional collaboration and communication, and biopsychosocial factors affecting individuals with IBD, with the ultimate goal of optimizing IBD care. Improving individuals' satisfaction as well as health and population outcomes, while also decreasing costs associated with IBD healthcare is central to IMC program development.[45] A prospective cohort study conducted in Australia reported that implementing a formal gastroenterologist-led IBD service reduced hospital admissions, lowering healthcare utilization and costs associated with inpatient care.[85] However, costs associated with outpatient services were not measured in that study. A Canadian study from Saskatchewan comparing outcomes between individuals with an IMC and those without an IMC demonstrated that individuals with an IMC had a lower risk of IBD-related surgeries, and (for individuals with ulcerative colitis) a lower risk of IBD-related hospitalizations and corticosteroid dependence.[44] Perioperative IBD care provided by an MDT was found to provide greater diagnostic accuracy, decreased frequency of elective surgery, decreased disease recurrence, and greater albumin and hemoglobin levels in the blood.[78] A multidisciplinary approach is also recommended for people with IBD who have additional immune-mediated inflammatory diseases such as spondylarthritis, psoriasis, psoriatic arthritis, or uveitis to allow for a more comprehensive evaluation and treatment approach.[74]

The high rate of co-occurring anxiety and depression among people living with IBD is well documented.[86] Untreated mental health disorders have been associated with poor IBD outcomes including more severe IBD symptoms and more frequent flares,[87, 88] poor medication adherence,[89] higher hospitalization rates,[90] and increased healthcare costs;[91] therefore, a psychologist or counsellor should be embedded as a core member of the MDT.[45, 47, 53, 54] Additionally, experts and people living with IBD recommend that a psychological assessment be performed for each individual with IBD, rather than just those expressing mental health concerns.[42] When needed, IBD specialists should initiate referrals to psychology or have psychotherapists as integrated members of the MDT. IMCs that include regular psychological assessments and management of mental health concerns are associated with decreased anxiety, depression, general distress, healthcare resource use, opioid and corticosteroid use, as well as improved quality of life.[60, 66, 92] However, cost and limited access to psychologists who have expertise in IBD are barriers experienced by individuals with IBD when trying to access this needed care.[79] Additional information on mental health and IBD is provided in Chapter 8.

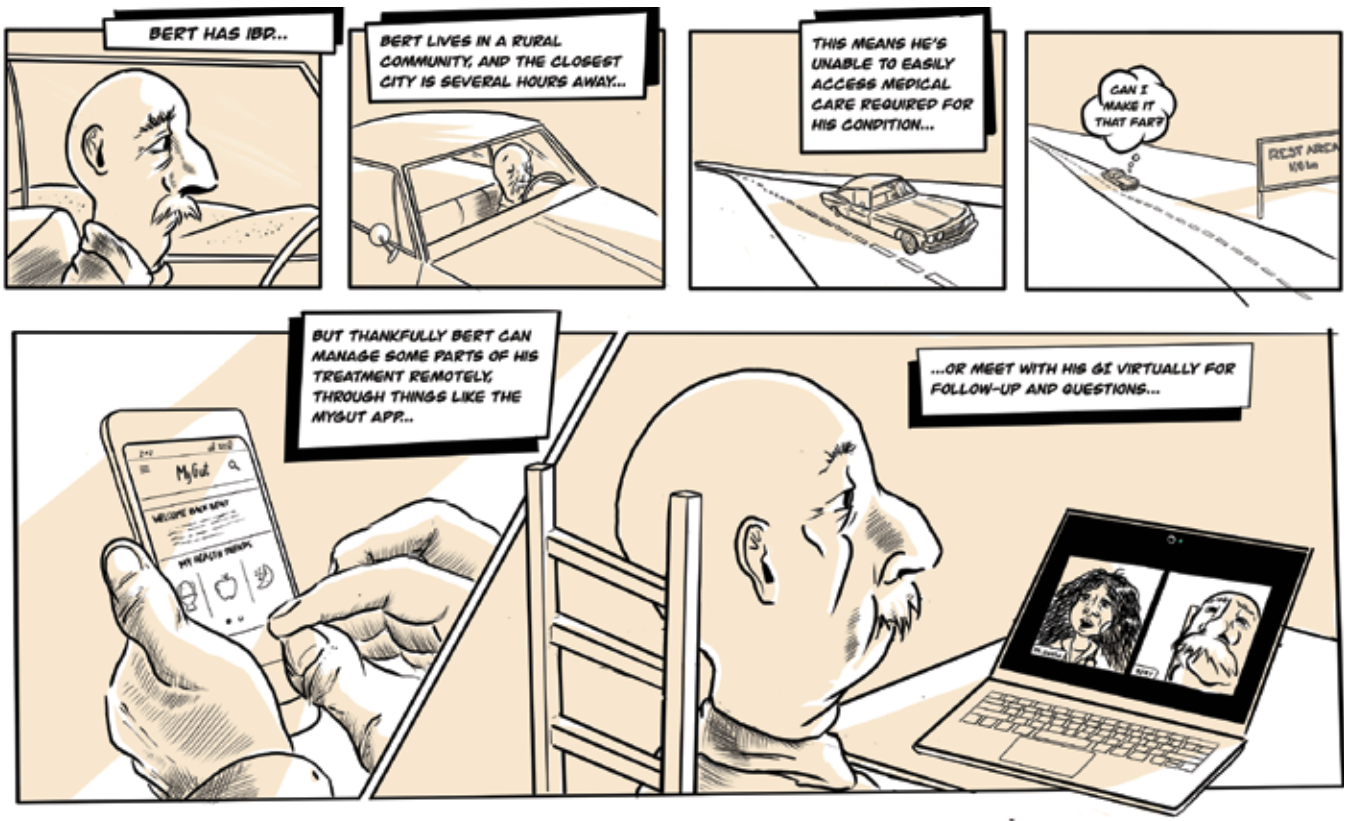
There is limited research about the perception of and satisfaction with IMCs by individuals living with IBD and by healthcare providers.[45] Joint provider clinics with a gastroenterologist and surgeon have been seen as satisfactory by individuals because of: decreased anxiety about their IBD, consistent provider communication, and decreased numbers of appointments and trips to hospital.[64] Many people with IBD do not have access to IMCs,[93] and those who do not have access often feel like they have an unmet healthcare need.[11]



Although the benefits of an IMC are now well recognized, several barriers to implementing this care model exist. Mikocka-Walus *et al.* conducted a multi-national mixed-methods study that included 135 health professionals caring for people with IBD to examine models of care in IBD, including patient-reported barriers to establishing an ideal IBD service.[42] The greatest patient-reported barrier was related to short and long-term funding (51%), followed by respondent perception that healthcare systems are not conducive to multidisciplinary care (14%).[42, 45]

eHealth

The COVID-19 pandemic has brought the importance of virtual healthcare (VC) to the forefront as a viable care delivery strategy for improving access to care. Defined as "an interaction between patients and their healthcare providers that occurs remotely,"[94] VC can take place through a variety of communication and technological formats. It can occur synchronously in which both individual and provider are present at the same time with real-time interaction between both parties—typically occurring through video conference or telephone. Conversely, asynchronous VC refers to an interaction that occurs and adopts an offline store-and-forward approach. Store-and-forward refers to collecting information that is sent to and assessed by health professionals outside of real-time consultations.



Examples include secure emailing or messaging functions that are integrated with electronic medical record systems.

During the COVID-19 pandemic, most people living with IBD gained exposure to VC.[95] A survey by the Canadian Medical Association suggests that individuals were satisfied with VC.[96] Nationwide focus groups consisting of people with IBD offered insight into how they experienced VC.[97] Telephone-based services were most common, but many felt videoconferencing would have improved the interaction. Individuals with IBD identified VC as convenient and feel that it saved them time, especially for short visits. VC visits were especially appealing for those who lived in more remote regions or far from an IBD centre. The main concern about VC expressed by focus group participants was that it may completely replace in-person care. Most participants felt a balance and choice among in-person, video, and phone visits was ideal. Some participants expressed concerns that technology was a potential barrier to accessing VC, especially video-based visits, and emphasized the importance of paying attention to eHealth equity considerations and flexibility of the modality. There is very little guidance in the current literature on how to implement VC for people with IBD that supports equity and patient-centredness, such as how to balance the mode of delivery and potential barriers to access; this is a key knowledge gap that has been identified in research on other health issues.[98] A study in the Netherlands developed a comprehensive eHealth implementation guide for healthcare providers and people with chronic myeloid leukemia.[99] The guide was co-designed through stakeholder focus groups and interviews to identify key individual, socioeconomic, political, and organizational barriers to eHealth implementation. The co-design of VC implementation guidelines, as well as greater research on key equity issues, could benefit the uptake and accessibility of VC among people with IBD and healthcare providers in Canada.

The adoption of synchronous and asynchronous VC options has had a significant impact on the delivery of IBD care. VC improves access to and communication with physicians, nurses, and other allied healthcare providers.[100] Many individuals with IBD and physicians recognize VC modalities as acceptable, feasible, and have expressed their willingness to use these in the future.[101] Increases in healthcare delivery through eHealth platforms has transformed IBD clinical practice patterns. In contrast to the traditional model of in-person care, eHealth can track individuals' disease activity, medical therapy, and mental health in real time. eHealth can support IBD clinical decision-making through algorithms integrated into electronic medical records allowing for more rapid and timely interventions when managing disease, flares, or mental health concerns.[102] Enhanced engagement can also be facilitated by eHealth modalities. Individuals can self-report symptoms or use virtual patient reported outcomes (PROs) systems to track their disease.[103] eHealth platforms can facilitate remote monitoring of objective disease measures, such as fecal calprotectin (FCal), which may allow for early detection of IBD flares through point of care assessment via home-based tests that are relayed to and acted upon by the healthcare team.[104]

Access to eHealth may also support improved access to specialty care and cost savings for both healthcare systems and individuals with IBD. Several studies have evaluated whether eHealth-facilitated IBD management can improve clinical outcomes. Generally, both individuals with IBD and healthcare providers in Canada have reported that eHealth improves access to specialty care, particularly in underserviced communities.[105]

ACCESSING CARE IS A HUGE CHALLENGE NOT ONLY FOR THOSE WITH IBD, BUT ALSO THOSE AWAITING A DIAGNOSIS OF IBD. HAVING AN INTEGRATED COLLABORATIVE MODEL OF CARE WITH AN INTERDISCIPLINARY TEAM WOULD BE A STEP FORWARD IN IBD CARE. GIVING PATIENTS HELP TO NAVIGATE THE MEDICAL SYSTEM, AND HELP PATIENTS FEEL SEEN AND HEARD BY THEIR TEAM.

Reduction in healthcare utilization—in particular, fewer outpatient visits—has consistently been reported in association with eHealth modalities.[106-108] However, the impact of eHealth facilitated care delivery on IBD-related hospitalizations and ED visits is less clear.[106, 109-111] eHealth tools (e.g., digital applications) may help screen for depression and anxiety helping prioritize individuals who need prompt psychosocial support; however, there is varying evidence that VC can reduce psychological distress [108, 112] or improve quality of life.[107] Some older studies have found an improvement in adherence to medical therapy, perhaps due to enhanced communication with healthcare providers. However, more recent systematic reviews and a meta-analysis found no benefit of VC on treatment adherence.[107, 113] Direct and indirect healthcare cost savings have also been observed in association with eHealth technologies.[107, 114, 115] A three-year follow-up Danish register-based study found that although there was a significantly higher cost to enrolling a person with IBD in eHealth compared to standard care (€2,949 vs. €1,621); by year four, eHealth costs became cost neutral or cost-saving to the healthcare system.[104] There are also anticipated savings for individuals who may save money by reducing or eliminating travel to in-person appointments (see Chapter 3 for more information on indirect and out-of-pocket costs).[104] Although data on the favourable impact of eHealth is promising, there remain inconsistent findings in the literature, highlighting the need for ongoing research relating to eHealth modalities for IBD management.

Limited resources for the set up and maintenance of eHealth platforms and user (both individuals with IBD and care providers) accessibility and familiarity remain barriers to equitable access to eHealth. The future of IBD care delivery will likely include a hybrid of both in-person and virtual care. eHealth delivery will continue to evolve and adapt to the needs of individuals and their healthcare providers and is bound to remain an integral part of the IBD care model moving forward.

Disease Monitoring

The Selecting Therapeutic Targets in IBD (STRIDE-II) guidelines recommend both endoscopic healing and clinical remission, defined by symptomatic relief and improved quality of life.[116] Participation and shared decision making are key when defining treatment goals and monitoring the disease course for a condition that is chronically relapsing and remitting like IBD.[117] For example, although ileocolonoscopy is the gold standard for objective disease monitoring, it is invasive and resource intensive, requires individuals to miss work or school, and requires a purging preparation and sedation, making it the least preferred test for individuals with IBD.[118] Access to frequent endoscopic evaluation in many centers in Canada is also limited, particularly in the pandemic recovery period.[119] An individual's engagement and participation in decisions around need can improve acceptance of endoscopy.[117]

Non-invasive alternatives for endoscopic activity are routinely used in clinical practice to detect inflammation.[120, 121] The most widely used biomarkers include blood-based C-reactive protein and stool-based FCal.[122] Although easily repeated for routine monitoring, both tests are non-specific. Levels can be elevated when a person has an infection or with other sources of inflammation (e.g, diverticulitis), do not reflect disease location nor disease extent, and cannot exclude IBD related complications.[122, 123] There is some intra-individual variability in measures of FCal, in addition to falsely elevated measures with commonly used over-the-counter medications such as non-steroidal anti-inflammatory medications.[124, 125] Despite these limitations, interval monitoring of biomarkers to objectively detect inflammation beyond symptom control has been shown to improve outcomes and is central to a treat-to-target strategy in IBD.[116, 126]

Due to limitations of ileocolonoscopy when assessing small bowel inflammation and disease processes due to strictures in Crohn's disease, additional modalities are often needed to fully gauge disease and complications. Therefore, current guidelines recommend baseline and interval evaluation with cross-sectional imaging, preferably safe, radiation free options such as magnetic resonance enterography (MRE) or intestinal ultrasound (IUS).[127] Although ulcerative colitis has been historically viewed as limited to the mucosa, cross-sectional imaging evidence in acute moderate-to-severe disease states also demonstrates involvement beyond the mucosa, with the submucosa and surrounding mesentery affected.[128] Given the presence of significant disease in IBD beyond the endoscopically visible mucosa, the concepts of transmural response and remission have developed as important treatment targets.[129] Transmural healing is associated with significant reduction in adverse outcomes including corticosteroid use, hospitalization, and surgery.[130, 131]

Access to routine, interval MRE in Canada is challenging due to long wait times resulting in separation between clinical assessment and imaging assessment of disease activity.[132] Prior to the COVID-19 pandemic, wait times for medical imaging in most Canadian provinces exceeded the recognized standard of 30 days. As of 2022, it is estimated that most Canadians will wait between 67–130 days for medical imaging, depending on the test. Long wait times for medical imaging are linked to limited imaging equipment, few trained technicians, and low government investment.[132] MRE requires intravenous and oral contrast. Many individuals prefer to have IUS to monitor their IBD when given the option.[118, 133] IUS has several advantages over MRE, as it can be performed during routine assessment at follow-up in clinic, requires no oral or routine intravenous preparation

nor medication (such as motility agents common during MRE), and presents an opportunity for engagement and education.[134] Importantly, mounting evidence supports the accuracy of IUS for detecting both disease activity and complications, when compared to accepted reference standards, including endoscopy and MRE.[135-139] In addition, changes in key sonographic parameters can be followed over time, demonstrating responsiveness of IUS to effective medical therapy.[128, 140]

There is rising interest in IBD-focused expert provision of IUS to effectively monitor individuals by both providers and individuals with IBD. The International Bowel Ultrasound Group developed an accredited training program, endorsed by the European Crohn's and Colitis Organization (https://ibus-group.org/). The provision of IUS in Canada is expanding annually, with at least eight expert adult and five pediatric centers currently performing routine IUS for monitoring purposes. IUS provides a person-centered innovation in a treat-to-target monitoring paradigm. Here cross-sectional imaging data (combined with standard bedside assessment, including biomarkers, ileocolonoscopy when indicated, and complementary cross-sectional imaging) contributes to clinical decisions in real time.[134, 141-143] This paradigm allows for the timely, appropriate optimization of medical therapy, avoidance of unnecessary corticosteroid use and investigations, in addition to improved individual experience.[134, 141-143] The future of IBD monitoring will likely include multiple monitoring approaches including PROs, quality of life, IUS and alternate imaging modalities and biomarkers, with interval ileocolonoscopy where needed. Monitoring strategies need to be person-centered to ensure reduction of disease burden, damage, and long-term disability.

Although IUS presents a novel, innovative, person-centered approach to effectively monitor individuals with IBD, there are several current barriers to widespread adoption and implementation across Canada. The technology required (high end ultrasound machine with specialized transducers) imparts costs beyond normal costs associated with maintenance and upkeep. These high-quality ultrasound machines are not a usual constituent of IBD-expert clinics in Canada. Moreover, acquisition of IUS expertise and training presents a challenge, with few supports and limited opportunities to acquire adequate training. Finally, system challenges including the lack of provider remuneration for IUS is a barrier to inclusion in busy, high throughput clinics where time constraints limit adoption. This innovation is disruptive and will require advocacy for change to optimize individuals' experience with IBD monitoring.

Conclusion

The rising number of people living with IBD in Canada has underscored the importance of timely and equitable access to speciality care and allied health professionals through IMCs. Improved access to care is associated with better health outcomes, yet there remains variation in access and quality of care across Canada. Implementing and evaluating standardized quality care indicators in clinical practice, such as the PACE clinical care pathways, may support access to care and improve health outcomes. Key focus areas include the implementation of IMCs and leveraging innovative eHealth platforms to support enhanced communication, implementation of evidence-based care, and multiple disease monitoring approaches that center around the individuals' quality of life and supports individual decision-making and outcomes.

Limitations in uptake and implementation of evidence-based clinical care guidelines and structural challenges, including system design and limited funding, highlight just a few of the behavioral and environmental barriers to high quality care. Moving forward, attention must focus on leveraging innovative eHealth technology and models of care to improve equitable, person-centered access to and delivery of evidence-based care. Potential interventions to address specific barriers to access experienced by subpopulations, such as pediatrics and those in rural areas, must also be further explored.

Knowledge Gaps & Future Research Directions

1. There is limited knowledge on the diverse lived experiences of IBD and access to services from many sub-populations, including those living in rural, remote, and Northern communities; transgender and gender diverse individuals; Indigenous peoples; and other equity-deserving groups.

2. Many individuals continue to utilize emergency departments as a point of care access to IBD care; however, there is limited knowledge on whether some sub-populations have greater reliance on emergency departments and how to support their care needs.

3. Person-oriented healthcare delivery interventions should also be evaluated for effectiveness in facilitating access to IBD care for sub-populations.

4. Next steps should involve addressing barriers to consistent physician uptake of clinical guidelines and further developing and adapting person-oriented healthcare delivery interventions (virtual and in-person) specific to Canada to support access.

5. Virtual healthcare should evolve and adapt to the needs of the provider and to the needs of the individuals it is servicing.

Patient & Caregiver Partner Perspective

Access to healthcare for individuals with IBD is reconceptualized as a multi-faceted experience that incorporates person-centered considerations. Patient partners recognize that barriers to accessing care remain, including lengthy wait times, limited access to mental health care, limited coordination of care, out of pocket costs, and geographic challenges. Improved access to quality medical care, including early diagnosis and treatment options for those living with IBD are encouraged. Patient partners frequently experience communication gaps between healthcare providers, such as challenges with connecting to dietitians and mental health supports, and they recognize that IBD related care is often siloed. Integrated, multidisciplinary, collaborative models of care can improve communication with and between healthcare providers, enhance access to care, and address the biopsychosocial needs of individuals living with IBD. Virtual care delivery is welcomed by patient partners as a strategy to enhance access to care and can result in a reduction in healthcare utilization, direct and indirect healthcare cost savings, and improved quality of life for persons living with IBD. An individualized, hybrid (in person and virtual) care delivery approach is deemed as ideal by patient partners. eHealth platforms can increase individuals' engagement in their care, enhance remote monitoring, and improve communication between individuals living with IBD and healthcare providers.

Policy Implications & Key Advocacy Outcomes

1. Increased government funds should be invested in interventions that improve access to care (e.g., increased staffing in under-resourced areas, augmented psychosocial supports, eHealth supports, patient navigator, peer support).

2. Universal healthcare coverage should be expanded to include out-of-pocket treatment expenses that limit access to care.

3. Quality improvement initiatives (e.g., PACE) should be embedded in institutional policies and practices to support standardized quality care regardless of geographic locale.

4. Crohn's and Colitis Canada should advocate for improved access to care for all individuals with IBD, but particularly for equity-deserving populations who face the greatest number of barriers to care, such as Indigenous peoples. Different care pathways should be developed to address the specific care needs of different sub-populations.

5. Crohn's and Colitis Canada should advocate for increased education of IBD in medical school curricula and as part of ongoing professional development for physicians and healthcare professionals.

6. Advocacy for access to care should incorporate policies that support quality of life for people living with IBD (e.g., accommodations/supports in the workplace and school, public restroom access).

7. Governments must continue to support virtual care, including telemedicine and video appointments, to enable care to remote populations or those who cannot physically travel to specialist clinics.

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