2018

IMPACT OF INFLAMMATORY BOWEL DISEASE IN CANADA

Crohn's and Colitis Canada
Crohn et Colite Canada

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CANGIEC
CANADIAN GASTRO-INTESTINAL EPIDEMIOLOGY CONSORTIUM

Foreword

It's no secret that Canada has one of the highest rates of inflammatory bowel disease in the world. While that fact in itself has much meaning, what's imperative is knowing just how Crohn's disease and ulcerative colitis affect individuals, and our country as a whole.

In 2012, we released our Impact of Inflammatory Bowel Disease in Canada report. In the six years that have followed, researchers have uncovered new findings about the disease, about the people who are living with it, and how Canada can take strides to better care for those affected. Those discoveries are presented here in our updated 2018 report, which serves as a comprehensive, data-laden resource about the impact Crohn's disease and ulcerative colitis have across the country.

We're grateful to Drs Gil Kaplan and Eric Benchimol, who led the creation of the 2018 report. They drew upon the nation's best scientific minds to amass a wealth of Canadian statistics, giving the report a clear Canadian focus that puts patients at the heart of recommendations on research and care. This is a report from the scientific community to Crohn's and Colitis Canada, and the information and recommendations put forth by its authors will inform our perspectives and positions.

From the impact of inflammatory bowel disease on children, to its impact on seniors, to its impact on our economy, there is much to learn within these pages. And for Crohn's and Colitis Canada, there is much information in this report to utilize as we continue to raise awareness, create understanding, advance research, and advocate for policy changes.

Our sincere thanks to everyone who had a hand in creating this essential report.

Mina Mawani
CEO, Crohn's and Colitis Canada

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REFERENCES

Glossary

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

- **ANKYLOSING SPONDYLITIS:** A chronic inflammatory disease of the spine.

- **CHOLANGIOCARCINOMA:** Cancer in the bile ducts.

- **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. Direct cost calculations can take the perspective of the public payer (*i.e.,* government-covered drugs and services) or all third-party payers (*i.e.,* government, private insurers, and other health plans).

- **DISABILITY:** Chronic limitations that hinder the ability to engage in usual daily activities.

- **DIZYGOTIC:** Twins who developed from two different eggs with each egg fertilized by its own sperm ("fraternal").

- **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.

- **GENOME-WIDE ASSOCIATION STUDIES (GWAS):** A study which examines the entire genetic structure (DNA) of a large number of people to determine genetic variants which may be associated with a trait or disease.

- **HAZARD RATIO:** This ratio is used in survival analysis. It measures the hazard rates or likelihood related to whatever condition is being measured among those exposed versus those not exposed to the condition.

- **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.

- **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.

- **IMMUNE-MEDIATED INFLAMMATORY DISEASES (IMID):** Chronic diseases in any organ system thought to involve unchecked inflammation secondary to a turned on immune system.

- **INCIDENCE:** The number of new diagnoses of 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.

- **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, lost productivity of caregivers, and out-of-pocket costs.

- **INDUCTION THERAPY:** Treatment for IBD aimed at reducing or eliminating active inflammation, healing the bowel, and putting the disease into remission.

- **IRITIS:** Chronic or recurrent inflammatory disease of the iris a layer in the eye.

- **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.

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

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

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

- **MONOZYGOTIC:** Twins who developed from one zygote (the combination of a single egg and one sperm) that splits to form two embryos ("identical").

- **MYELOSUPPRESSION:** A condition in which bone marrow activity is decreased, resulting in fewer blood cells (red and white) and platelets being produced.

- **NEWLY INDUSTRIALIZED COUNTRIES:** Countries who have experienced economic advancement leading to a societal shift towards industrialization and urbanization.

- **ODDS RATIO:** Represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure.

- **PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS):** Valid and reliable measures which have been developed to cover a number of subjects, such as quality of life, mental health scales (*i.e.,* depression, anxiety), stress, etc.

- **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).

- **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 RATIO:** The proportion with prevalent disease (disease being identified at any point in time) among those exposed to any variable.

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

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

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

- **WESTERN WORLD:** Western Europe and countries in North America and Oceania that were colonized by Western Europeans.

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

EXECUTIVE SUMMARY

Executive Summary

Inflammatory bowel disease (IBD) is a group of disorders that causes sections of the gastrointestinal tract to become severely inflamed and ulcerated.[1] An abnormal response of the body's immune system plays a role in each of the two main forms of IBD: Crohn's disease and ulcerative colitis. In the absence of a cure, current therapies are directed at inducing and maintaining remission.[2,3] Most people afflicted with IBD require ongoing medication. When this fails, surgery is often required.[4,5] These are lifelong diseases, usually starting in adolescence or early adulthood in otherwise healthy, active individuals. Crohn's disease and ulcerative colitis also occur in children, and IBD is increasingly being diagnosed in very young children (under five years of age).[6] IBD severely impacts quality of life through ongoing and debilitating symptoms, reduction in the ability to work, social stigma, management of washroom access issues, challenges with physical intimacy, and restrictions in career choices.[7,8]

IBD in Canada

Canada has among the highest reported prevalence (total number of afflicted people) and incidence (number of new cases per year) rates of IBD in the world.[9-11] In 2018, approximately 270,000 Canadians are living with IBD: 135,000 individuals with Crohn's disease,120,000 with ulcerative colitis, and 15,000 with IBD type unclassified (IBD-U).[12] Currently, seven out of every 1,000 Canadians has IBD.[12] By 2030, the number of people living with IBD is expected to rise to over 400,000, or approximately 1% of the population.[12]

The highest reported incidence of IBD is in Nova Scotia at 54.6 per 100,000 new cases per year,[13]and the lowest is in British Columbia at 18.7 per 100,000 people per year.[16] The incidence of IBD in Alberta, Manitoba, Ontario, Quebec, and Saskatchewan are similar, ranging from 21.6 to 28.3 per 100,000 people per year.[14-17]

IBD can be diagnosed at any age but has a typical age of onset in adolescence or early adulthood.[18] Because of this, IBD often affects Canadians during critical years of schooling and career growth.[18] IBD in Canada impacts the lives of all ethnicities and religions.[19] However, the rate of new diagnoses of IBD is higher among those of Ashkenazi Jewish and South Asians, and lower among those of East Asian descent.[19,20]

People with Crohn's disease face a significantly elevated risk of premature death compared to the general public,[21] and people with IBD face a higher risk of bowel cancer.[22] The risk of several extra-intestinal diseases, such as osteoporosis, liver disease, venous thromboembolism, and cardiovascular disease, is high in patients with IBD.[23,24] Moreover, many people with IBD are co-diagnosed with one or more immune mediated

inflammatory diseases, such as iritis, ankylosing spondylitis, or primary sclerosing cholangitis.[23,24] IBD is more than twice as common as multiple sclerosis or Parkinson's disease; about as common as Type 1 diabetes or epilepsy; and, slightly less common than rheumatoid arthritis and psoriasis.[25-27] Consequently, with the exponentially rising number of Canadians with IBD, health policy makers will need to prepare our healthcare system for the rising burden of IBD.[11]

Rising Rates of IBD in Canadian Children

There are over 7,000 children under the age of 18 years living in Canada with IBD, and the prevalence of IBD in children has risen more than 50% in the last 15 years.[14,28,29] The rate of new diagnoses of IBD in children is rising rapidly: in particular, the number of newly diagnosed children under five years old rose by 7.2% per year between 1999 and 2008, and this rate is expected to continue rising due to improved recognition, greater availability of pediatric IBD specialists, and potentially, changes to the environment.[14,28,29] Children with IBD experience different complications, respond differently to treatments, and are at greater risk for some medication side effects when compared to adults.[30-32] Children with IBD also incur greater costs of treatment than their adult counterparts due to more severe disease course and more frequent health visits.[33,34] Moreover, the effects of having a chronic disease can affect the entire family and other caregivers.[35,36]

Seniors with IBD: The Fastest Growing Group

The Canadian healthcare system must be prepared for a rising number of senior patients living with IBD.[14] Seniors with IBD are the fastest growing group of people living with IBD, which will present a challenge to patients, families, and care providers.[14] The rising prevalence of IBD in seniors is the result of new diagnoses made in this population as well as the advancing age of previously diagnosed patients with IBD who carry the disease with them for the rest of their lives.[37,38] Seniors with IBD face complications of longer disease duration and the challenge of caring for age-related comorbid conditions such as diabetes and cardiovascular disease.[37,38] Therapeutic interventions need to balance the goal of clinical remission against the increased susceptibility to complications of the medications faced by seniors.[39-41] Accordingly, IBD healthcare providers must be prepared to work in multidisciplinary teams with other specialists in order to optimize IBD management in the context of the unique challenges faced by seniors with IBD.[38]

Quality of Life (QOL) for People with IBD

IBD often affects individuals in adolescence and early adulthood, at a time when they are pursuing employment, building their family, and reaching key milestones.[7,42] The impact of IBD on QOL is multifaceted, from direct physical impairment due to symptoms like diarrhea and abdominal pain, to financial burdens associated with healthcare encounters, to psychological distress stemming from factors such as symptoms, distorted perception of body image, fear of sexual inadequacy, social isolation, fear of dependency, concern about not reaching one's full potential, and fear of stigmatization.[8,43,44] Even patients in remission frequently experience psychological distress.[42-45] IBD affects QOL of the family unit as well, as stress on immediate family members is commonly experienced.[35,36] Mitigating the burden of QOL faced by people with IBD requires transdisciplinary care, including mental healthcare providers who can work with patients to develop adaptive coping mechanisms that help manage illness perceptions and reduce psychological distress.[46,47]

Challenges Facing Patients with IBD

In addition to the tremendous impact that IBD has on QOL, people living with IBD face a myriad of other challenges. These include prolonged symptoms due to late or inappropriate diagnosis, social stigma of having a chronic disease that affects toileting habits, difficulty with excursions due to limited or uncertain access to bathroom facilities, affordability of medications, diminished employment prospects, limited community-based supports, and inequitable access to healthcare services and specialists.[48-50] Reducing these inequities should be a priority for physicians and policy makers to improve QOL and productivity of IBD patients in society. Of particular note is the issue of equal access to care across Canada. Patients cared for by gastroenterologists have better outcomes, including lower risk of surgery and hospitalization.[49,51] Canadians with IBD who live in rural and underserviced areas are less likely to be cared for by gastroenterologists.[52] Improving timely access to gastroenterologist care may reduce the risks of requiring surgery and emergency care among patients with IBD.[49,51,52] Reducing variation in care for patients with IBD should focus on timely diagnosis of IBD and regular follow-up of patients with IBD with gastroenterologists.

Economic Costs of IBD

The health economic impact of IBD in Canada is high. Economic costs for IBD are conservatively estimated at $2.6 billion in Canada in 2018. Direct medical costs are approximately $1.28 billion, dominated by costs of prescription drugs and hospitalizations.[53,54] There is a steady shift towards pharmaceuticals being the predominant driver of direct costs in IBD patients, due to the introduction and widespread use of effective, yet expensive, biological therapies.[55-57] The introduction and gradual penetration of biosimilar agents at a lower price point than their originator counterparts could mitigate escalating costs of IBD care in coming years. However, increasing use of biologics overall alongside a growing IBD prevalence may still dominate the cost impact for years to come.[11]

The high direct cost of treating IBD is compounded by the high indirect costs of illness, including loss of economic productivity of patients and their caregivers and out-of-pocket expenses.[58] The indirect health-related costs attributable to IBD are estimated to be $1.29 billion annually in 2018. Indirect costs are dominated by productivity losses, particularly premature retirement ($629 million CAD in permanent lost wages accrued annually). Other factors include medical absenteeism ($88 million CAD annually), premature death ($34 million CAD annually), and out-of-pocket expenses ($541 million CAD annually).[58-60] Importantly, other factors that may contribute substantially to indirect costs, such as costs related to presenteeism, reduced professional development and lost caregiver productivity, are not accounted for in the overall estimate due to limited data and should be a focus of future studies in IBD patients.[58-60]

Recommendations

Adults and children living with IBD face a number of critical challenges. The personal and fiscal burden that IBD places on individuals, the healthcare system, and society is significant and will become more problematic as the number of patients with IBD increases. We provide the following recommendations to address the burden of IBD in Canada:

1. Increase funding for research into preventing and treating IBD and to address the physical, psychological, and social issues caused by IBD;
2. Introduce greater public and private investment in IBD research and commercialization strategies so as to expedite translation of academic-based research discoveries into clinical applications in humans;
3. Improve recognition and funding for research into special populations of people with IBD, including children, seniors, and pregnant women;
4. Recognize IBD is a national health priority and increased resource allocation for chronic care models that reflect the episodic nature of IBD to optimize healthcare delivery to this population. This is the responsibility of the federal government;
5. Enact a national public health campaign and patient education programs to raise awareness and knowledge among the general public and healthcare professionals in order to facilitate earlier diagnosis and reduce social stigma associated with IBD; leadership for such a campaign could come from Crohn's and Colitis Canada;
6. Introduce public and private sector programs (including laws) that foster open access to washroom facilities for people with IBD or incontinence;
7. Ensure timely and appropriate access to gastrointestinal specialists, allied healthcare professionals, endoscopy, and radiology services for those who are waiting for diagnosis or treatment of IBD, particularly in rural and underserviced areas;
8. Enhance and harmonize public and private drug plans so that patients with IBD—no matter where they live in Canada, their age or their socio-economic status—have equal and better access to medically-prescribed pharmaceuticals that improve a patient's health and quality of life;
9. Improve drug review processes reflecting the latest research and best practices so that therapies of benefit to people with IBD are approved and available more quickly;
10. Introduce appropriate income security measures and employee assistance programs that offer support for chronic disease patients.

To improve the current IBD care and awareness in Canada, Crohn's and Colitis Canada must advocate to government, media, the general public, and other key stakeholders to move these recommendations forward.

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INTRODUCTION

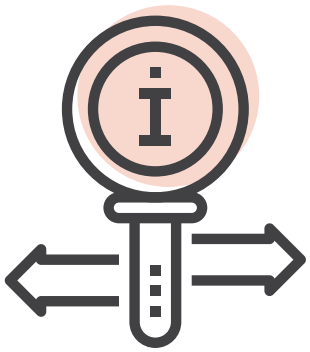
1.0 Background

Inflammatory bowel disease (IBD) is the name of a group of disorders that cause the intestines to become inflamed (red and swollen). The main forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). IBD has a tremendous impact on quality of life due to a host of devastating symptoms. In the broader community and among the families and coworkers of people with IBD, there is sometimes a lack of understanding of the disease and the intimate nature of symptoms. IBD usually starts in adolescence or early adulthood (but may occur at any age) and is a lifelong disease. Although most people with IBD can lead full, productive lives with the use of medications and surgery, there is currently no cure for IBD.

Crohn's and Colitis Canada was established with a twofold purpose. First, Crohn's and Colitis Canada believes cures will be found for IBD and is committed to raising funds for research. Second, Crohn's and Colitis Canada believes it is important to educate all individuals affected by IBD, their families, and the general public about these diseases.

Canada has among the highest rates of IBD in the world and the number of people living with these disorders is growing rapidly. This has placed a high burden on the healthcare system and on the Canadian economy, a burden that is only expected to grow in the future. It is important to understand IBD and its impact on Canadian society in order to appropriately plan for healthcare expenditures, reduce the burden on patients and their families, and improve the quality of life for those afflicted with IBD. In Canada, there is a lack of public awareness of the impact of Crohn's disease and ulcerative colitis. Raising awareness is crucial to reducing the social stigma that is common with these diseases and to help individuals maximize their overall quality of life. A better public understanding of IBD can also help to raise and direct funds for research, which could lead to improved treatments and, ultimately, to a cure.

To fulfill this vision, Crohn's and Colitis Canada has partnered with the Canadian Gastro-Intestinal Epidemiology Consortium (CanGIEC), a national network of researchers and clinicians with expertise in the epidemiology, burden, and health system evaluation of IBD. CanGIEC's overall aim is to assess the burden of IBD, provide evidence for environmental risk factors of IBD, and to improve the way that healthcare systems treat people living with IBD in Canada and abroad (see CanGIEC.ca). CanGIEC and partnering clinician-researchers have provided this report to Crohn's and Colitis Canada in order to make recommendations regarding the burden of IBD in Canada, future directions for advocacy efforts, areas to emphasize for research spending, and gaps in knowledge in the fields of clinical, health systems, and epidemiological research. This report is also aimed at the general public, patients with IBD, and stakeholders to help them understand the overall Impact of IBD in Canada in 2018.



1.1 Objective

This Impact of IBD report is intended to communicate information on IBD that is relevant to Canada and that can be appreciated by the lay public. Through this work, we aim to raise awareness and understanding of IBD in Canada, resulting in new research opportunities to enhance the quality of life for people with IBD. This report builds on, updates and extends the Crohn's and Colitis Canada-commissioned report from 2012: *The Impact of Inflammatory Bowel Disease in Canada: 2012 Final Report and Recommendations.*

The different areas of information addressed in this report include:

- Background information on IBD
- Occurrence of IBD
  (how many Canadians have IBD)
- Projection of IBD occurrence into the future
- Costs of IBD to the healthcare system, individuals, and society
- Special populations with IBD
  (children and seniors)
- Non-financial costs of IBD
  (quality of life impact)
- Directions for future strategies.

1.2 Methods

1.2.1 General Overview

This work builds on the existing high-quality, scientific research on IBD in Canada—much of which has been funded by Crohn's and Colitis Canada—to generate recommendations to Crohn's and Colitis Canada and stakeholders and to provide a comprehensive overview of the impact of IBD in Canada.

To undertake this review, a Steering Committee was formed, comprised of academic experts in gastroenterology and health system research. The Steering Committee selected and defined the topics and provided overall research guidance. The report was researched and written by a Working Committee, organized into various topics.

1.2.2 Steering Committee

The Steering Committee was comprised of:

- Gastroenterologists:
  - Gilaad Kaplan, MD, MPH, FRCPC, University of Calgary (Co-Chair)
  - Eric Benchimol, MD, PhD, FRCPC, University of Ottawa (Co-Chair)
  - Charles Bernstein, MD, FRCPC, University of Manitoba
  - Sanjay Murthy, MD, MSc, FRCPC, University of Ottawa
  - Geoffrey Nguyen, MD, PhD, FRCPC, University of Toronto
  - Alain Bitton, MD, FRCPC, McGill University
- Crohn's and Colitis Canada Staff
  - Kate Lee, PhD, MBA, Vice President of Research and Patient Programs
  - Jane Cooke-Lauder, MBA, DM, CMC, Consultant, Bataleur Enterprises Inc.
- CanGIEC Staff:
  - Shabnaz Siddiq, MSc, Project Coordinator
  - Joseph Windsor, PhD, Editor
  - Fox Underwood, MSc, Copy Editor

The Steering Committee was also responsible for identifying appropriate research and data sources, creating the Working Groups, reviewing and approving the report.

1.2.3 Working Committee

The Working Committee was divided into groups to correspond with the sections in this report. Each section was also assigned one or more members of the Steering Committee to help guide its creation. Sections were written by the following members:

- Section 3: Epidemiology
  - Eric Benchimol, MD, PhD, FRCPC, University of Ottawa
  - Charles Bernstein, MD, FRCPC, University of Manitoba
  - Alain Bitton, MD, FRCPC, McGill University
  - Stephanie Coward, PhD (cand.), University of Calgary
  - Gilaad Kaplan, MD, MPH, FRCPC, University of Calgary

- Section 4: Direct Costs & Health Services Utilization
  - Eric Benchimol, MD, PhD, FRCPC, University of Ottawa
  - Ellen Kuenzig, PhD, University of Ottawa
  - Lawrence Lee, MD, PhD, FRCSC, McGill University
  - Sanjay Murthy, MD, MSc, FRCPC, University of Ottawa
  - Geoffrey Nguyen, MD, PhD, FRCPC, University of Toronto
  - Harminder Singh, MD, MPH, FRCPC, University of Manitoba
  - Laura Targownik, MD, MSc, FRCPC, University of Manitoba

- Section 5: Indirect Costs of IBD Care
  - Wael El-Matary, MD, MSc, FRCPC, University of Manitoba
  - Ellen Kuenzig, PhD, University of Ottawa
  - Lawrence Lee, MD, PhD, FRCSC, McGill University
  - Sanjay Murthy, MD, MSc, FRCPC, University of Ottawa
  - Adam Weizman, MD, MSc, FRCPC, University of Toronto

- Section 6: Quality of Life in Patients with IBD
  - Jennifer Jones, MD, MSc, FRCPC, Dalhousie University
  - Geoffrey Nguyen, MD, PhD, FRCPC, University of Toronto
  - Anthony Otley, MD, MSc, FRCPC, Dalhousie University

- Section 7: Special Populations: Children with IBD
  - Eric Benchimol, MD, PhD, FRCPC, University of Ottawa
  - Matthew Carroll, BMed(Hons), MHSc, FRACP, University of Alberta
  - Anne Griffiths, MD, FRCPC, University of Toronto
  - Ellen Kuenzig, PhD, University of Ottawa
  - David Mack, MD, FRCPC, University of Ottawa
  - Anthony Otley, MD, MSc, FRCPC, Dalhousie University

- Section 8: Special Populations: IBD in Seniors
  - Geoffrey Nguyen, MD, PhD, FRCPC, University of Toronto
  - Harminder Singh, MD, MPH, FRCPC, University of Manitoba
  - Laura Targownik, MD, MSc, FRCPC, University of Manitoba
- Section 9: Extra-Intestinal Disease
  - Charles Bernstein, MD, FRCPC, University of Manitoba
  - Gilaad Kaplan, MD, MPH, FRCPC, University of Calgary
- Section 10: IBD Research Landscape in Canada
  - Keeley Rose, Project Manager, Canadian Institutes for Health Research, Institute of Nutrition, Metabolism and Diabetes
  - Philip Sherman, MD, PhD, FRCPC, Canadian Institutes for Health Research Institute of Nutrition, Metabolism and Diabetes
  - Jane Cooke-Lauder, MBA, DM, CMC, Bataleur Enterprises
  - Mina Mawani, President and CEO, Crohn's and Colitis Canada
  - Eric Benchimol, MD, PhD, FRCPC, University of Ottawa
  - Gilaad Kaplan, MD, MPH, FRCPC, University of Calgary
  - Kate Lee, PhD, MBA, Crohn's and Colitis Canada

The Working Committee was responsible for identifying appropriate research and data sources, writing of the sections, and providing feedback on the final report.

1.2.4 Overview

Section 2: Disease background
General information about both Crohn's disease and ulcerative colitis are presented to provide background information about these diseases. Symptoms are described, followed by current recommended treatment options (including medications and surgeries).

Section 3: Epidemiology
Epidemiology is the science that examines the patterns and occurrence of disease. This section estimates the current number of individuals in Canada with Crohn's disease and ulcerative colitis. Other aspects of epidemiology covered in this report include: factors associated with getting the disease; the rate at which individuals are newly diagnosed with disease; the age of people with IBD; mortality associated with IBD, and a comparison of Canadian statistics with other geographic areas.

Section 4: Direct costs
Direct costs are costs incurred by the public healthcare systems in Canada and include: medications, hospitalizations, surgeries, physician visits, emergency room visits, allied healthcare professional visits, laboratory tests and procedures, etc. The total Canadian cost is calculated by multiplying the amount that was used per person by the total number of individuals who have disease.

Section 5: Indirect costs
Indirect costs are costs incurred by individuals and society outside of the healthcare system. Individuals incur costs such as: non-prescription medications, travel to medical appointments, care giving, and household support. Society incurs costs for worker absences and loss of productivity associated with: short- and long-term disability, reduced participation in the work force, and premature death. Workforce absences are due to the individual with IBD or a caregiver of the individual with IBD (such as a parent) needing time off for disease-related reasons (e.g., disease flare or medical appointments). The total Canadian cost is determined by multiplying the costs per person by the total number of individuals who have disease.

Section 6: Quality of Life
IBD has a substantial impact on quality of life. It causes considerable personal, emotional, and social burdens. The impact of IBD on quality of life cannot readily be quantified as a cost, however the impact places a significant burden on the patient and caregivers. Therefore information on quality of life is discussed for individuals with IBD without determining a specific cost.

Section 7: Pediatrics

Children diagnosed with IBD are one of the fastest growing sub-populations of Canadians with the disease. Children are at risk of additional and unique risks related to the use of certain medications in childhood. Children have different common complications from the disease and, due to the age of onset, children will live with the disease longer than adult- or senior-onset patients, further necessitating different treatment options. The psychological well-being of both children with IBD and their families is at the forefront of this discussion, and the need for clinical trials of new therapies specific to children is highlighted.

Section 8: Seniors with IBD

Seniors with IBD (commonly defined as those aged 65 and older) also present unique challenges for care. Given there is no cure, the number of senior IBD patients is rising significantly in Canada. Patients diagnosed at younger ages carry their disease with them into their senior years. Risks associated with IBD-related surgeries and complications from other illnesses associated with age and their medications, further complicate treatment options and may lead to higher healthcare utilization. The need for Canadian healthcare systems to prepare for an increasing utilization by senior patients with IBD and for healthcare providers to be prepared to work in multidisciplinary teams with other specialists is highlighted.

Section 9: Extra-Intestinal Disease

The burden of extra-intestinal disease is high in patients with IBD. The most common extra-intestinal manifestations are other chronic immune mediated diseases such as erythema nodosum, ankylosing spondylitis and primary sclerosing cholangitis. Patients with IBD are at higher risk of complications in other organ systems ranging from osteoporosis to venous thromboembolism to cardiovascular disease. In addition, patients with IBD have a higher risk of cancer including colon cancer. Consequently, patients and care providers need to be vigilant in the surveillance of extra-intestinal manifestations and complications of IBD.

Section 10: Research Landscape

Canada has among the highest per capita funding of research dedicated to the investigation of IBD. Research funding supports all pillars of research from basic science to clinical to health services to population health research. Funding of IBD research in Canada is multi-sourced including dedicated funding from Canadian Institutes of Health Research, Crohn's and Colitis Canada, and Genome Canada.

1.2.5 Methods

For each section of this report, an extensive literature review was conducted to obtain the most recent and relevant research. Wherever possible, Canadian-based data and research were used. Scientific publications were the most important source for data. The scientific literature was searched using key words such as IBD, Crohn's disease or ulcerative colitis, in addition to costing, quality of life, or epidemiology. Published literature was supplemented, where appropriate, by the expertise and unpublished research of the Steering and Working Committee members. Since this report represents an expansion on the 2012 report, where possible, the scientific literature produced since 2012 was used. Some of the most recent studies cited are published (at the time of writing) only in abstract form and/or presented at national and international medical/scientific conferences. Therefore, some conclusions of those studies may change when published in final manuscript form in a scientific journal. Nothing in this report critically hinges on the information provided in any single study. Thus, the outcomes suggested in this report are unlikely to be affected by updated data in the studies cited herein.

Additional data sources were also used where appropriate. For example, data from Statistics Canada is used to determine the overall Canadian population during the time periods in question.

Strong and robust research has been conducted in Canada with respect to epidemiology, utilization of healthcare resources, productivity, patient costs, and quality life. Much of this research was produced by Canadian investigators. On occasion, it was necessary to use non-Canadian research to supplement locally-derived data.

1.2.6 Analysis

Information from the various data sources was combined and converted into a burden of illness summary. First, it was necessary to determine best estimates for important factors, such as: the current number of individuals with IBD in Canada; the average per-person cost for medications and hospitalizations; and, the average per-person costs in lost productivity. Where there was one particularly strong information source, it was used to generate the best estimate. For example, a landmark study in The Lancet (2017) summarizes the studies reporting the number of Canadians living with IBD.[1] This study was used as the primary data source for the epidemiology of IBD (see Section 3: Epidemiology). Further, where data was compiled in meta-analyses or forecasting models, these data were used to represent national or international estimates. Where there were a number of different information sources, with differing results, the range of available data was reported. Second, it was necessary to attach prices or costs to the amount of resources devoted to IBD treatment and care. For example, studies estimate the average number of hospitalizations or the average amount of lost productivity per person. This was multiplied by the total number of people with Crohn's disease or ulcerative colitis in 2018 in order to determine the total amount of resource utilization. Prices were then determined for each element such as the cost of a hospitalization or physician visit, or the average wage rate. These prices were determined from public sources. Costs for healthcare resources were determined primarily from the Ontario healthcare system. Productivity losses were priced using the Canadian average wage rate, as reported by Statistics Canada.

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BACKGROUND

2.0 Introduction

2.1 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is the name of a group of disorders that cause the intestines to become inflamed and ulcerated. The main forms of IBD are Crohn's disease and ulcerative colitis. Because the symptoms of Crohn's disease and ulcerative colitis are similar, it is sometimes difficult to establish the diagnosis definitively. In fact, approximately 10% of colitis cases are unable to be defined as either ulcerative colitis or Crohn's disease and are called IBD-type unclassified.[1]

Both Crohn's disease and ulcerative colitis are marked by an abnormal response by the body's immune system. Normally, the immune system protects the body from infection. In people with IBD, however, it reacts inappropriately. For unknown reasons, the immune system mistakes microbes, such as bacteria that are normally found in the intestines, as foreign or invading substances and launches an attack. In the process, the body sends white blood cells into the lining of the intestines, where they produce chronic inflammation. These cells then generate harmful products that ultimately lead to ulcerations and bowel injury. When this happens, the patient experiences the symptoms of IBD.[2]

Currently, there is no cure for Crohn's disease. Therapies focus on maintaining remission and achieving a normal quality of life. The approach is similar with ulcerative colitis, although ulcerative colitis technically can be cured by surgical removal of the large intestine. However, this option is reserved until medical therapy fails.[3,4]

Although Crohn's disease most commonly affects the ileum at the lower end of the small intestine and the colon at the beginning of the large intestine, it may involve any part of the gastrointestinal (GI) tract. In ulcerative colitis, the GI involvement is limited to the colon (or, to a lesser extent, the stomach). In Crohn's disease, inflammation may extend through the entire thickness of the wall of the intestine. This can result in deep ulcers that go through the wall of the bowel completely. These ulcers can cause complications such as abscesses in the abdomen or can lead to the development of connections (fistulas) between the bowel and other organs (e.g., fistulas that form between the small bowel and bladder, which frequently lead to recurrent urinary tract infections). Crohn's disease is often discontinuous, with patches of diseased bowel in between normal healthy bowel. By contrast, ulcerative colitis affects only the superficial layers of the colon (the mucosa) in a more even and continuous distribution, starting from the anus. Differences between Crohn's disease and ulcerative colitis have been summarized by health organizations[5-7] and in the literature,[8] as well as in Table 2-1.

Patients with IBD experience symptoms such as abdominal pain, rectal bleeding, fatigue, vomiting, diarrhea, itchiness or irritation around the anus, flatulence, and bloating. Weight loss and anemia also pose significant problems. Additionally, complications associated with IBD can affect a patient's bones (leading to a higher risk of developing osteoporosis), liver, skin, eyes, height and weight, and mental health (leading to depression or anxiety).[9]

Table 2-1:

Comparisons of characteristics of Crohn's disease and ulcerative colitis.

	Crohn's Disease	Ulcerative Colitis
Occurrence	More females than males All ages, peak onset 15-35 years	Similar for males and females All ages, usual onset 15-45 years
Symptoms	Diarrhea, fever, sores in the mouth and around the anus, abdominal pain and cramps, anemia, fatigue, loss of appetite, weight loss	Bloody diarrhea, mild fever, abdominal pain and cramps, anemia, fatigue, loss of appetite, weight loss
Terminal ileum involvement	Common	Never
Colon involvement	Common	Always
Rectum involvement	Common	Always
Peri-anal disease	Common	Never
Distribution of disease	Patchy areas of inflammation	Continuous area of inflammation but can be patchy once treated
Endoscopic findings	Deep and snake-like ulcers	Diffuse ulceration
Depth of inflammation	May be transmural, extending through the entire thickness of the wall of an organ or cavity deep into tissues	Shallow, mucosal
Fistulas between organs	Common	Never
Stenosis	Common	Never
Granulomas on biopsy	Common	Never
Effect of surgery	Often returns following removal of affected parts Decreased likelihood of pregnancy	Usually cured by removal of colon (colectomy) Decreased likelihood of pregnancy after ileoanal pouch
Treatment options	Drug treatment (corticosteroids, immune modifiers, biologic therapies) Exclusive formula diet in children Surgery (repair fistulas, remove obstruction, resection, and anastomosis)	Drug treatment (5-aminosalicylates, sulfasalazine, corticosteroids, immune modifiers, biologic therapies) Surgery (rectum/colon removal) with creation of an internal pouch (ileoanal pouch)
Cure	No existing cures Maintenance therapy is used to reduce the chance of relapse	Through colectomy only Maintenance therapy is used to reduce the chance of relapse
Bowel complications	Blockage of intestine due to swelling or formation of scar tissue. Abscesses, sores or fistulas Malnutrition Colon cancer	Bleeding from ulcerations Perforation (rupture) of the bowel Malnutrition Colon cancer
Extra-intestinal disease	Osteoporosis Liver inflammation (primary sclerosing cholangitis) Blood clots Pain and swelling in the joints (arthritis) Growth failure (in children) Mental illness	Liver inflammation (primary sclerosing cholangitis) Blood clots Eye inflammation (iritis) Pain and swelling in the joints (arthritis) Mental illness
Smoking	Higher risk of acquiring for smokers	Higher risk of acquiring for ex-smokers
Mortality risk	Increased risk of colorectal cancer and overall mortality Increased risk of lymphoma and skin cancer (due to treatments)	Increased risk of colorectal cancer Uncertain change in mortality risk Increased risk of lymphoma and skin cancer (due to treatments)

IBD is a lifelong disease, typically starting in otherwise healthy, active individuals in late adolescence or early adulthood. Increasingly, it is being diagnosed in childhood. IBD can impact significantly the quality of life of the patient, caregiver(s) and family, workplace, and community. It can impact career choices, lead to reduced work hours, impact family planning decisions, and lead to income disparity and depression. IBD can also complicate travel and working arrangements due to the need for sudden, and possibly urgent, washroom access.[10]

Generally, people with IBD can lead normal lives most of the time, but with ongoing medication needs and occasional flares that may require surgery. The unpredictability of symptoms and the prospect of eventual surgery burden daily life. This burden is exacerbated by the fact that, due to the intimate nature of the symptoms, there may be a stigma attached to the disease from family, friends, and workplace colleagues.

2.2 Crohn's Disease

As noted above, Crohn's disease is a chronic disorder that causes inflammation of any area of the GI tract from mouth to anus; although, it most commonly affects the small intestine and/or colon. The symptoms and complications of Crohn's disease differ depending on what part of the intestinal tract is inflamed. Crohn's disease is classified as mild, moderate, or severe based on the age at diagnosis, the location of the disease, and the disease behaviour (*i.e.,* whether there is penetrating, stricturing, both, or neither).[10,11]

2.2.1 Symptoms

Persistent diarrhea (loose, watery, or frequent bowel movements), cramping abdominal pain, fever and, at times, rectal bleeding are the hallmark symptoms of Crohn's disease, but they vary from person to person and may change over time. Loss of appetite and subsequent weight loss may also occur. However, the disease is not always limited to the GI tract. Individuals may experience symptoms outside of the intestine which may affect the joints, bones, eyes, skin and liver. Fatigue is another common complaint. Children who have Crohn's disease may suffer osteoporosis and may fail to develop or grow properly.[12]

Some patients may develop tears (fissures) in the lining of the anus, which may cause pain and bleeding, especially during bowel movements. Inflammation may also cause a fistula to develop. A fistula is a tunnel that leads from one loop of intestine to another, or that connects the intestine to the bladder, vagina, or skin. Fistulas occur most commonly around the anal area. If this complication arises, the patient may drain mucus, pus, or stool from this opening.

Symptoms may range from mild to severe. Because Crohn's disease is a chronic but fluctuating disease, patients will go through periods in which the disease flares up, is active and causes symptoms. These episodes are followed by times of remission—periods in which symptoms disappear or decrease and good health returns. In general, people with Crohn's disease lead full, active, and productive lives.[8]

2.2.2 Treatment Options

Since there is no cure for Crohn's disease as of yet, the short-term goal of medical treatment is to reduce or bring symptoms under control by suppressing the inflammatory response to induce a remission. Remission allows healing of the damaged bowel and can normalize quality of life. In the medium-term, clinicians now believe that it is important to achieve mucosal healing, defined as complete healing of the bowel from ulcers or inflammation. The long-term goal is to maintain remission and healing, to decrease the frequency of disease flares and to prevent complications.[13]

People with Crohn's disease in Canada are treated with various approaches, depending on the characteristics of their disease. The traditional approach is to treat patients with corticosteroids during periods of disease flare in order to reduce symptoms and induce remission. These drugs are not prescribed on a long-term basis due to side effects and poor effectiveness for maintaining remission. For long-term control, immune modifiers or biologics are typically initiated. If remission has not been achieved through treatment with immune modifiers, then biological therapies (biologics) are used.[14] In some cases, biologics may be started early, even before steroids or immune modifiers. Patients with fistulizing disease, severe disease, or contraindications to steroids or immune modifiers could be started on biologics at diagnosis, or early in the course of illness. Some contraindications to steroids and immune modifiers include: growth failure (in children), osteoporosis, mental illness, hepatitis, allergy, or genetic testing that shows a patient cannot metabolize an immune modifier. Best practices for the use of biologics are still being defined, and there may be a variety of current practice patterns. Many researchers and clinicians now believe that it is worthwhile, in selected patients, to try biologics early since they

can be very effective and they could change the course of the disease by reducing bowel damage and eventual surgery. Researchers are currently conducting trials to help understand who should start biologics early and who might respond better to immune modifiers.[15]

Several types of therapies are used to treat Crohn's disease today, including:

- Corticosteroids: Prednisone and budesonide, among other steroids, are available orally and rectally. Methylprednisolone can be given intravenously (IV). These medications non-specifically suppress the immune system and are used to treat moderately to severely active Crohn's disease. They are very effective agents but may be associated with significant short- and long-term side effects. They should not be used as a maintenance medication.[16]

- Exclusive enteral nutrition: Not a medication, this therapy involves patients with mild to moderate Crohn's disease drinking a liquid diet only, avoiding all solid foods for six to 12 weeks. Sometimes, patients request a tube from the nose into the stomach (nasogastric tube) to administer the formula overnight or at other times. This therapy has been found to reduce the inflammation in the bowels effectively and leads to short term remission. Medications are then used to maintain the remission. This therapy avoids the need for corticosteroids in some patients. Exclusive enteral nutrition is typically used for children with Crohn's disease.[17]

- Immune modifiers: sometimes called immunomodulators, drugs such as azathioprine, 6-mercaptopurine (6-MP), methotrexate, and cyclosporine are used to help decrease corticosteroid dependency and may help maintain disease remission.[18]

- Antibiotics: Metronidazole and ciprofloxacin are used to treat peri-anal fistulas, abscesses, or other infections.[19]

- 5-Aminosalicylates (5-ASA): This class of anti-inflammatory drugs includes sulfasalazine and oral and rectal formulations of mesalamine and 5-ASA. These medications typically are used to treat mild symptoms of proctocolitis. They are less effective in treating Crohn's disease.[20]

- Biological therapies (biologics) are antibodies that target specific proteins of the immune system:
  - Anti-TNF biologics: Infliximab and adalimumab are currently approved in Canada for moderately to severely active Crohn's disease and ulcerative colitis. Given by infusion or injection, these drugs are produced by live cells, hence the name 'biologics'. They work by blocking the immune system's production of tumour necrosis factor-alpha (TNF), a cytokine that intensifies inflammation. In addition to the originally approved version of infliximab (Remicade®), biosimilars are now available for infliximab. Biosimilars are analogous in structure, but not identical, to the original.[21]
  - Although ustekinumab was previously used for the treatment of psoriasis, it is approved for used in moderately to severely active Crohn's disease. It is an antibody to other inflammatory chemicals in the blood (IL-12 and IL-23), and therefore works through a different pathway from the anti-TNF biologics.[22]
  - Vedolizumab is a biologic approved for use in moderate to severe ulcerative colitis and Crohn's disease. Vedolizumab blocks $\alpha_4\beta_7$-integrin molecules in the gut, which help white blood cells cross from blood vessels into the tissue of the intestines. Since white blood cells help drive inflammation, blocking their migration into the tissue helps reduce inflammation. Vedolizumab is gut-selective meaning the biologic blocks trafficking of immune cells primarily to the gastrointestinal tract.[23]

2.2.3 Surgery

Historically, two thirds to three quarters of patients with Crohn's disease have required surgery at some point during their lives, With modern medical management,[24,25] surgery has become less frequent with the ten year risk for surgery now less than 50%.[26] Surgery becomes necessary when medications are ineffective (medically refractory disease) or if complications arise such as fistulas, abscesses, scarring and narrowing of the bowel, or if dysplasia (precancerous cells) or cancer of the colon is detected. In most cases, the diseased segment of bowel and any associated abscess is resected. The two ends of healthy bowel are then joined together in a procedure called an anastomosis. While resection and anastomosis may allow symptom-free years, the disease frequently recurs at or near the anastomosis – the site where the bowel is joined together.

An ostomy, an ileostomy or a colostomy, depending on the location of the operation, may be required when surgery is performed for Crohn's disease when there is no healthy bowel to connect. This may happen in patients with disease of both the rectum and the colon. After the surgeon removes the diseased bowel, the colon or the small bowel is brought to the skin, so that waste products may be emptied into a pouch attached to the abdomen. Ostomies may be permanent or temporary, depending on the surgery. The overall goal of surgery in Crohn's disease is to conserve bowel, where possible, and return the individual to the best possible quality of life.[27]

2.2.4 Complications

The most common complication of Crohn's disease is blockage of the intestine due to swelling and the formation of scar tissue. This usually results from repeated bouts of inflammation and ulceration, or incomplete healing of the bowel despite treatment. The result is thickening of the bowel wall and a significantly narrowed intestinal passage. Symptoms of intestinal blockage include crampy pain around the mid-abdomen, vomiting, or a bloated and distended abdomen. Medications may relieve the obstruction by reducing the inflammation, but surgery may be required if the obstruction is severe and does not respond to medical treatment. Surgery may also be required if the blockage recurs frequently.[28]

Another complication that arises in patients with Crohn's disease is ulcers within the intestinal tract that penetrate through the wall of the bowel and turn into fistulas. Fistulas affect about 30 percent of people with Crohn's disease and often become infected. The areas that most frequently present with fistulas are the anus and rectum. If the fistula is small, medical treatment may heal it. Large or multiple fistulas, on the other hand, may require surgery, particularly if they are accompanied by fever, abdominal pain, or severe diarrhea. Occasionally a fistula forms an abscess, or collection of pus, near the intestine. This is a pocket of infection that requires drainage, either through a catheter inserted by a radiologist or a special drain that is surgically inserted. In addition to fistulas, cracks or fissures may also develop in the lining of the mucus membrane of the anus.[29]

Another complication commonly encountered in people with Crohn's disease is related nutritional deficiencies of proteins, calories, and vitamins. Nutritional deficiencies generally do not develop unless the disease is extensive and of long duration. The intestinal scarring resulting from extensive disease may lead to inadequate dietary intake and poor absorption of nutrients, which is usually treated effectively by medical treatment and/or nutritional supplements.[30] A low risk of cancer of the colon and small bowel is also associated with longstanding Crohn's disease.

Some complications of Crohn's disease can occur at any time, even at the time of diagnosis. These include growth failure in children, osteoporosis, mental illness (especially anxiety and depression), heart disease, stroke, autoimmune hepatitis and liver disease (primary sclerosing cholangitis). These are known as extra-intestinal manifestations of IBD and are thought to be due to the inflammation spreading from the gut to other regions of the body, affecting other tissues (such as bones, muscle, brain, heart, and liver). Effectively treating Crohn's disease usually, but not always, reduces the risk of these conditions.[31]

2.3 Ulcerative Colitis

Ulcerative colitis is a chronic disease of the colon. This disease is marked by inflammation and ulceration of the colon mucosa — the innermost lining. Ulcers form on the surface of the lining where they bleed and produce pus and mucus. Because the inflammation makes the colon empty frequently, symptoms typically include diarrhea (frequently bloody) and crampy abdominal pain. Most patients experience urgency, and a sensation of, dry heaves, of the rectum after bowel movements is commonly reported. Some patients will experience false urges and pass only tiny amounts of blood and mucus or gas.

The symptoms of ulcerative colitis, as well as possible complications, vary depending on the extent of inflammation in the rectum and the colon. The rectum is mostly involved but the inflammation can extend up to and including the entire colon.[4]

2.3.1 Symptoms

Often, the first symptom of ulcerative colitis is a progressive loosening of the stool. The stool is generally bloody and may be associated with crampy abdominal pain and severe urgency to have a bowel movement. Bouts of diarrhea may begin slowly or quite suddenly. Loss of appetite with subsequent weight loss and fatigue are common. In cases of severe bleeding, anemia may also occur. Additionally, ulcerative colitis patients may present with skin lesions, joint pain, eye inflammation and liver disorders. Children with ulcerative colitis may fail to develop or grow properly due to malabsorption of nutrients by the diseased bowel.

Approximately half of all patients with ulcerative colitis have relatively mild symptoms: multiple stools a day (with or without blood), some pain and abdominal cramping, a constant feeling of the need to empty the bowel, and either no fever or a low-grade fever. Severely ill people may experience more than six bloody stools a day, with fever and/or anemia. In general, the severity of symptoms correlate with the extent of colon involved with the disease. The symptoms of ulcerative colitis tend to come and go, with fairly long periods of remission between flare-ups in which patients may experience no symptoms at all. Periods of remission can span months or even years, although symptoms do eventually return. The unpredictable course of ulcerative colitis may make it difficult for physicians to evaluate whether a particular course of treatment has been effective or not.[32]

2.3.2 Treatment Options

The treatment of ulcerative colitis involves medications that inhibit abnormal inflammation in the colon lining and thereby control the symptoms. Treatment options for ulcerative colitis are similar to Crohn's disease with several important exceptions. Patients with mild ulcerative colitis are treated primarily with 5-ASAs, which is a topical therapy administered either by mouth or rectally (in enema form). Patients with moderate to severe inflammation often require corticosteroids to control their flare. Immune modifiers (*i.e.,* azathioprine or 6-mercaptopurine) can be used to replace corticosteroids once symptoms of a flare come under control. However, biologics are often required to control a severe flare of ulcerative colitis. The anti-TNF biologics used to treat ulcerative colitis include infliximab, adalimumab, and golimumab. Vedolizumab is the newest biologic approved for the treatment of ulcerative colitis in patients who do not achieve remission via conventional therapy. Patients hospitalized with severe ulcerative colitis and do not improve with corticosteroids are treated with anti-TNF therapy.[33]

2.3.3 Surgery

Sometimes, medical therapy for ulcerative colitis is not completely successful or complications arise. Under these circumstances, surgery may be considered. Up to one fifth of ulcerative colitis patients need colectomy within ten years of diagnosis.[26] This operation involves the removal of the colon (colectomy). Unlike Crohn's disease, which can recur after surgery, ulcerative colitis is cured once the colon is removed although some patients may experience disease of the rectal stump and/or be diagnosed later with Crohn's disease.

Depending on a number of factors, such as the extent of the disease, the patient's age and overall health, one of two surgical approaches may be recommended. The first option involves the removal of the entire colon and rectum, with the creation of an ileostomy or external stoma (an opening on the abdomen through which wastes are emptied into a pouch, which is attached to the skin with adhesive). The second option is a procedure that also calls for removal of the colon, but it avoids an ileostomy. By creating an internal pouch (a J-pouch) from the small bowel and attaching it to the rectal stump, the surgeon can preserve bowel integrity and eliminate the need for the patient to wear an external ostomy appliance. Sometimes, this procedure is performed in two or three steps, with a temporary ileostomy eventually being closed after creation of the J-pouch. Ulcerative colitis patients who have a J-pouch may suffer from pouchitis (*i.e.* inflammation of the J-pouch) that requires treatment with antibiotics. Approximately five percent may be re-classified as having Crohn's disease after the creation of a pouch.[34]

2.3.4 Complications

Complications of ulcerative colitis include profuse bleeding from deep ulcerations, perforation of the bowel, or simply failure of the usual medical treatments to induce remission.

Another possible complication is severe abdominal distension. A mild degree of distention is common in individuals without any intestinal disease and is somewhat more common in people with ulcerative colitis. However, if the distention is severe or of sudden onset, and if it is associated with active ulcerative colitis, fever, and constipation, a physician may suspect toxic megacolon: a rare development that is produced by severe inflammation of the entire thickness of the colon, with weakening and ballooning of its wall. The dilated colon is at risk of rupturing which is an urgent, life-threatening condition. Treatment is aimed at controlling the inflammatory reaction and restoring losses of fluid, salts, and blood. However, if improvement is not rapid, surgery may be necessary to avoid rupture of the bowel.

As with Crohn's disease, risk of colorectal cancer is a potential complication of longstanding, poorly controlled ulcerative colitis. Patients with ulcerative colitis can also experience extra-intestinal manifestations found in patients with Crohn's disease, such as an increased risk of blood clots, primary sclerosing cholangitis, iritis and joint arthritis. Growth failure is less common in children with ulcerative colitis.[28]

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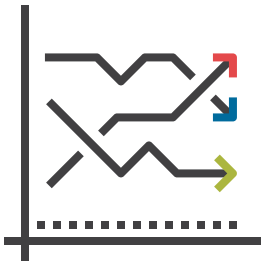
EPIDEMIOLOGY

Epidemiology

Highlights

1. Canada continues to have among the highest prevalence of IBD in the world.

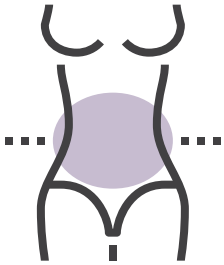
2. Today, approximately 270,000 Canadians live with IBD. By 2030 it is estimated that nearly 403,000 Canadians will have a diagnosis of IBD.



3. IBD has become a worldwide disease with increasing rates in Asia, Africa, and South America: continents where IBD was rarely diagnosed prior to 1990.

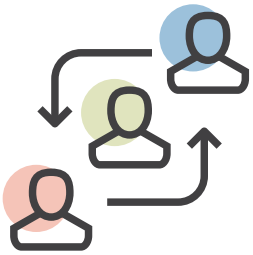
4. The causes of IBD are unknown but the high rates of disease over the past 60 years in western countries and the emergence of disease in developing countries, suggest that factors associated with urbanization, modernization, or western diets may be pertinent to understanding the pathogenesis of the disease.

5. Many of the leading hypotheses as to the causes of IBD tie in with alteration of the gut microbiome, the suite of organisms that reside in the bowel and maintain bowel health throughout life.



Gaps in Knowledge and Future Directions

1. While the incidence of IBD appears to be stabilizing in some regions in Canada, IBD may be occurring more frequently in certain populations such as in children, South Asians, Ashkenazi Jews, and immigrants. Future research should focus on the changing demographics of IBD in Canada.



2. The prevalence of IBD will rise steadily over the next decade. To enable better healthcare system planning and to respond adequately to the increasing burden of IBD, ongoing surveillance of the epidemiology and health services utilization of IBD in Canada is necessary.

3. Most studies have focused on the mortality associated with IBD. Future research is necessary to assess health-adjusted life expectancy and overall life expectancy for those living with IBD.

4. Analyses of resources, infrastructure, and personnel need to be modeled into the future in order to prepare our healthcare system for the rising burden of IBD.

5. Research on the interaction between genes, microbes, and our environment will inform our understanding of the pathogenesis of IBD: information necessary to prevent IBD in the future.

3.0 Introduction

Canada has among the highest rates of inflammatory bowel disease (IBD) in the world.[1-3] Since the middle of the 20th century, diagnoses of ulcerative colitis and Crohn's disease increased dramatically in Canada.[1] In the 21st century, IBD affects nearly 0.7% of Canadians.[1,4] In 2018, over 270,000 Canadians are believed to be afflicted with IBD, which is estimated to cost over $1.28 billion to the healthcare system annually (see Section 4: Direct Healthcare Costs of IBD).[5,6] Outside the healthcare system, IBD is estimated to cost Canadian society nearly $1.29 billion in 2018 from expenses known as indirect costs such as lost work productivity, disability coverage, and premature retirement or death (see Section 5: Indirect Costs of IBD).[7-9] Moreover, patients with IBD and their families experience a reduction in quality of life that may affect their school, work, and social interactions (see Section 6: Quality of Life).[10]

IBD is a global disease.[1] At the turn of the 21st century, countries in Asia, Africa, and South America reported a rise in IBD locally.[11-15] While the occurrence of IBD in Canada greatly exceeds those of newly industrialized countries, IBD is rising at a considerably faster rate in many countries in Asia, Africa, and South America.[2] The evolution of IBD following urbanization and westernization of developing countries highlights the importance of environmental risk factors associated with these societal changes in the pathogenesis of IBD.[16] Moreover, immigrants from non-western countries who arrive in Canada as children and their Canadian-born offspring have an elevated risk of developing IBD compared with immigrants who arrive later in life.[17] This observation suggests that early life exposure to the Canadian environment is an important risk factor for IBD.[3]

Without discoveries that lead to a cure of IBD or prevention of disease development, the number of people living with IBD is predicted to rise rapidly over the next decade in Canada.[18] Consequently, healthcare systems throughout the nation must prepare for the rising burden of IBD. Over the next decade, gastroenterology clinics will need to optimize the infrastructure, resources, and personnel needed to care for patients with IBD living in Canada.[18] This section of the Report will characterize the evolution in the rates of IBD in Canada, including the future predicted burden of the disease. Further, we will introduce the genetic, environmental, and microbial associations with IBD.

3.1 Incidence, Prevalence, and Mortality of IBD in Canada

3.1.1 Historical Perspective

Ulcerative colitis was first recognized in the late 1800s by Sir Samuel Wilks, followed by Crohn's disease in the 1930s by Dr. Burrill Crohn and colleagues.[16] Since the 1950s, numbers of newly diagnosed cases of IBD rose in North America, Europe, and Australia. A comprehensive review that compiled over 200 epidemiological studies on the occurrence of IBD demonstrated that over three quarters of studies reported rising incidence rates of Crohn's disease and ulcerative colitis throughout the 20th century. However, since 1990, most studies from the western world have reported that the incidence of Crohn's disease and ulcerative colitis has stabilized and may be decreasing in several regions.[1] However, it continues to rise in Canada in certain populations (e.g., children, immigrants).[19]

3.1.2 Incidence of IBD Today

Canada has among the highest incidence rates of IBD in the world.[2] Robust disease surveillance systems have tracked the incidence of IBD in provinces across Canada. Table 3-1 describes the incidence of IBD in provinces with available data. Incidence varies between provinces: the highest incidence of IBD is reported in Nova Scotia at 54.6 per 100,000 people (1996-2009). In contrast, the incidence of IBD in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan were similar, ranging from 18.7 to 28.3 per 100,000. The ratio of Crohn's disease to ulcerative colitis was equal in all provinces with the exception of Quebec which has nearly twice the rate of new diagnoses of Crohn's disease compared to ulcerative colitis. Since 1990, the incidence of IBD was stable in Manitoba, increasing in Ontario, and decreasing in Alberta, Nova Scotia, and Quebec (Table 3-1).[1,2,20]

Table 3-1:

Incidence of IBD in Canada. Incidence is reported per 100,000 people. Most recent data available is reported in the table.

Province	Study Period	Incidence of IBD*	Incidence of Crohn's Disease	Incidence of Ulcerative Colitis	Change in Incidence Over Time
Alberta	2010 to 2015	25.0	10.2	8.4	Incidence is stable
British Columbia	1998 to 2000	18.7	8.8	9.9	Unknown
Manitoba	1990 to 2013	19.8	8.9	10.8	Incidence is decreasing
Nova Scotia	1996 to 2009	51.8	22.6	21.4	Incidence is decreasing
Ontario	1999 to 2011	23.0	10.6	11.1	Incidence is increasing in children and adults aged 30-60, stable in other ages.
Quebec	2001 to 2008	27.3	16.6	10.7	Incidence is decreasing
Saskatchewan	1998 to 2000	23.9	13.5	10.4	Unknown

*Incidence of Crohn's disease plus ulcerative colitis does not necessarily add up to the incidence of IBD because some provinces combine IBD unclassified (IBD-U) with ulcerative colitis and others report IBD-U separately.

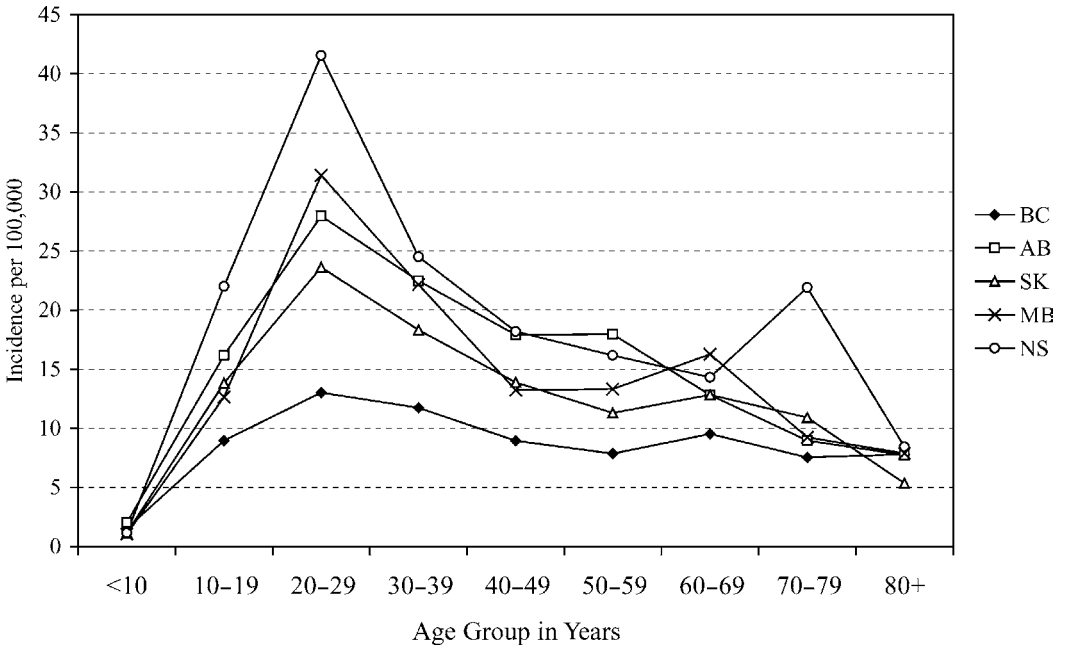


Figure 3-1: Age distribution of the incidence of Crohn's disease for British Columbia, Alberta, Saskatchewan, Manitoba, and Nova Scotia from 1998 to 2000.[21]

3.1.3 Age and Sex Distribution of Incidence of IBD

IBD can be diagnosed at any age, from infancy to octogenarian. However, the age groups that are most likely to be diagnosed with Crohn's disease and ulcerative colitis are adolescents and those between the ages of 20 to 30 (Figure 3-1 and 3-2).[1,2,20] Although both ulcerative colitis and Crohn's disease may be diagnosed in seniors (over age 65), ulcerative colitis is more common in this population. In contrast, children are more likely to have Crohn's disease as opposed to ulcerative colitis. See Sections 7 (Children with IBD) and 8 (Seniors with IBD) for a comprehensive discussion on these special populations.

Women may be more likely to be diagnosed with Crohn's disease as compared to men in Canada. The ratio of newly diagnosed females as compared to males ranges from 1.2 to 1.3 in Manitoba, Quebec, Nova Scotia, and Ontario. In contrast the risk of being diagnosed with ulcerative colitis is the same for females and males.[1,21]

3.1.4 Incidence by Ethnicity

During the 20th century, IBD was primarily considered a disease of Caucasians who descended from Western Europe given the highest incidence rates were found in Western Europe, North America, and Australia with low occurrence in developing countries.[22] However, this notion has been modified over the past generation. Individuals who immigrated from South Asia, where IBD was uncommon, to the United Kingdom were found to be more likely to develop IBD. The risk of developing IBD is most striking among the first and second-generation offspring of these immigrants.[23,24] Immigrants from developing countries are less likely to have IBD than natural born Canadians. However, these immigrants who arrive to Canada at younger ages are at increased risk: for every decade earlier in life that these immigrants arrive to Canada, the risk of IBD increases by almost 10%.[25] There are also differences among the offspring of immigrant groups. First-generation Canadian-born offspring

from parents who immigrated from the Middle East, South Asia, and Africa have a similarly high risk of developing IBD as the children born from non-immigrant parents.[25] In a Vancouver-based study, children of South Asian descent have a much higher incidence of IBD (15.2 per 100,000) compared to non-South Asians (3.7 per 100,000).[26] By contrast, immigrants from East Asia (primarily China and Hong Kong) to Ontario are at very low risk of developing IBD, as are their children.[25] These trends suggest that the Canadian environment triggers IBD in certain populations, but not others (perhaps due to protective genetics). That being said, IBD in Canada now affects the lives of Canadians of all ethnicities, including those thought previously to be at low risk.

Familial and genetic studies have reported a particularly high occurrence of Crohn's disease among Ashkenazi Jews—Jewish people descendant from those who settled in Eastern/Central Europe. An early study shows that Ashkenazi Jews have a twofold higher likelihood of being diagnosed with Crohn's disease than non-Jews.[27] A more recent population-based study from Manitoba reports that individuals who are Jewish are over four-times more likely to have Crohn's disease as compared to non-Jewish residents.[28] Clinicians believe that risk of IBD clustered in Jewish families is inherited, a hypothesis that was subsequently substantiated by genetic studies. Ashkenazi Jews have been found to carry gene mutations that are common to all patients with Crohn's disease but also have unique mutations that may drive their increased susceptibility.[29] The rates of IBD among Jewish Israelis are much lower than rates reported from Canada and Australia, likely due to the more mixed Jewish ethnicities living there. However, recent studies display much higher rates of IBD than previously reported in the Sephardic Jewish and Arab populations in Israel, suggesting that westernization and environment may have more impact on risk than genetics.

Table 3-2:

Prevalence of IBD – Historical and Predicted.[4] Prevalence reported per 100,000. Most recent data available is reported in the table.[4]

Province	Historical Prevalence of IBD for 2008	Predicted Prevalence of IBD in 2018	Predicted Prevalence of IBD in 2030
Alberta	529	729	1048
British Columbia	515	682	912
Manitoba	567	652	819
Nova Scotia	870	1224	1657
Ontario	507	731	1156
Quebec	445	671	940
Saskatchewan	555	636	893
Canada	-	725	981

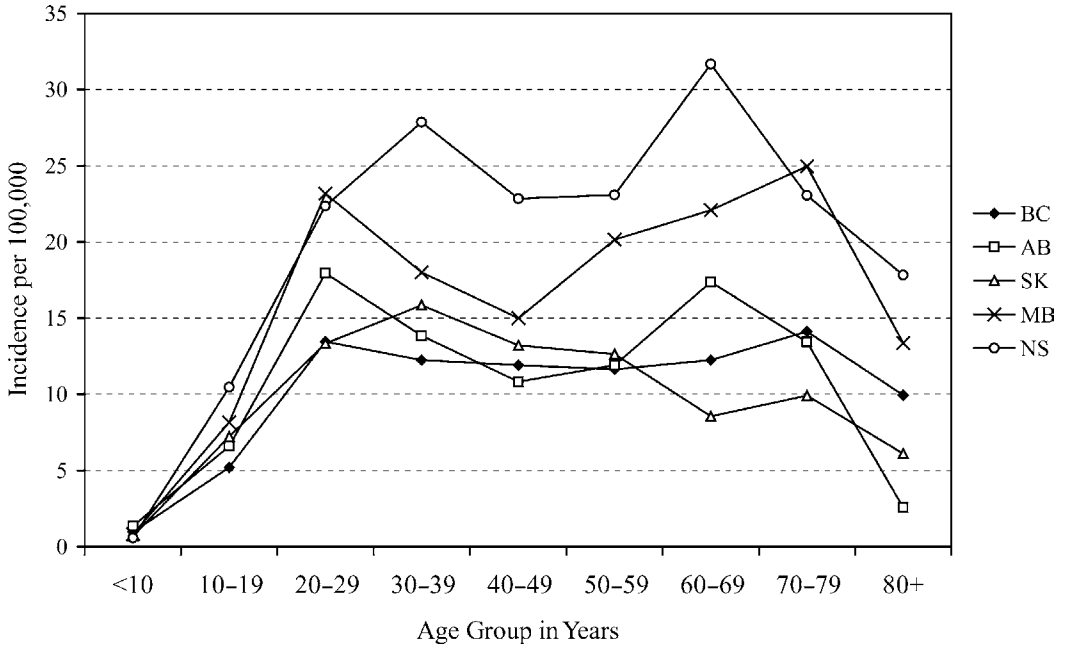


Figure 3-2: Age distribution of the incidence of ulcerative colitis for British Columbia, Alberta, Saskatchewan, Manitoba, and Nova Scotia from 1998 to 2000.[21]

3.1.5 Prevalence of IBD Today

Prevalence is the proportion of the population that suffers from IBD at a particular moment in time. After decades of rising incidence (the number of new cases annually) of IBD in the 20th century and low death rates among young patients affected by these diseases, the prevalence of IBD has ballooned in Canada during the 21st century.[2] Based on prevalence data from Alberta, British Columbia, Manitoba, Nova Scotia, and Saskatchewan, the average prevalence of IBD in Canada was estimated to be 0.47% in 1998-2000.[21] Table 3-2 provides historical data on the prevalence of IBD by different provinces; including data from Quebec (0.45% in 2008) and Ontario (0.51% in 2008).[2,4] The number of people with IBD in Canada is estimated to be approximately 270,000 (0.7%) as of 2018.[4] This number breaks down as 135,000 individuals living with Crohn's disease and 120,000 with ulcerative colitis. An additional 15,000 patients have IBD, but their diagnosis is not clearly classified as Crohn's disease or ulcerative colitis.[4]

3.1.6 Prevalence of IBD Tomorrow

The prevalence of IBD is expected to climb over the next decade due to the compounding effect of prevalence. IBD is a lifelong disease with no cure that is most commonly diagnosed in young individuals. However, the risk of dying from IBD is very low.[30,31] Because the incidence of IBD is much higher than the risk of death from IBD, the prevalence of IBD is estimated to increase by 2.9% per year such that the estimated prevalence of IBD in 2018 (0.7%) is forecasted to climb to nearly 1% by 2030 (Figure 3-3).[4] Table 3-2 presents statistical models of the changing prevalence of IBD over the next decade. By 2030, statistical models predict that approximately 403,000 people will be living with IBD in Canada.[4]

3.1.7 Mortality from IBD

The risk of death from IBD is low. IBD is unlikely to kill patients directly. However, it is associated with cancers and other complications that result in a slightly higher death rate than the general population. Patients with Crohn's disease have approximately a 25% higher risk of dying than the general population. The risk of death in ulcerative colitis patients is increased in the first year after diagnosis but beyond that is the same as the general populaton.[31]

Examining data from Manitoba:

- persons with Crohn's disease are more likely than the general population to die of colorectal cancer, non-Hodgkin's lymphoma, pulmonary embolism, or sepsis;
- persons with ulcerative colitis are more likely to die from colorectal cancer or respiratory diseases;
- and, the greatest risk for death associated with both Crohn's disease and ulcerative colitis is within the first 30 days following gastrointestinal surgery.[31]

Analyzing data from Ontario:

- persons over age 65 with Crohn's disease have higher rates of mortality directly attributable to IBD compared with middle-age or younger adults;
- IBD-attributed mortality is not different by age in persons with ulcerative colitis;
- the leading cause of death in senior Crohn's disease and ulcerative colitis patients is solid malignancies—accounting for one quarter of all IBD-attributed deaths.[32]

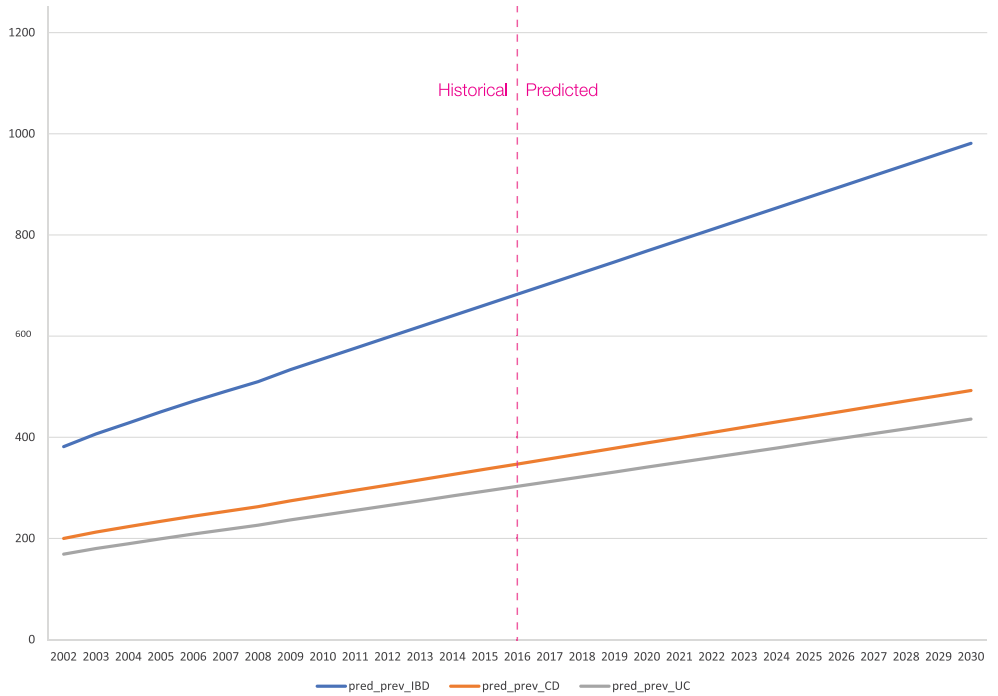


Figure 3-3: Projected prevalence of IBD in Canada.[4]

Analyzing data from Quebec:

- All-cause mortality was increased in both Crohn's disease and ulcerative colitis when compared to the general population

- Mortality from digestive conditions, and neoplasms (e.g. colorectal, lymphatic, and lung cancer) was significantly higher in Crohn's disease as compared to the general population.[72]

- Mortality from digestive, respiratory, and infectious conditions increased for ulcerative colitis.[33]

3.1.8 Implications

This high prevalence of IBD in Canada will challenge us to provide safe, high quality, and cost-efficient care to patients with IBD without overwhelming our fiscal, staffing, and infrastructure resources. This challenge can only be met by physicians and healthcare systems prioritizing innovations in the delivery of care and information technology, and finding resources to address the increasing volume of patients in IBD clinics.

3.2 Comparing the Burden of IBD in Canada to the Rest of the World

3.2.1 Global Perspective of IBD in the 20th Century

During the 20th century, IBD was considered a disease of the western world with the greatest predominance in North America, Europe, and Australia.[18] Studies have consistently documented that the incidence and prevalence of IBD in Canada is comparable or greater than most countries in the western world.[1,2] A nationwide study in the USA reports 0.49% prevalence of IBD in 2008-2009.[33] Epidemiologic studies from Europe have shown considerable geographic variability with the highest incidence of IBD in Western Europe and Scandinavia, lower rates of IBD in countries alongside the Mediterranean Sea, and sharp discrepancies throughout Eastern Europe.[10] In contrast, the incidence of IBD in the 20th century in developing countries in Asia, Africa, and South America is extremely low.[1] At the turn of the 21st century, important epidemiological patterns have shifted that have changed the global perspective of IBD.[2]

3.2.2 Global Perspective of IBD in the 21st Century

In the 21st century, the incidence of IBD is plateauing in most western world countries.[2] The incidence of IBD is coalescing around a range of three to 15 per 100,000 persons for both Crohn's disease and ulcerative colitis. While some countries are reporting higher incidence rates, it appears that the ceiling for incidence is between 20 and 30 per 100,000 persons for each of Crohn's disease and ulcerative colitis.[2] This information is vital to healthcare systems in Canada and the rest of the western world to anticipate the rising burden of newly diagnosed patients with IBD.[18]

In the 21st century, IBD is considered a global disease that can manifest in any geographic region and within any race or ethnicity.[22] Figure 3-4 and 3-5 displays global maps comparing the incidence of Crohn's disease (Figure 3-4) and ulcerative colitis (Figure 3-5). Collectively, data from newly

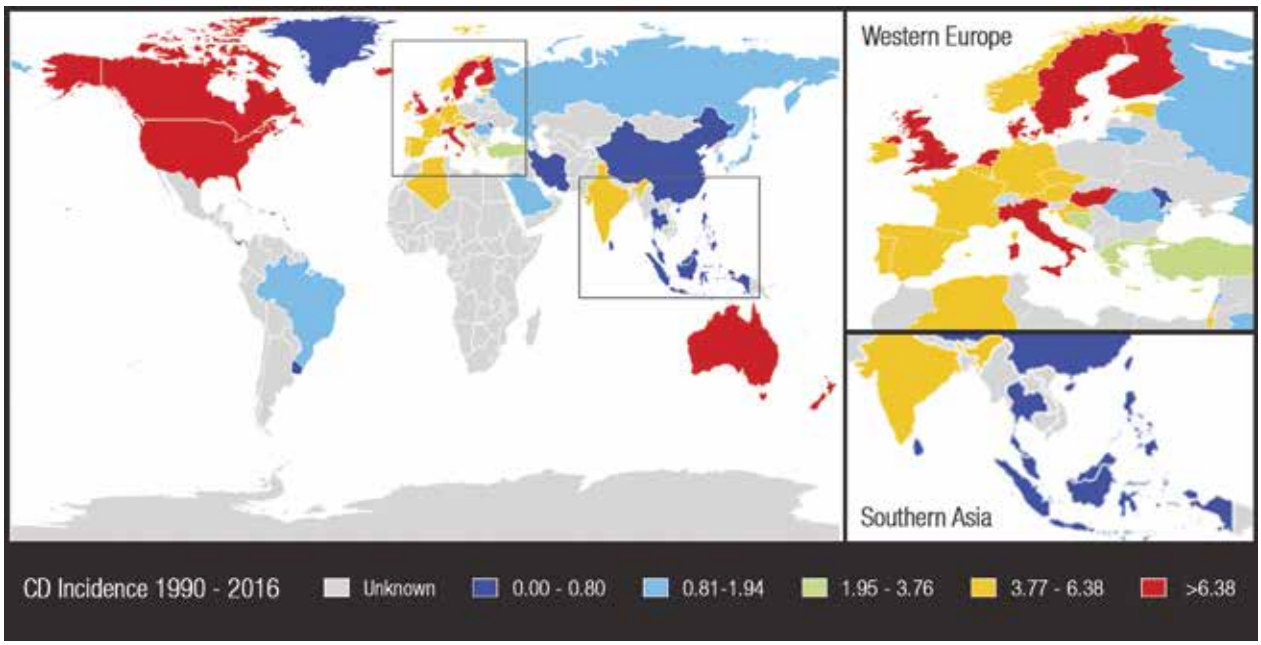


Figure 3-4: Worldwide incidence of Crohn's disease stratified from low to high incidence (per 100,000). CD: Crohn's disease. An interactive global map of IBD can be found online: https://people.ucalgary.ca/~ggkaplan/IBDG2016.html.[2]

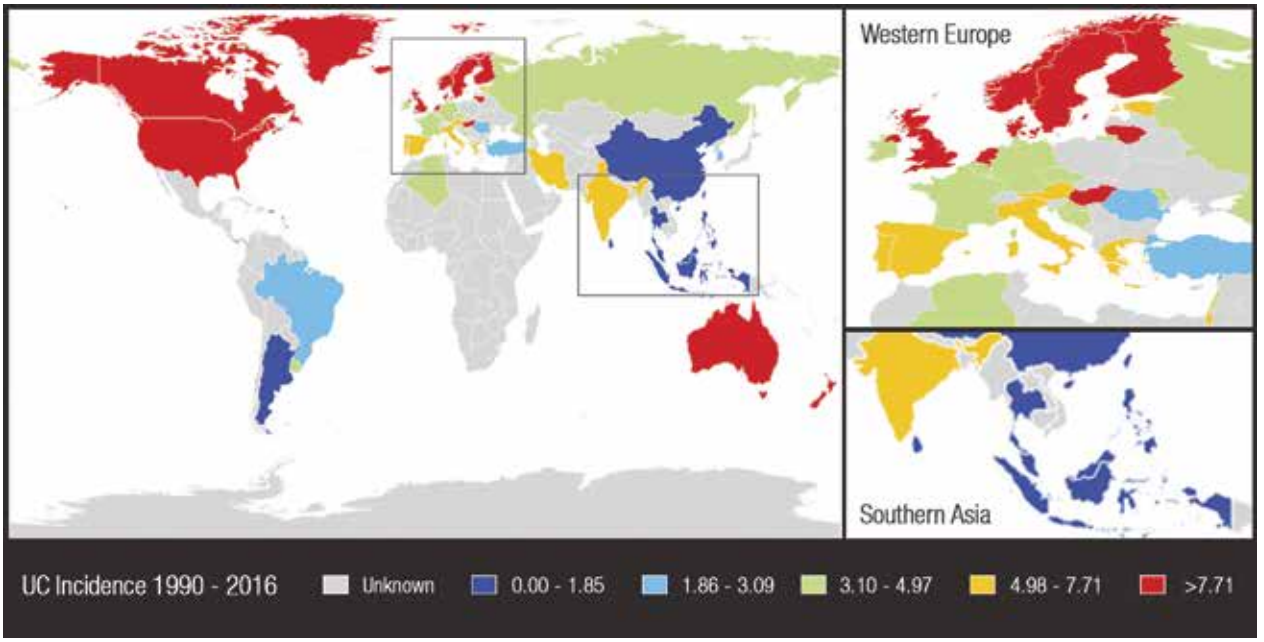


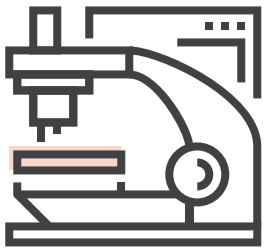
Figure 3-5: Worldwide incidence of ulcerative colitis stratified from low to high incidence (per 100,000). UC: ulcerative colitis. An interactive global map of IBD can be found online: https://people.ucalgary.ca/~ggkaplan/IBDG2016.html.[2]

industrialized countries in Asia, Africa, and South America highlight the global rise of IBD. The peak in the incidence of IBD has yet to unfold in these continents.[18] Only time will tell if the incidence and prevalence of IBD in Asia, Africa, and South America will approximate those of the western world. If so, the implications are profound for countries like China and India whose populations exceed one billion people.

3.2.3 Implications

In order to manage this relatively new disease, newly industrialized countries in Asia, Africa, and South America need to prime their clinical infrastructure and brace their personnel for an escalating burden. Moreover, the globalization of IBD demands a collective effort to develop strategies to drive down the incidence of IBD in Canada and throughout the world. Preventing IBD requires a fundamental understanding of the genetic, environmental, and microbial factors underpinning its pathogenesis.

3.3 The Biology Behind IBD: Genes, Microbes, and Environment



Crohn's disease and ulcerative colitis are believed to occur in genetically predisposed individuals who have an abnormal immune response to microorganism in the gut.[22] Understanding the biology behind IBD is critical in developing novel strategies to improve the quality of life for people living with the disease including: enhancing treatment approaches, exploring possibilities in curing the disease, and identifying avenues for prevention.[35]

3.3.1 Genetics

The genetic underpinning of IBD has long been recognized. Early studies on twins show that identical twins are more likely to both have Crohn's disease or ulcerative colitis as compared to fraternal twins.[36] In 2001, NOD2 the very first gene linked to Crohn's disease was discovered. The NOD2 gene provides a clue that Crohn's disease may be driven by the intestinal microbiome because NOD2 is involved in the immune response to gut bacteria.[37-39] Subsequently, genetic analyses that sequence vast regions of the human genome (genome-wide association studies) have identified more than 200 genetic mutations associated with the development of Crohn's disease and ulcerative colitis. In many cases, these genetic mutations are shared across both forms of IBD.[40] Importantly, around two thirds of gene mutations linked to IBD are also shared with other immune-mediated disorders including type 1 diabetes mellitus, celiac disease, rheumatoid arthritis, ankylosing spondylitis, and psoriasis.[41] The collective knowledge of the proteins made by these genetic loci paints a clear picture of the critical role between the immune response in the bowel and the 100 trillion microbes living there.

3.3.2 Microbiome

A leading hypothesis on the etiology of IBD is that changes in the gut microbiome trigger immune responses that cause abnormal inflammation.[42] Considering that persons with IBD are studied after the disease has manifested, it is not clear as to whether the changes in the microbiome and immune response are a cause or effect of the disease.[43] If changes in the microbiome prove to be germane to the cause of IBD, another key question is how and when do these changes emerge? One working hypothesis suggests that the use of antibiotics, which can alter the gut microbiome even long after the antibiotics are discontinued, may be a sufficient trigger to allow IBD to develop.[44] If that hypothesis proves to be viable, then we need to discern the critical period of antibiotic ingestion that impacts on the gut microbiome to facilitate the emergence of IBD. Early childhood is a critical time for microbiome evolution and hence may be a critical time for antibiotic use. In other words, is there a developmental period in which antibiotic use should be restricted as much as possible in order to prevent, or lower the risk, of a person developing IBD?[45] Much more work is required to understand the exact causes of microbiome changes and the changes that are most relevant to triggering disease so that treatments be developed to prevent or reverse IBD.

3.3.3 Environmental Exposures

Numerous studies have indicated that environmental exposures are critical in triggering the development of IBD.[3] Figure 3-6 illustrates the most commonly implicated environmental determinants of IBD.[46]

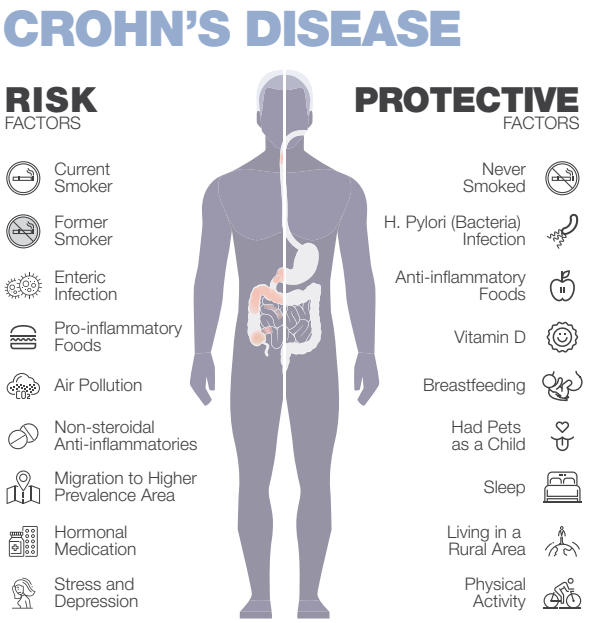


Figure 3-6: Environmental determinates of IBD.[46]

3.3.3.1 Hygiene Hypothesis

One prominent explanation for the emergence of IBD is the Hygiene Hypothesis.[47] This hypothesis postulates that children growing up in relatively sterile environments—without adequate exposure to microbes—insufficiently educate their immune system for handling microorganisms. They then develop an abnormal immune response that attacks their organs later in life when exposed to harmful microorganisms. Indirect evidence supporting the Hygiene Hypothesis includes research showing that Crohn's disease and ulcerative colitis are less likely to occur in individuals who: live with pets in childhood; are raised on a farm or rural region; have a larger family; or drink unpasteurized milk.[21,48]

More recent research has shed additional light on the Hygiene Hypothesis. This research indicates that susceptibility to IBD may be due to early-life exposures that alter the composition of the intestinal microbiome, including the loss of so-called friendly microorganisms that could benefit the host immune response. IBD is more likely to develop in those who were exposed to antibiotics within the first year of life and also in those who were not breastfed. Antibiotics and breastfeeding strongly influence the diversity of the microbiome in children, laying down the foundation for either the future development of, or protection against, IBD. Individuals with a history of infectious gastroenteritis are more likely to be diagnosed with Crohn's disease or ulcerative colitis, particularly among childhood-onset IBD.[49-52]

3.3.3.2 Nutrition

Diet has been studied extensively in IBD with recent evidence supporting the strong influence of dietary factors on the intestinal microbiome. Studies have postulated that a western diet, one with a higher consumption of fats and refined sugars[53-56] and reduced consumption of dietary fibre,[57,58] profoundly changes our gut's microbiome. Moreover, recent research implicates processed food in a western diet is a contributor to developing IBD. Work in animal studies, yet to be corroborated in humans, indicates that food additives such as sweeteners and emulsifiers may also incite inflammation in the bowel. In addition to processed foods, pervasive fast food consumption is also associated with IBD. The association between fast food consumption and IBD may be direct via exposure to fatty foods or food additives, or indirect via correlated lifestyles, such as reduced levels of physical activity.[59,60]

3.3.3.3 Other Environmental Determinates

Several other environmental determinates have been demonstrated consistently to influence the development of IBD among Canadians:

- Cigarette smoking increases the risk of developing Crohn's disease in adults. However, adults who quit smoking are at increased risk of ulcerative colitis.[61]

- Oral contraceptives increase the risk for Crohn's disease particularly among women who smoke.[62]

- Non-steroidal anti-inflammatory drugs may also trigger IBD.[63-67]

- Appendicitis diagnosed before the age of ten years protects against ulcerative colitis.[68]

- A lack of vitamin D from reduced sun exposure has been hypothesized to increase the risk of developing IBD. This hypothesis stems from the fact that IBD occurs more commonly in countries in northern latitudes, such as Canada and Scandinavia. Vitamin D is important in regulating the immune system and its deficiency has been associated with an increased risk of IBD.[69]

- Air pollution may increase the risk of developing Crohn's disease in children and young adults[70] as a result of the way it alters the intestinal microbiome.[71]

3.3.3.4 Implications

Identifying environmental risk factors of IBD is important because modifying environmental exposures is a potential avenue to prevent the development of IBD. For example, over the past 10 years, we have observed the stabilization of incidence rates in Canada. This may be related to declining cigarette smoking rates, the most strongly associated environmental risk factor for development of IBD. The frequency of smoking in the general population has dropped by more than half: from ~40% of the population in the 1980s to less than 20% today. Canadian public health programs educating adolescents to avoid smoking in the 1980s and 1990s, led to a generation of non-smokers who are unlikely to develop smoking related complications like cardiovascular disease, lung cancer, and possibly IBD. A recent study from the UK, which adopted similar anti-smoking programs as Canada, shows that from 1999 to 2009, the proportion of newly diagnosed people with Crohn's disease who had a prior history of smoking dropped significantly, by some 3% per year.[72]

The growing knowledge of environmental determinates of IBD serves as a guide for clinicians and policy makers to focus on preventing the onset of IBD. Future research is necessary in order to substantiate the effectiveness of these recommendations and to identify additional environmental determinates of IBD.

3.4 Conclusion

IBD has been predominantly a disease of the western world and while incidence rates remain considerably higher in western nations, newly industrialized nations have seen a marked rise in incidence over the past 25 years. Since population genetics have not changed in such a short period of time, this observation suggests that environmental factors are likely to be of much greater importance in driving the emergence of these diseases. Some potential culprits are environmental changes that alter the gut microbiome, thought to be an important trigger of the disease. Therefore, exposures such as changing breastfeeding patterns, the early childhood use of antibiotics, dietary changes throughout life, and cigarette smoking all may be critical areas of research for the prevention, or reversal, of IBD.

The consistently high incidence rates of IBD in the western world, and the increasing rates in newly industrialized countries of Asia, Africa, and South America, lead to a growing worldwide burden of disease that is accompanied by increasing costs in providing care to the growing population of affected individuals. This is especially the case in light of the expensive medications often needed for treatment. Ongoing epidemiologic study of IBD will be critical in determining disease burden as well as to identify potential etiological clues for management and prevention.

Key Summary Points: Epidemiology

1. The incidence (the number of new diagnosis annually) of IBD rose throughout the 20th century in Canada, and then stabilized at the turn of the 21st century.

2. The prevalence (the total number of diagnosed persons in the population) of IBD in Canada is among the highest in the world.

3. Today 270,000 (0.7%, or 7 in 1,000) Canadians are estimated to live with IBD. By 2030, that number is expected to rise to 403,000 Canadians (1% or 1 in 100).

4. IBD can be diagnosed at any age. However, the age groups that are most likely to be diagnosed are adolescents and young adults from 20 to 30 years of age.

5. IBD in Canada affects the lives of Canadians of all ethnicities, including known high-risk groups such as Ashkenazi Jews and those thought previously to be at low risk, such as first generation offspring of South Asian immigrants.

6. Canadian health policy makers will need to prepare the Canadian healthcare system for the rising burden of IBD.

7. As newly industrialized countries in Asia, Africa, and South America are transitioning to a westernized society, IBD has emerged and its incidence in these countries is rising rapidly.

8. The gut microbiome includes microorganisms that maintain digestive health. Thus, changes in the microbiome, which may change the immune system's response to triggers, may be important in initiating and perpetuating IBD.

9. A number of factors can alter the gut microbiome and early childhood may be a particularly important time such that breastfeeding, early life diet, use of antibiotics, infections, and other environmental exposures may impact the gut microbiome in such a way that facilitates developing IBD.

10. Smoking is associated with an increased risk and worsening disease course of Crohn's disease. Quitting smoking is associated with an increased risk of developing ulcerative colitis. Therefore, never initiating smoking can mitigate the risk for IBD. Educational programs aimed at those at-risk for IBD should emphasize the risk of starting to smoke tobacco.

11. Modifying exposure to environmental risk factors associated with the westernization of society (e.g., western diet and lifestyles) may provide an avenue for reducing the risk of IBD in Canada and worldwide.

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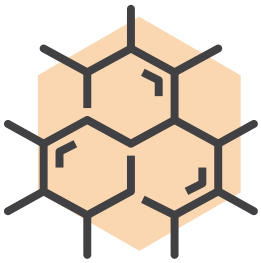
DIRECT COSTS & HEALTH SERVICES UTILIZATION

Direct Costs & Health Services Utilization

Highlights

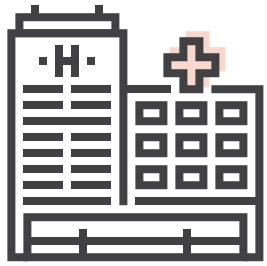
1. In Canada, the direct cost of caring for people living with IBD is estimated to be approximately $1.28 billion in 2018 (roughly $4,731 per person with IBD).

2. The costs of caring for people living with IBD are dominated by prescription drugs, followed by hospitalization costs. There has been a shift away from hospitalizations and towards pharmaceuticals as the predominant driver of direct healthcare costs in IBD patients, due to the introduction and widespread use of expensive biologic therapies.

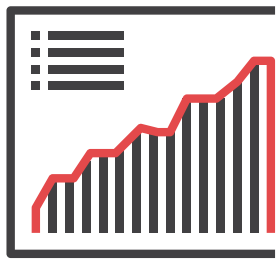


3. The rates of hospitalizations and major abdominal surgeries have been declining in IBD patients in Canada over the past two decades, However, with increasing penetration of biologics into the marketplace, direct costs of care can be predicted to rise for years to come.

4. IBD patients cared for by gastroenterologists have better outcomes, including lower risks of surgery and hospitalization. Canadians who live in rural and underserviced areas are less likely to receive gastroenterologist care, potentially due to care preferences or poorer access, which may result in poorer long-term outcomes.



5. Introduction of biosimilar agents at a lower price point than originator biologic therapies, increased gastroenterologist care of IBD patients and improvements in IBD care paradigms may improve health outcomes and quality of life for IBD patients while tempering rising costs of care.



Gaps in Knowledge and Future Directions

1. Forecasting models are necessary to predict the rising costs attributable to biologics associated with increasing prevalence of IBD, more frequent use of these medications, and the introduction of newer agents.

2. Research into ways to minimize the escalating costs associated with increasing use of biologic therapies to treat IBD (and other chronic diseases) is necessary to ensure sustainability of our publicly funded healthcare system. Biosimilars offer an opportunity to drive down the cost of biologic therapies and future research should assess the uptake of biosimilars as new biosimilars are introduced into the marketplace.

3. Cost-utility models and budget impact analyses that integrate changes in direct costs (reduced hospitalizations and increased pharmaceutical costs) with indirect cost savings from improved quality of life are necessary to inform policy decisions.

4. Research into ways to reduce IBD hospitalizations further through targeted outpatient interventions is equally important for health system sustainability and to improve patient quality of life.

5. Research into reasons for reduced gastroenterologist care among rural and underserviced IBD residents would allow targeted interventions to improve specialist care and thereby improve patient health outcomes and quality of life.

4.0 Abstract

Direct healthcare costs of illness reflect the costs of medically necessary services and treatments paid for by public and private payers, including hospital-based care, outpatient physician consultations, prescription medications, diagnostic testing, complex continuing care and home care.

The costs of caring for persons with IBD have been rising well above inflation over the past 15 years in Canada, largely due to the introduction and penetration of expensive biologic therapies. Changing paradigms of care towards tighter patient monitoring and achievement of stricter endpoints for disease control have also increased health services utilization and costs among IBD patients

While the frequency and costs of surgeries and hospitalizations have declined slightly in parallel with increased biologic use (due to better overall disease control), the direct medical costs of care for IBD patients are largely dominated by prescription drug costs. Introduction and penetration of biosimilar agents (at a markedly lower price point than the originator drugs) and increasing gastroenterologist involvement in the care of IBD patients may help to balance rising healthcare costs while improving health outcomes and quality of life for IBD patients. Ultimately, however, the predicted rise in the prevalence of IBD over the next decade, combined with increasing use of expensive biologic therapies, will likely dictate a continued rise in the direct costs of IBD patient care in Canada for years to come.

In 2018, direct healthcare costs of IBD are estimated to be at least CAD$1 billion and possibly higher than CAD$2 billion.

4.1 Introduction

Direct healthcare costs are the costs associated with medically necessary products and services, including hospital-based care, outpatient physician consultations, prescription medications, diagnostic testing (laboratory tests and diagnostic imaging), complex continuing care (*i.e.* rehabilitation, long-term care, etc.) and home care. In Canada, these costs are borne by each province's public healthcare system, while a significant proportion of prescription drug costs are borne by either private payers (through drug plans) or patients.

As there is no cure for IBD, patients require long-term medical care, including frequent physician visits, multiple medical tests and treatments, hospitalizations, and surgeries. There has also been a push towards more aggressive monitoring and treatment of individuals with IBD over the past decade, with a revised goal of establishing and maintaining complete healing of the bowel.[1] This new focus promotes increased use of endoscopy, diagnostic imaging, and laboratory services; increased frequency of specialist visits to monitor disease response; and, more aggressive (and expensive) targeted therapies to achieve strict endpoints. Additionally, "top-down" and "accelerated step-up" approaches to treatment, reflecting earlier introduction of biologic therapies in persons with aggressive disease phenotypes or who are failing early conventional treatments, are being increasingly adopted based on evolving literature and expert opinion.[2,3]

Introduction of newer biologic therapies and evolving paradigms of care have increased the complexity of caring for IBD, underscoring the importance of early and continued specialist involvement. Moreover, these factors, which are intended to improve patient outcomes and quality of life, have likely driven up the costs of IBD care in recent years.

4.2 Total Direct Costs of Caring for Patients with IBD in Canada

In population-based studies from Quebec, Manitoba, and Alberta, persons with ulcerative colitis cost the healthcare system, on average, between CAD$3,552 (Manitoba) and CAD$8,900 (Quebec) per person annually, while persons with Crohn's disease costs the healthcare system CAD$4,232 per person annually (Manitoba).[4-6] On average, caring for older IBD patients costs more than caring for younger IBD patients.[4,5] In Manitoba, the most costly IBD patients are those within one year of diagnosis (mean CAD$6,611), those that are hospitalized (15% of IBD patients, mean CAD$13,495), those that undergo major surgery (2% of IBD patients, mean CAD$18,749), and those that use anti-TNF therapy (0.7% of IBD patients, mean CAD$31,440).[5] Table 4-1 provides a comparison of the direct healthcare costs of IBD across Canadian provinces, the United States, Europe, and Australia.

In Manitoba, the mean and median direct costs of IBD care were more than two times greater in IBD patients than age- and sex-matched controls (CAD$3,896 vs CAD$1,826 for mean, CAD$1,562 vs CAD$448 for median) in 2005.[5] The cost gap between persons with and without IBD was greatest among children. Prescription drug use accounted for 42% and 37% of total direct costs while hospitalizations were responsible for 39% and 40% of total direct costs, among IBD patients and controls, respectively. In contrast, among IBD patients in Quebec, prescription drugs contributed to just 20% of total direct healthcare costs, while hospitalizations contributed to 67% of direct healthcare costs.[6] In Alberta, the median cost per hospitalization for ulcerative colitis ranged from CAD$5,499 (persons with disease flare not requiring colectomy) to CAD$23,698 (persons requiring emergent colectomy).[4] In all three provinces, the costs of biologics were significant drivers of medication costs. For example, while only 6.6% of newly diagnosed patients with ulcerative colitis in Quebec were receiving anti-TNFs, these medications represented 57.4% of the total cost of medications for these patients.

Based on these three studies, there are significant differences in direct costs of IBD care depending on the province and method of ascertaining cost. Applying the Manitoba estimates for mean cost per person with IBD and adjusting for inflation (CAD$4,731 per person in 2018), the total direct medical cost of managing the predicted 270,000 patients living with IBD in Canada in 2018 is close to CAD$1.28 billion (range 1.26 to 1.30 billion). However, based on estimates of direct costs in ulcerative colitis patients from Alberta and Quebec, total direct medical costs may be as much as twice this estimate.

Across non-Canadian cohorts, sector-specific expenditures in IBD patients have been highly variable (see Table 4-1). A cohort study from Australia reported that about 18% and 12% of direct healthcare costs among persons newly diagnosed with ulcerative colitis were attributable to medical and surgical hospitalization costs, respectively.[7] Among those newly diagnosed with Crohn's disease, 14% and 32% of total direct costs resulted from medical and surgical hospitalizations, respectively.[7] This same study reported that 32% and 39% of direct costs of care were related to prescription medications among patients with Crohn's disease and ulcerative colitis, respectively.[7]

In a large European prospective population-based inception cohort of IBD patients, medical therapies and surgeries accounted for 36% and 26% of total healthcare expenditures, respectively, in the first year following diagnosis.[8] Anti-TNF use accounted for just 14% of total healthcare costs, while standard medical therapy accounted for 22% of total direct costs. Conversely, in a large Dutch cohort, hospitalization costs accounted for less than 20% of healthcare costs in persons with Crohn's disease and 23% of healthcare costs in persons with ulcerative colitis; anti-TNFα use accounted for 64% and 31% of the total healthcare cost in Crohn's disease and ulcerative colitis patients, respectively.[9]

Table 4-1: Summary of the literature on direct healthcare costs of patients with inflammatory bowel disease.

[a] unless otherwise stated; [b] median; [c] includes medical and surgical hospitalizations; [d] costs do not include deductibles and other costs to the patient; * does not include the cost of infliximab

Country/ Province	Study	Time period of study	Type of IBD	Overall cost (mean cost per person[a])	Cost of outpatient physician visits (% of total)	Cost of emergency department visits (% of total)	Cost of diagnostic procedures (% of total)	Cost of hospitalization (% of total)	Cost of surgical care (% of total)	Cost of medications (% of total)
Alberta	Coward 2015[4]	Cost per hospitalization	UC					Non-surgical hospitalization: $5,499[b] (IQR 5,530)	Elective colectomy: $14,316[b] (IQR 6,399) Emergent colectomy: $23,698[b] (IQR 14,404)	
Alberta	Loomes 2011[10]	Costs before and after starting infliximab	CD	**Pre-infliximab** Year 2: $3,981 Year 1: $3,930 **Post-infliximab** Year 1: $25,346 Year 2: $20,098	**Pre-infliximab** Year 2: $264 Year 1: $285 **Post-infliximab** Year 1: $478 Year 2: $497	**Pre-infliximab** Year 2: $118 Year 1: $191 **Post-infliximab** Year 1: $107 Year 2: $131	**Pre-infliximab:** Year 2 Colonoscopy: $423 CT: $99 MRI: $45 X-ray: $14 Year 1: Colonoscopy: $426 CT: $114 MRI: $38 X-ray: $10 **Post-infliximab** Year 1: Colonoscopy: $242 CT: $75 MRI: $53 X-ray: $8 Year 2: Colonoscopy: $255 CT: $72 MRI: $32 X-ray: $7	**Pre-infliximab** Year 2: $2,881[c] Year 1: $2,715[c] **Post-infliximab** Year 1: $968[c] Year 2: $1,037[c]	**Pre-infliximab** Year 2: $1,895 Year 1: $1,504 **Post-infliximab** Year 1: $263 Year 2: $351	Infliximab only (post-infliximab): Year 1: $23,328 Year 2: $17,969
Manitoba	Bernstein 2012[5]	Varying disease duration	IBD (all types)	All patients: $3,896 (se 90) Newly diagnosed: $6,611 (se 593) Long standing disease (4+ years): $3,621 (se 94)	All patients: 13% Newly diagnosed: 11% Long-standing disease (4+ years): 14%		All patients: 6% Newly diagnosed: 6% Long-standing disease (4+ years): 6%	All patients: 39%[c] Newly diagnosed: 63%[c] Long-standing disease (4+ years): 35%[c]		All patients: 42% Newly diagnosed: 20% Patients with long-standing disease (4+ years): 45%
			CD	All patients: $4,232 (se 137) Newly diagnosed: $6,570 (se 686) Long-standing disease (4+ years): 3,918 (se 145)	All patients: 12% Newly diagnosed: 11% Long-standing disease: 13%		All patients: 5% Newly diagnosed: 7% Long-standing disease: 5%	All patients: 39%[c] Newly diagnoswed: 63%[c] Long-standing disease (4+ years): 35%[c]		All patients: 44% Newly diagnosed: 19% Long-standing disease (4+ years): 47%
			UC	All patients: $3,552 (se 117) Newly diagnosed: $6,650 (se 958) Long-standing disease (4+ years): 3303 (se 119)	All patients: 14% Newly diagnosed: 10% Long-standing disease (4+ years): 14%		All patients: 7% Newly diagnosed: 5% Long-standing disease (4+ years): 7%	All patients: 39%[c] Newly diagnosed: 63%[c] Long-standing disease (4+ years): 36%[c]		All patients: 40% Newly diagnosed: 21% Long-standing disease (4+ years): 43%
Manitoba	Targownik 2018[11]	Costs in the year before and after starting anti-TNF.	IBD (all types)	Pre-anti-TNF: $10,206 Post-anti-TNF: $44,786				Pre-anti-TNF: $6,419 Post-anti-TNF: $5,627		Pre-anti-TNF: $1,861 Post-anti-TNF: $37,448 (95% of total drug costs)
Quebec	Dan 2017[6]	Incident cases with a 1-year washout period. Costs are reported per day.	UC	$59.34 (sd 159.29)	GI visits to non-gastroenterologists: $0.38 (sd 0.77) Visits to gastroenterologists: $0.52 (sd 0.76)	GI-related visits: $1.61 (sd 5.28)		$41.27 (sd 112.74) per day	$9.90 (sd) 110.290 per day	5-ASA: $1.42 (sd 2.00) per day immunomodulators: $0.25 (0.93) per day anti-TNF: $3.23 (sd 15.67) per day corticosteroids: $0.16 (sd 0.35) per day GPAs: $0.61 (sd 0.87) per day Other UC medications: $0.02 (0.17) per day
United States	Gleason 2013[12]	Prevalent cases	IBD (all types)	US$22,070						**Biologic only** $2,929 (13.3%)
United States	Karve 2012[13]	Incident cases with a 6-month washout. Costs incurred in the first 12 months.	IBD (all types)	US$18,302 (sd 41,955)	Office visits: US$1,013 (1,573)	US$366 (1,224)	Outpatient visits: US$4,063 (sd 9,027)	US$10,185 (sd 36,306)		US$2,677 (sd 5,536) Steroids: US$67 (sd 276) | Anti-TNFs: US$35 (sd 513) | Immunomodulators: US$151 (sd 397) | Salicylates: US$857 (sd 1308) | Other: $1568 (sd 5040)
United States	Park 2016[14]	Prevalent cases	CD	US$18,637 (sd 32,023)[d]	MD office: 8.2%	2.6%	Outpatient hospital procedures: 15.7% Outpatient setting other: 8.6%	23.1%[c]		45.5%
United States	Wan 2014[15]	Costs before and after starting infliximab	IBD (all types)	**Pre-infliximab:** US$22,463 (sd 25,376) **Post-infliximab:** Adherent: US$41,713 Non-adherent: US$47,411	**Pre-infliximab:** US$10,264 (sd 12,489) **Post-infliximab:** Adherent: US$7,357 Non-adherent: US$10,909			**Pre-infliximab:** US$7,814 (sd 20,092)[c] **Post-infliximab:** Adherent: US$2,458[c] Non-adherent: US$17,634[c]		Post-infliximab: Adherent: Infliximab: US$28,289 Other: US$3,373 Non-adherent: Infliximab: US$14,889 Other: US$3,521
Australia	Niewiadomski 2015[7]	Incident cases; costs incurred in the first 12 months following diagnosis	CD	A$10,477 (sd 12,737)	A$258 (sd 34) (2%)		A$2,196 (sd 956) (21%)	A$6,493 (sd 2,884) (14%)	A$15,283 (sd 18,656) (32%)	A$3,366 (sd 5,912) (32%)
			UC	A$6,292 (sd 6,96)	A$242 (sd 37) (4%)		A$1,825 (sd 743) (29%)	A$6,282 (sd 5,276) (18%)	A$35,506 (sd 31,228) (12%)	A$2,447 (sd 1,898) (39%)
Australia	Gibson 2014[16]	Prevalent cases. Costs are reported per 3-month period	UC	A$2,914 (sd 3,447, 95% CI 2,399 to 3,428)	GP: A$371 (4%) Specialist: A$1,100 (13%) ED visit: A$46 (<1%)			A$6,643 (82%)[c]		
Europe Multi-national	Odes 2010[17]	Incident cases, followed for up to 10 years. Costs are reported per 3-month period	CD	€569.10 (sd 2,188.90)						
			UC	€324.80 (sd 1,659.90)						
Europe Multi-national	Burisch 2015[8]	Incident cases. Costs were those incurred in the first 12 months following diagnosis	IBD (all types)	€3,956			€1,495 (38%)		€1,044 (26%)	Biologics: €571 (14%) Standard medication: 22% 5-ASA: €567 | Glucocorticoids: €217 | Immunomodulators: €63
			CD	€5,942			€1,857 (31%)		€1,995 (34%)	Biologics: €1,168 (20%) Standard medication: 15% 5-ASA: €328 | Glucocorticoids: €509 | Immunomodulators: €85
			UC	€2,753			€1,248 (45%)		€476 (17%)	Biologics: 8% Standard medication: 30% 5-ASA: €734 | Glucocorticoids: €29 | Immunomodulators: €51
Netherlands	Severs 2016[18]	Prevalent cases	IBD	€4,866 (95% CI 3,290 to 6,443)			€58.8 (95% CI 19.5-98.1)	€597.30 (95% CI 188.30-1006.3)	€91.3 (95% CI 4.7-177.8)	Anti-TNF only: €3,924.0 (95% CI 2,427.0-5,420.9)
Netherlands	van der Valk 2014[9]	Prevalent cases. Costs are per 3-month interval	CD	€1,625.18 (95% CI 1,475.87 to 1,774.50)	Gastroenterologist: €60.65 (54.70 to 66.59) (3.7%) Specialized nurse: €5.67 (95% CI 4.86 to 6.47) (0.3%) Internist: €5.61 (95% CI 3.66 to 6.66) (0.3%) Dietician: €3.52 (95% CI 2.33 to 4.70) (0.2%) Surgeon: €6.24 (95% CI 3.71 to 8.78) (0.4%) Rheumatologist: €4.06 (95% CI 2.62 to 5.50) (0.2%) Dermatologist: €3.50 (95% CI 1.90 to 5.11) (0.2%) Occupational physician: €1.88 (95% CI 0.87 to 2.88) (0.1%) Psychiatrist: €7.68 (95% CI -5.12 to 20.47) (0.5%) GP visits (evening/weekend): €4.99 (95% CI 3.85 to 6.13) (0.3%)	€5.83 (95% CI 3.73 to 7.94) (0.4%)	€40.60 (95% CI 33.58-47.56) (2.6%) Colonoscopy: €24.31 (95% CI 19.71 to 29.46) (1.5%)	€315.25 (95% CI 231.18 to 399.33) (19.4%)	€9.90 (95% CI 2.71 to 17.10) (0.6%)	€1,145.33 (95% CI 1,041.80 to 1,248.86) (70.5%) Mesalazine: €54.82 (95% CI 49.27 to 60.38) (3.4%) Budesonide: €10.83 (8.44 to 13.21) (0.7%) Prednisone: €0.40 (0.27 to 0.53) (0.0%) Azathioprine: €23.30 (95% CI 21.15 to 25.44) (1.4%) 6-mp: €6.13 (4.90 to 7.37) (0.4%) Methotrexate: €8.12 (95% CI 5.73 to 10.52) (0.5%) Infliximab: €490.84 (95% CI 411.65-570.03) (30.2%) Adalimumab: €550.89 (95% CI 427.46-629.33) (33.9%)
			UC	€594.89 (95% CI 504.90 to 684.89)	Gastroenterologist: €41.06 (95% CI 36.22 to 45.90) (6.9%) Specialized nurse: €3.76 (2.97 to 4.56) (1.0%) Internist: €4.26 (95% CI 2.57 to 5.95) (0.7%) Dietician: €2.34 (95% CI 139 to 3.28) (0.4%) Surgeon: €3.06 (95% CI 1.40 to 4.72) (0.5%) Rheumatologist: €1.28 (95% CI 0.30 to 2.27) (0.2%) Dermatologist: €1.71 (95% CI -0.13 to 3.43) (0.3%) Occupational physician: €1.07 (95% CI -0.09 to 2.23) (0.2%) Psychiatrist: €0.36 (95% CI -0.15 to 086) (0.1%) GP (daytime visit): €2.48 (1.71 to 3.25) (0.4%) GP (evening/weekend visit): €4.33 (95% CI 3.11 to 5.55) (0.7%)	€2.67 (95% CI 1.14 to 4.20) (0.4%)	€29.85 (95% CI 22.97-36.73) (5.1%) Colonoscopy: €24.31 (18.22 to 30.22) (4.1%)	€138.64 (83.85 to 193.42) (23.3%)	€8.16 (95% CI 0.78 to 15.54) (1.4%)	€349.86 (95% CI 290.86 to 409.58) (58.8%) Mesalazine: €136.47 (95% CI 129.9 to 143.01) (22.9%) Budesonide: €4.86 (95% CI 2.93 to 6.79) (0.8%) Prednisone: €0.39 (95% CI 0.23 to 0.54) (0.1%) Azathioprine: €13.83 (95% CI 11.74 to 15.92) (2.3%) 6-mp: €5.51 (4.12 to 6.90) (0.9%) Methotrexate: €1.86 (95% CI 0.48 to 3.23) (0.3%) Infliximab: €145.02 (95% CI 92.2 to 198.02) (24.4%) Adalimumab: €41.92 (95% CI 14.61 to 69.22) (7.0%)
Spain	Aldeguer 2016[19]	Prevalent cases	UC	€1,754.10 (sd 2418.08; 95% CI 1,479.37 to 2,034.83)	GP visits: €250.52 (sd 203.79; 95% CI 226.86-274.18) GI visits: €54.89 (sd 116.70; 95% CI 41.37-68.44) Mental health visits: €1.19 (sd 11.23, 95% CI -0.11 to 2.49)	€61.07 (sd 90.77; 95% CI 50.53-71.61)	€50.06 (sd 69.74, 95% CI 41.96 to 58.16)	€853.30 (sd 2,157.77; 95% CI 602.79-1,103.81) (47.88%)		€596.52 (sd 574.63; 95% CI 429.81 to 563.23) (28.31%)
United Kingdom	Sprakes 2010[20]	Costs in the year before and the year after starting infliximab	CD	**Pre-infliximab:** £4,965.20[a] **Post-infliximab:** £2,214.37[a]	**Pre-infliximab:** £479.30 **Post-infliximab:** £448.45		**Pre-infliximab:** Radiology: £315.79 | Endoscopy: £397.64 | Lab tests: £48.52 **Post-infliximab:** Radiology: £89.46 | Endoscopy: £77.86 | Lab tests: £37.13	**Pre-infliximab:** £2588.36 **Post-infliximab:** £670.90	**Pre-infliximab:** £536.88 **Post-infliximab:** £124.06	**Pre-infliximab:** £598.71 **Post-infliximab:** £448.45 Infusion costs: £393.86
United Kingdom	Lindsay 2013[21]	Costs in the year before and the two years after starting infliximab (per year)	CD		**Pre-infliximab:** £913.48 **Post-infliximab:** £823.23		**Pre-infliximab:** £411.00 **Post-infliximab:** £190.04	**Pre-infliximab:** £1,908.85 **Post-infliximab:** £1,194.01		**Post-infliximab:** £7,128.02

TABLE 4-1: COMPARISONS OF CHARACTERISTICS OF CROHN'S DISEASE AND ULCERATIVE COLITIS.

4.3 Specialist care for IBD

Early care by gastroenterologists is associated with reduced risks of undergoing surgery [22,23] and a reduced number of emergency department (ED) visits among IBD patients.[24] Admission directly under a gastroenterologist's supervision has also been associated with a lower risk of dying among hospitalized ulcerative colitis patients.[25]

Over the past two decades, there has been a rise in gastroenterologist care for individuals living with IBD in Canada.[23,26] Between 63% and 88% of Crohn's disease patients see a gastroenterologist at least once in the year following diagnosis.[23,27] However, specialist involvement remains sub-optimal as the average time from symptom onset to IBD diagnosis (which is typically made by a specialist) still exceeds six months,[22] and only a third of patients receive continued follow-up care with a gastroenterologist over the first five years following diagnosis.[27]

Seniors diagnosed with IBD are less likely to receive ongoing care from a gastroenterologist as compared to persons who are younger at diagnosis. These differences are particularly pronounced for seniors living in rural areas.[27] Overall, rural residents with IBD are about half as likely to ever see a gastroenterologist in Canada and have 20% fewer annual visits with gastroenterologists compared with their urban counterparts.

In Canada, patients with IBD see a physician for their IBD between two and four times per year,[22,28] with the greatest number of visits occurring in the year following diagnosis. Children with IBD see a physician a median of 11 times per year (IQR 7), with 90% of these visits being related to their IBD.[29] Children with IBD visit a doctor more often than children without IBD for at least five years following diagnosis.[29]

4.4 Hospitalizations

About one in five adults with Crohn's disease and one in eight adults with ulcerative colitis are hospitalized every year.[22,30] Hospitalizations are most common during the first year after diagnosis. Young adults (18-40y) have higher rates of hospitalization as compared to middle-aged adults (41-64y) and senior (≥65y) individuals. Roughly one in four Ontario children with IBD are hospitalized in the first year of diagnosis and almost half are hospitalized within five years of diagnosis.[28]

In a Canadian population-based study, 2.3% of hospitalized IBD patients were re-hospitalized within one month of discharge, while 5.6% and 7.7% were readmitted to hospital within 6 and 12 months respectively.[31] Additionally, 11% of children with IBD were readmitted within a year of hospitalization, compared to 5.3% of senior patients. The average length of Crohn's disease and ulcerative colitis-related hospitalizations were 8.8 (sd 12.3) and 10.2 (sd 11.7) days, respectively. Senior patients stayed in hospital longer than younger patients (13 and 8 days, respectively).[31]

In a population-based study from Manitoba, 0.74% of patients with IBD were found to be admitted to an intensive care unit every year, which was higher than for matched controls (hazard ratio (HR), 1.79; 95% confidence interval (CI), 1.58-2.02).[32] The risk of ICU admission was greater for Crohn's disease patients (HR, 2.31; 95% CI, 1.95-2.75) than ulcerative colitis patients (HR, 1.37; 95% CI, 1.13-1.65) as compared to matched controls.

4.5 Surgeries

4.5.1 Ulcerative Colitis

In a systematic review and meta-analysis of population-based studies, the risk of colectomy following ulcerative colitis diagnosis was 4.9% at one year, 11.6% at five years, and 15.6% at ten years.[33] Canadian ulcerative colitis patients may have lower colectomy rates based on a recent Manitoba study that reported five, ten, and 20-year risks of colectomy to be 7.5%, 10.4% and 14.8%, respectively.[34] In Ontario, the ten-year risk of colectomy is 13.3% among young adults, and 18.5% among individuals with senior-onset ulcerative colitis (see Figure 4-1).[35] Several studies have shown that colectomy rates have declined in ulcerative colitis over the last two decades, possibly related to the introduction of better therapies to treat IBD.[29,36-40]

In children, the risk of colectomy is slightly higher than in adults and comparable to senior-onset ulcerative colitis patients (see Figure 4-1). Colectomy rates within the first year of ulcerative colitis diagnosis range from 4.8% to 6%.[28,29] This number increases to 15-17% by ten years following diagnosis. The risk of early surgery is similar across pediatric age groups. However, males diagnosed with ulcerative colitis before six years of age were less likely to undergo colectomy within ten years of diagnosis than males diagnosed at older ages.[28]

Patients hospitalized for acute severe ulcerative colitis are at particular high risk of requiring colectomy. A Canadian population-based study reported that 11% of patients with ulcerative colitis admitted to hospital underwent colectomy during their first hospitalization.[31] Another Canadian multi-centre study reported that 18% of hospitalizations among patients with ulcerative colitis resulted in colectomy, although colectomy rates varied widely across centres (range 6 to 40%).[41] A separate study conducted in Calgary found that almost 60% of patients with ulcerative colitis admitted to hospital within three years of their diagnosis required a colectomy during their hospitalization.[40] It is noteworthy that patients who undergo emergency colectomy have much higher mortality rates that patients who have elective colectomy (5.3% vs. 0.7%).[42] Therefore, avoidance of emergency surgery with high quality and prompt medical and surgical physician support is paramount in the management of refractory colitis.

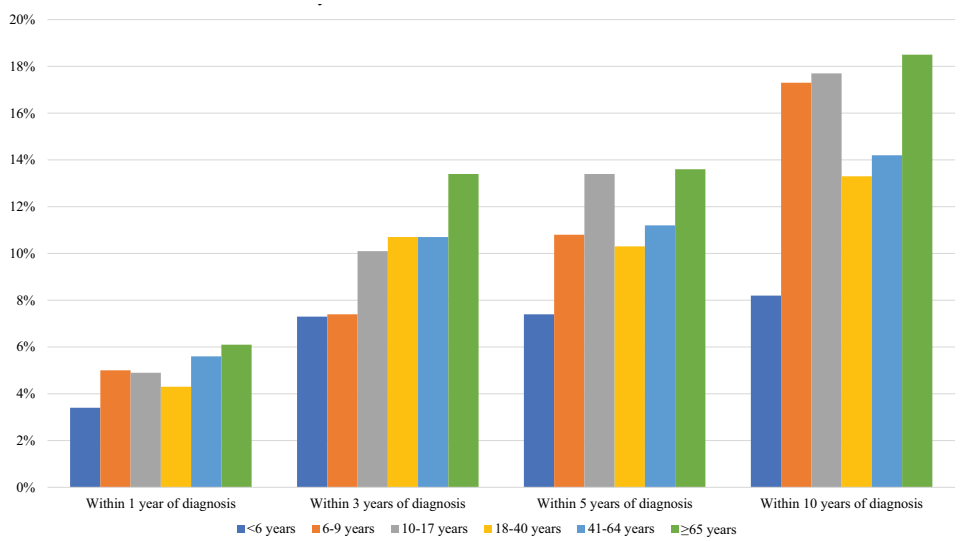


Figure 4-1: Risk of colectomy in patients with ulcerative colitis in Ontario. Data derived from *Gastroenterology* 2014;147:803-13 and *Inflamm Bowel Dis* 2017;23:218-23.[28,35]

4.5.2 Crohn's Disease

In a systematic review and meta-analysis of population-based studies, 16.3%, 33.3%, and 46.6% of persons with Crohn's disease required surgery within one, five, and ten years of diagnosis,[33] respectively. The most common operation was a limited intestinal resection. Of persons who undergo surgery, 24.2% and 35.0% undergo repeat surgery after five and ten years, respectively.[43] This risk is higher among rural Canadians, possibly related to lower use of outpatient specialist care for their IBD.[44]

Canadian Crohn's disease patients may have lower rates of surgery as compared to patients from other jurisdictions. Between 21% and 24% of adult-onset Crohn's disease patients undergo intestinal resection within five years of diagnosis, and 27% to 31% undergo intestinal resection within ten years (see Figure 4-2).[35] As with ulcerative colitis, the rates of intestinal resection in patients with Crohn's disease have decreased over time.[29,45] A study from the Calgary Health Zone reported a decrease of 3.5% per year in the need for intestinal resection between 2002 and 2011.[45] This decrease was driven by a decrease in emergency surgeries (which decreased by 10.1% per year), while the rate of elective surgeries remained constant.[45]

Studies evaluating the risk of surgery in Canadian children with Crohn's disease estimate that surgical rates are lower in pediatric-onset disease. The one, five, and ten-year risks of requiring an intestinal resection are between 6 and 9%, 12 and 23%, and 15 and 36%, respectively.[28,29] The lower risk of surgery in childhood-onset disease is likely due a much lower rate of early fibrostenotic or penetrating disease among children as compared to adults.[46] As with adults, the rates of surgery for children with Crohn's disease have decreased significantly over the past 20 years.[29]

Of patients hospitalized for Crohn's disease in Canada, 16% undergo an intestinal resection during their first hospitalization.[31] Another study found that 20% of patients admitted to Canadian academic centres between 2011 and 2013 underwent an intestinal resection during hospitalization, although there were significant differences in surgery rates across centres (range 9 to 36%).[41] As with ulcerative colitis, patients who underwent emergency surgery had higher mortality rates than those who underwent elective surgery (3.6% vs. 0.6%).[42]

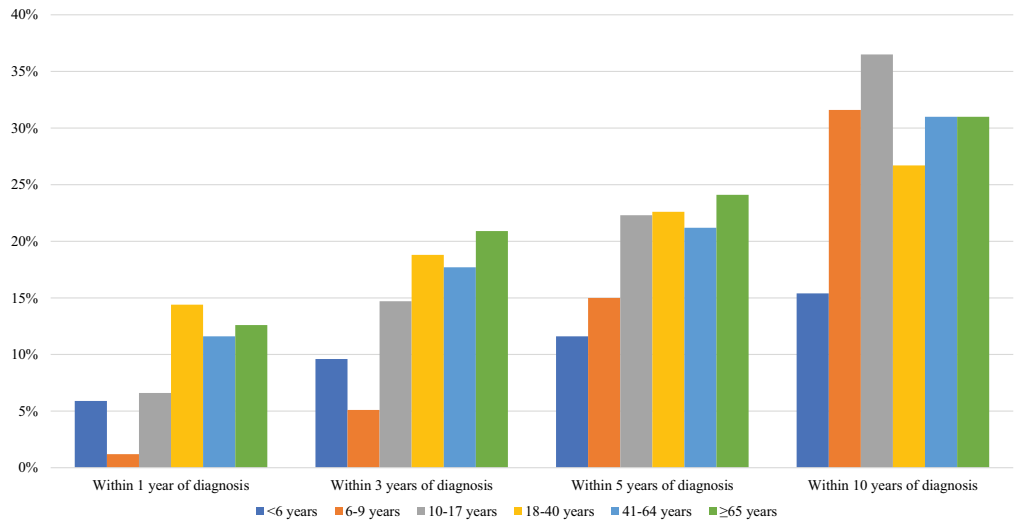


Figure 4-2: Risk of intestinal resection for Crohn's disease in Ontario. Data derived from *Gastroenterology* 2014;147:803-13 and *Inflamm Bowel Dis* 2017;23:218-23.[28,35]

4.6 Cost of Prescription Drugs

In the post-biologic era, prescription drugs account for between 30% and 70% of IBD-related healthcare costs internationally (see Table 4-1).[7,8,9,14,19] Prior to the introduction of biologic therapies to treat IBD, prescription drugs accounted for less than 25% of costs while hospitalizations accounted for more than 50% of direct costs of IBD care.[47,48] Data from Manitoba indicate that prescription drug costs now account for 20% of direct healthcare costs in newly diagnosed IBD patients and 45% of costs in patients with long-standing disease.[5] Therefore, studies evaluating the direct costs of IBD care in the pre-biologic era have little relevance to the present-day circumstance.

Prescription drug costs have continued to rise, relating to the increased use of anti-TNF biologic agents (infliximab, adalimumab, golimumab) as well as the introduction of additional biologic therapies into the marketplace (ustekinumab, vedolizumab). In 2016, seven out of the top ten selling drugs in Canada were biologic drugs.[49] Across all approved indications, Canadian sales of immunobiologic drugs has nearly doubled since 2010, reaching $2.2 billion in 2015 (10.3% of the Canadian pharmaceutical market share). This represents a considerably higher share of the pharmaceutical market than what is observed in France, Germany, Italy, Switzerland, the United Kingdom, and the United States (which range from 4.1% to 7.7%).[49] While rising drug costs have been partly offset by fewer IBD-related surgeries,[33,45] likely due to improved disease control, the introduction of biologics has led to a substantial net increase in overall costs of IBD care.[20,50]

An audit of a Canadian national drug claims database[51] in 2012 estimated that public and private drug claims for the year 2011, specific to IBD indications, amounted to $460 million, roughly 84% of which was for the biologic drugs infliximab and adalimumab. There were important differences observed in costs across the country, with per-capita drug costs twice as high in some provinces compared with others. There was also a threefold difference among provinces in the percentage of drug costs that were covered by public plans versus private plans.[52]

Based on population-level health administrative data from Manitoba, the mean and median direct costs of IBD care, including prescription pharmaceuticals (imputing drug costs covered by private insurers), hospitalizations (day surgery and inpatient), and physician office visits, were more than two times greater among IBD patients than age- and sex-matched controls (CAD$3,896 vs $1,826 for mean, CAD$1,562 vs $448 for median) for the 2005/2006 fiscal year.[5] Prescription drug use accounted for 42% and 37% of total direct costs in IBD patients and controls respectively (see Table 4-1). In an updated study from this group using population-level data spanning 2004 to 2016, the mean total drug costs and healthcare utilization costs (including drug costs) for persons with IBD were CAD$1,861 and $10,206, respectively, in the year prior to initiation of anti-TNF therapy, and CAD$37,448 and $44,786, respectively, in the year following initiation of anti-TNF therapy (see Table 4-1).[11] Mean annual hospitalization costs decreased by 12% in the year following anti-TNF initiation, from CAD$6,419 to $5,627 per person. Similar decreases in inpatient care costs have been observed in Alberta (decreasing from CAD$2,715 to $968 in the year before and after infliximab initiation),[10] the United States,[15,53] and the United Kingdom (see Table 4-1).[20,21] Outpatient costs appear to be similar before and after treatment with infliximab.[15,20,21,53] Overall, 14.2% of adults with Crohn's disease, 4.1% of adults with ulcerative colitis, and 50% of children are using the anti-TNF biologic agents infliximab and adalimumab.[54,55]

The introduction of biosimilar anti-TNF agents to the marketplace may reduce the cost of treating patients with IBD. Inflectra, the first biosimilar infliximab, was approved for use in Crohn's disease and ulcerative colitis in Canada on June 14, 2016 and is roughly half the cost of the originator infliximab (Remicade).[49,56] Additional biosimilar infliximab agents, as well as biosimilar adalimumab agents, are being developed, which may bend the cost curve even further.[57] In 2016, Canadian sales of infliximab (Remicade) and adalimumab (Humira) were roughly CAD$1 billion and $650 million, respectively.[56] It is estimated that if even 10% of infliximab usage in Canada was biosimilar infliximab (across all indications), it would translate to more than a CAD$41 million reduction in drug expenditures.[49]

Market penetration of biosimilar infliximab has been slow in Canada, reaching just 1% of the total infliximab market share by the end of 2016.[56] However, as a cost savings measure, some provinces now mandate use of biosimilar infliximab for new infliximab starts among persons with IBD requiring provincial drug coverage, which could improve market penetration. Moreover, many private drug insurance companies are starting to follow this example. Unlike in some European nations, forced switching from originator to biosimilar infliximab has not been mandated in Canada, which has also impacted market penetration of biosimilar infliximab.

4.7 End of Life Costs

The end-of-life period represents a time of rapidly rising healthcare demands.[58] Healthcare services provided in the last year of life account for close to 10% ($4.7 billion) of the annual Ontario healthcare budget, even though decedents constitute only 0.67% of the Canadian population.[58,59] Therefore, the end-of-life period is an important target for the development of cost-effective strategies for healthcare delivery.

In a population-based cohort study of Ontario decedents between 2010 and 2013, IBD decedents (N = 2,214) had CAD$7,210 (95% CI $5,005 to $9,464) higher adjusted per-patient cost in the last year of life as compared to non-IBD decedents (N = 262,540), including most other decedents with chronic disease (15 of the 16 chronic diseases studied; only renal disease was associated with greater costs).The cost differential was largely related to hospitalizations cost (76% of differential), particularly in the last 90 days of life.[60] Improving end-of-life care for IBD patients outside of the hospital setting could substantially reduce healthcare system costs while improving quality of life.

4.8 Conclusions

IBD is a costly disease. In Canada, the direct cost of caring for people living with IBD is estimated to be at least CAD$1.28 billion in 2018 and possibly higher than CAD$2 billion. The primary drivers of direct healthcare costs are hospitalizations and pharmaceuticals. Over time, the source of direct cost of care is shifting from hospitalizations and surgeries to pharmaceutical treatments. The introduction of biologics has improved the care of IBD but at a significant expense to the healthcare system. Biosimilars will have an impact on reducing the cost of biologics. However, the absolute cost of pharmaceuticals will likely continue to rise for years to come due to an increasing prevalence of IBD and greater penetration of biologics in the treatment of patients with IBD. The silver lining in the wake of rising costs of care associated with increasing biologics use has been improvement in health outcomes and quality of life among IBD patients, evidenced by declining rates of hospitalizations and surgeries and an increasing amount of care provided directly by gastroenterologists.

Summary of Section 4: Direct Costs & Health Services Utilization

1. The costs of healthcare for patients with IBD are more than double those without IBD.

2. Prescription drug use accounts for 42% of total direct costs in IBD patients and costs to treat IBD continue to rise due to increased use of existing biologic therapies and the introduction of several new biologic therapies in recent years.

3. In Manitoba, the mean healthcare utilization and medication costs for persons with IBD in the year before beginning anti-TNF therapy was $10,206 and increased to $44,786 in the first year of therapy.

4. Biosimilar agents to anti-TNF drugs are now entering the Canadian marketplace and may result in cost savings in patients using biologic agents to treat IBD.

5. Timely gastroenterologist care has been associated with reduced risks of requiring surgery and emergency care among ambulatory IBD patients as well as a reduced risk of death among hospitalized patients with ulcerative colitis.

6. IBD care provided by gastroenterologists has increased over the past two decades. Even then, the average time from symptom onset to IBD diagnosis exceeds six months and only a third of IBD patients receive continuing care with a gastroenterologist during the first five years following diagnosis.

7. Seniors (age ≥65), rural-dwelling, and non-immigrant IBD patients have less frequent gastroenterologist care than other groups.

8. About one in five adults with Crohn's disease and one in eight adults with ulcerative colitis are hospitalized in Ontario every year. Hospitalizations are most common during the first year following IBD diagnosis. Children with IBD (aged <18) have the highest rates of hospitalizations and hospital re-admissions.

9. In Canada, 16% of patients hospitalized for Crohn's disease undergo an intestinal resection and 11% of patients hospitalized for ulcerative colitis undergo a colectomy during their initial hospitalization. Rates of intestinal resection and colectomy are declining in Canada in persons with Crohn's disease and ulcerative colitis, respectively.

10. In Ontario, one-third of adult-onset Crohn's disease patients undergo intestinal resection within ten years of diagnosis. Among Canadian children with Crohn's disease, approximately one in 15 children will require intestinal surgery within the first year of diagnosis and up to one-third will require surgery within ten years of diagnosis.

11. In Ontario, the ten-year colectomy risk following ulcerative colitis diagnosis is 13.3% among young persons and adults and 18.5% among individuals with senior-onset ulcerative colitis. In children with ulcerative colitis, the risk of colectomy is 4.8% to 6% in the first year following diagnosis and increases to 15 to 17% by ten years.

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INDIRECT COSTS OF IBD CARE

Indirect Costs of IBD Care

Highlights

1. Indirect costs account for a major portion of total healthcare costs among persons with IBD and are higher than indirect costs among persons without IBD.

2. Persons with IBD are more likely to require time off work (absenteeism) and have reduced productivity at work (presenteeism) due to illness as compared to persons without IBD.

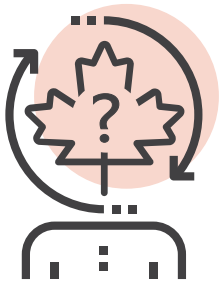
3. Premature retirement and long-term disability are major factors contributing to indirect costs among IBD patients.

4. A substantial proportion of individuals with IBD pay out-of-pocket for complementary and alternative medicines.

5. Extrapolating from multiple sources, the total annual indirect cost of IBD in Canada is estimated to be CAD$1.29 billion in 2018, or CAD$4,781 per person with IBD.

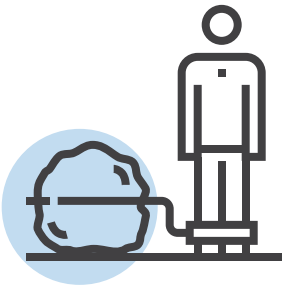
Gaps in Knowledge and Future Directions

1. Canadian-specific data on indirect health-related costs of IBD is sparse across all domains of indirect costs.



2. In particular, the rates of absenteeism, presenteeism and premature retirement among IBD patients living in Canada require further study to gauge more accurately the indirect health-related costs of IBD in Canada.

3. Indirect costs relating to decreased professional development, caregiver burden and out-of-pocket purchases among IBD patients are largely unknown and require further study.



4. Indirect costs incurred by Canadian children with IBD and their families or caregivers are largely unknown.

5.0 Abstract

The indirect cost of illness represents the portion of human capital that is foregone due to lost productivity of patients and their caregivers, as well as out-of-pocket healthcare expenses borne directly by patients. Indirect costs among persons with inflammatory bowel diseases (IBD) may be substantial, as disease onset occurs during the teens and twenties for most persons and is lifelong. Thus, most persons with IBD are affected during periods of study or employment. The literature on indirect health-related costs among persons with IBD is limited, particularly with regards to Canadian studies. The greatest burden of indirect costs in this population relates to absenteeism and presenteeism among working individuals and premature retirement. However, costs related to reduced professional development and personal achievement due to illness, as well as caregiver costs, are largely unknown. Extrapolating from multiple sources, the total indirect health-related cost of IBD in Canada in 2018 is estimated to be CA$1.29 billion. Notably, this may be a significant underestimate, as costs relating to presenteeism, reduced achievement and caregiver burden could not be estimated and are excluded from this calculation.

5.1 Introduction

The indirect cost of illness represents the portion of human capital that is foregone due to illness or disability. Indirect costs include lost productivity of patients and their caregivers, as well as out-of-pocket healthcare expenses borne directly by patients, including costs of non-prescription drugs and devices, co-pay or deductibles, public health and preventative care.

Lost productivity due to illness consists of two major components:

1. Absenteeism, which reflects absence from paid work due to sick days/leave, unemployment, short-term and long-term disability, early retirement, premature death, and caregiver leave; and,

2. Presenteeism, which denotes reduced productivity at work due to illness. An under-recognized aspect of lost productivity relates to reduced professional development and career achievement due to illness.

Most studies of indirect costs in IBD patients use the human capital approach (HCA), which converts the gross income that is not earned by an individual due to illness into real costs from a societal perspective.[1] The actual cost impact can be described in a variety of ways, such as in dollar units or as a proportion of the gross domestic product (GDP) per capita.[1]

In this section, we summarize older data on the estimates of indirect costs, as well as present new data published since the 2012 Impact of IBD in Canada Report.

5.2 Sick Days and Disability

A systematic review has summarized studies published between 1992 and 2014 on indirect costs of illness among persons with IBD,[1] including nine from North America, (one from Canada),[2-10] eight from Europe,[11-18] and one from New Zealand.[19] Importantly, each of these studies included different components in the calculation of absenteeism costs, with some studies incorporating one or more of long-term disability, premature retirement, premature death and caregiver costs, in addition to sick leave and short-term disability. Fifteen studies evaluated indirect costs relating to absenteeism and presenteeism, and two studies reported indirect costs of presenteeism.

Adjusting for purchasing power disparity, the annual indirect cost estimates relating to absenteeism for IBD patients ranged from US$515.67 (U.S.A.) to US$14,727 (Germany) per patient, with a pooled estimate of US$7,189 per patient per annum. Standardized to each country's GDP, the pooled estimate was US$9,622 per patient per annum. Among studies that reported indirect costs relating to both absenteeism and presenteeism, the estimates were US$2,753 (Sweden) and US$5,677 (Hungary) after adjusting for purchasing power disparity, and US$2,991.14 (Sweden) and $25,194.92 (Hungary) after standardizing to each country's GDP.[15,16] A literature review from 2007 of eight studies further reported that, on average, 7.2 days per year per patient (range 4.2 to 9.9) are lost due to medical absenteeism secondary to IBD amongst the IBD-workforce.[20]

One Canadian study and three U.S. studies have recently been published on lost productivity among persons with IBD. In a study of more than 90,000 individuals (200 with IBD) from the U.S. Medical Expenditures Panel Survey between 1996 and 2006, 72% of IBD patients and 58.3% of non-IBD patients missed time from work because of illness, with a resultant 3.5 more days off of work (13.4 versus 9.9 days) and US$783 in excess lost wages per person per annum for IBD patients.[21] IBD patients were nearly two-fold more likely to miss work than controls. Extrapolating IBD prevalence and costs, and adjusting for the national employment rate, the incremental IBD absenteeism cost aggregated over the entire U.S. IBD population was estimated to be US$249 million annually.

Another study used data from a large U.S. private insurance claims database to report on short-term and long-term disability claims among ulcerative colitis patients and matched controls, aged 18 to 64, employed in the U.S. between 2005 and 2013.[22] A higher proportion of individuals with ulcerative colitis had disability days (10.9% vs. 6.7%) and medically-related absenteeism days (98.7% vs. 80.1%), equating to roughly a two-fold greater number of total disability or sick days per person (16.4 vs. 8.8 days) as compared to individuals without IBD. Disability days were more frequent among individuals with moderate-to-severe ulcerative colitis. The adjusted total indirect cost per patient per annum was significantly higher in individuals with ulcerative colitis as compared to those without IBD (US$4,125 vs. US$1,961) and was even more pronounced in individuals with moderate-to-severe ulcerative colitis (US$5,666).

A survey study from an IBD referral center estimated indirect costs relating to absenteeism and presenteeism in their adult IBD population and selected controls.[23] Presenteeism was substantially more frequent in patients with Crohn's disease (61.4%) and ulcerative colitis (64.3%) as compared to non-IBD controls (27.3%), even for IBD patients in remission (54.7%). There was a non-significant trend towards higher rates of absenteeism in patients with ulcerative colitis

(22.4%) and Crohn's disease (20%) relative to controls (13.6%), although rates were similar to controls for IBD patients in remission (14.4%). As compared to IBD patients in remission, IBD patients with active disease had much higher rates of absenteeism (46.6% vs. 14.4%), presenteeism (94.8% vs. 54.7%), and overall activity impairment (98.9% vs. 62.7%). Among IBD patients, the most common work limitations were fatigue (41.8%), irritability (12.2%), and decreased motivation (11.7%), and the most frequent reasons for missing work were physician appointments (39%), abdominal discomfort (24.4%), and hospital/ER visits (22.1%). Using a "lost wages" approach,[24] this translated to an average indirect cost of US$1,133 per week (55.1% of total weekly compensation) for IBD patients with active disease, US$370 per week (18% of total weekly compensation) for IBD patients in remission, and $191 per week (9.3% of total weekly compensation) for controls (see Figures 5-1 and 5-2).

In a survey study of 744 individuals living with IBD in Manitoba, reduced workplace productivity during the previous 14 days was reported by 37% of individuals, including a reduction for 1-2 days by 18% of patients, for 3-9 days by 16% of patients, and on most days by 3% of patients.[25] In a related study, the authors reported that the most common workplace accommodations required by persons with IBD were for medical appointments (81%), toilet access (71%), and respites (54%). Female sex, more severe symptoms, and a high level of current distress were associated with the need for more accommodations.[26]

Overall, working persons with IBD may expect to miss an extra 3.5 to 7.5 days from work annually due to illness relative to non-IBD persons. Based on the average Canadian salary in 2016 from Statistics Canada reports (CAD$956.50 per week or CAD$49,738 per year),[28] the estimated

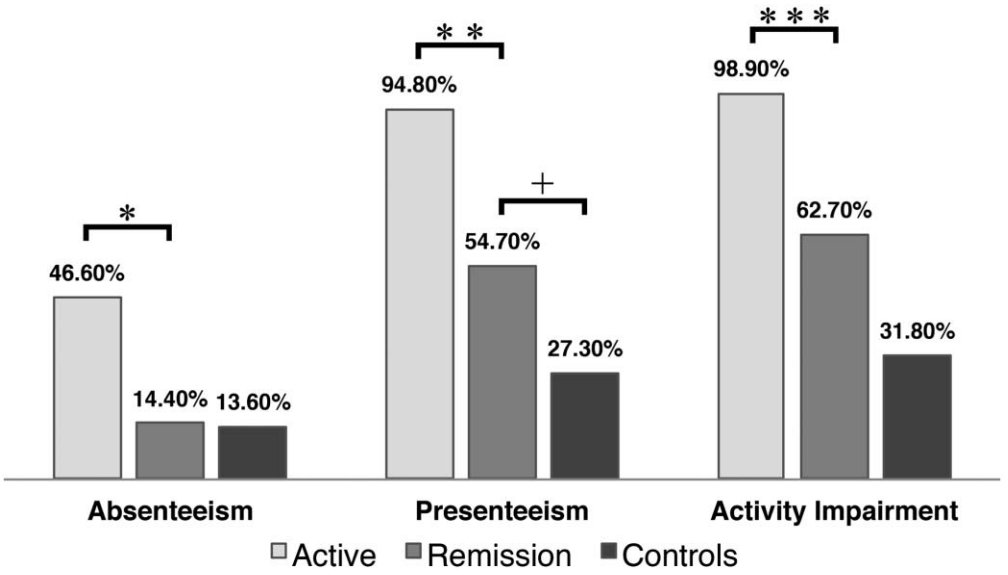


Figure 5-1: Prevalence of absenteeism, presenteeism, and activity impairment in controls and patients with IBD with active and inactive disease. *P < 0.01, **P < 0.01, ***P < 0.01, +P = 0.02.[23]

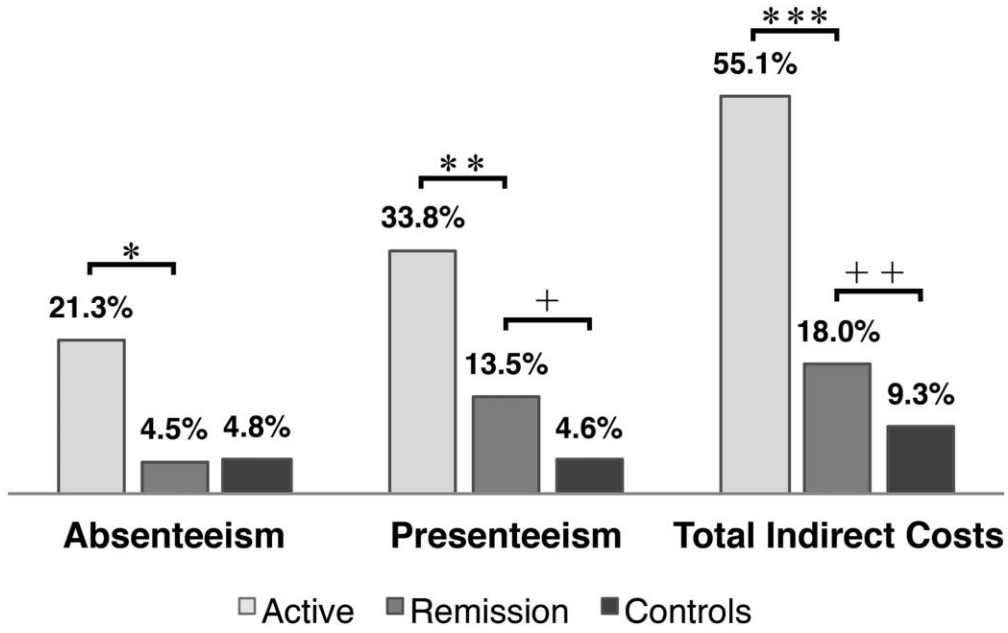


Figure 5-2: Indirect costs as a percentage of maximum weekly compensation for employees. *P < 0.01, **P < 0.01, ***P < 0.01, +P = 0.02, ++P < 0.03.[23]

mean annual per patient cost related to medical absenteeism is CAD$752 (range CAD$478 to CAD$1,025). In 2018, it is estimated that there are 97,809 and 80,266 Canadian working age adults (age 18-64) with Crohn's disease and ulcerative colitis, respectively.[27] Based on estimated workforce rates of 68% and 63% among persons with Crohn's disease and ulcerative colitis living in Canada, respectively,[29] roughly 66,510 and 50,568 (117,078 total) persons with Crohn's disease and ulcerative colitis would be eligible to experience medical absenteeism. Extrapolating the mean per person absenteeism cost to the entire Canadian IBD workforce, the annual cost due to medical absenteeism is estimated to be more than CAD$88 million (range CAD$56 to CAD$120 million).

This estimate does not include productivity losses due to presenteeism, which may be 1.5 times greater than absenteeism costs. However, there are limited data to account for presenteeism costs in the Canadian context.

5.3 Premature Retirement

Few studies have reported on early retirement in patients with IBD, and only a fraction of these studies have evaluated disease-related early retirement in the post-biologic era. A systematic review was conducted in 2013 to identify studies evaluating the impact of IBD on employment.[30] Among two European studies that evaluated retirement among adults younger than age 65, less than 4.4% of people with Crohn's disease were retired and 2.6 to 4.5% of people with ulcerative colitis were retired.[18-31] The rates of early retirement among people with IBD were similar to those of people without IBD. Another European study of individuals with IBD, 27% of whom were retired, reported that 6.5% retired because of their IBD.[32]

A more recent study from Germany reported annual retirement rates of 440 and 226 per 100,000 employees per year for persons with Crohn's disease and ulcerative colitis, respectively, with average annual retirement ages of 41.7 and 43.5, respectively, for women and 43.6 and 44.0, respectively, for men.[33] Although we are unaware of the age at which Canadians with IBD retire, the retirement age for the general population in Canada is similar to that of Germany (roughly 64 years of age).[33-36]

In 2018, it is estimated that there are 97,809 and 80,266 Canadian working age adults (18-64) with Crohn's disease and ulcerative colitis, respectively.[28] Extrapolating annual retirement rates from the German study to working age Canadians with IBD,[33] 430 persons with Crohn's disease and 181 persons with ulcerative colitis may be expected to retire each year in Canada, assuming that all working age persons with IBD would otherwise be employed. Using the mean retirement ages from the German study of roughly 43 and 44 among Crohn's disease and ulcerative colitis patients, respectively,[33] and the average earnings for Canadians in 2016 (CAD$956.50 per week or CAD$49,738 per year),[27] the average lifetime lost wages from premature retirement among IBD persons in the workforce is calculated to be CAD$1,044,498 per person with Crohn's disease and CAD$994,760 per person with ulcerative colitis (based on an average retirement age among working Canadians of 64). Aggregated across all IBD retirees each year, this equates to roughly CAD$449 million among persons with Crohn's disease and CAD$180 million among persons with ulcerative colitis (total CAD$629 million) in permanent lost wages annually, assuming a similar wage distribution among IBD retirees and non-retirees.

5.4 Premature Mortality

Premature mortality (before the age of 65) also contributes to lost productivity among persons with IBD. Population-based studies from Ontario and Manitoba report higher mortality rates among patients with Crohn's disease compared to the general population, particularly among young and middle-aged individuals.[37,38] In comparison, people with ulcerative colitis are not at an increased risk of death compared to people without IBD. Almost one quarter (88/379) of all deaths among patients with Crohn's disease in Manitoba occurred in those who were younger than 50, and 5% (20/379) of Crohn's disease-related deaths occurred in patients younger than 30 (data spanning 1984 to 2010).[37] In Ontario, there are 5.66 and 1.0 Crohn's disease-related deaths and 1.33 and 1.0 ulcerative colitis-related deaths per 10,000 person-years among middle-aged (41-64) and young adults (18-40) respectively.[38]

According to Statistics Canada data from 2010-2014, there are an average of 33 deaths directly resulting from Crohn's disease per year and 12 deaths directly attributable to ulcerative colitis per year among individuals under the age of 65.[39] The average age of Canadians with IBD who die before the age of 65 has been previously estimated as 49, corresponding to an average of 15 years of lost employment per individual that dies prematurely (based on the average retirement age of 64 in Canada).[40] Based on the average earnings for Canadians in 2016 (CAD$956.50 per week or CAD$49,738 per year),[27] the 45 IBD-specific premature deaths would result in 675 lost years of productivity and roughly CAD$33 million in permanent lost wages (CAD$746,070 per decedent) accrued annually across all working age IBD persons (over and above lost wages due to premature mortality from non-IBD related causes), assuming a similar distribution of wage among employed IBD persons.

In 2012, the cost of premature death among IBD persons in Canada was estimated to be just CAD$9.4 million. The rise in estimated indirect costs of premature mortality in people with IBD over the past five years is the result of (1) higher wages; and (2) a higher number of deaths due to IBD, likely because of the increasing prevalence of IBD in Canada.

5.5 Professional Development

As a chronic disease that is often diagnosed during childhood and adolescence, IBD may negatively impact academic performance and subsequent professional development. There is limited data on the impact of IBD on academic success. A large population-based study from Manitoba compared 337 IBD patients in grade 12 to 3,093 healthy grade 12 controls.[41] There were no differences in academic outcomes between the two groups. However, a co-morbid mental health diagnosis within six months before or after an IBD diagnosis was associated with worse educational outcomes.

In a small survey study of undergraduate students at the University of Michigan, IBD disease activity was inversely associated with adjustment to college life.[42] Poor college adjustment has been associated with worse academic outcomes, lower graduation rates, and impairments in career development.

IBD is also associated with a high rate of unemployment, with one study reporting unemployment in up to 39% of patients with moderate-severe Crohn's disease.[43] Among those patients who are employed, IBD can impact salary growth. Loftus *et al.* demonstrated that while annual salary did not differ among patients with moderate-severe Crohn's disease and healthy controls in the first year of study, salary growth rate was 31% lower in those with Crohn's disease.[44] Whether earlier and more aggressive medical therapy can potentially improve academic and professional development and income potential warrant further study.

5.6 Caregiver Costs

Caregivers are people who provide informal and unpaid care to others who may need assistance for health reasons and may take time off work to provide this care. Caregivers are needed for the most severely affected people with IBD, as well as for children (where parents are usually the caregivers) and seniors (where children are usually the caregivers) with IBD. However, there are very few data available on the economic impact of IBD caregivers.

There are minimal data available on caregiver costs, and even less in a Canadian context. In a U.S. study of pediatric IBD patients using health insurance databases, 200 patients with Crohn's disease and their caregivers were compared to age-matched controls without IBD and their caregivers. Unadjusted annual hours of work loss were 214.4 ± 171.5 and 169.6 ± 157.5 for caregivers of Crohn's disease patients and controls, translating to annual lost productivity costs of US$5,243 and US$4,121 per caregiver, respectively.[45]

5.7 Out of Pocket Costs

Literature on the out-of-pocket expenses among individuals living with IBD is limited. These expenses include complementary and alternative medicines (CAM), ostomy supplies, travel to attend appointments, and dietary/nutritional therapy. A U.S. study estimated annual per-person out of pocket costs of US$1,603 for persons with Crohn's disease and US$1,263 for persons with ulcerative colitis.[46] Per-person out-of-pocket expenses were higher in persons with IBD as compared to persons without IBD. Out of pocket costs in pediatric IBD patients have been reported to be even higher than those in adults.[47]

CAM is generally defined as therapy that falls beyond the realm of conventional medicine (*i.e.* herbal therapy, homeopathy, massage therapy, chiropractor, prayer)[48,49] and is not based on rigorous scientific evidence for a particular indication.[50] Most CAM are not covered under public or private drug plans. Canadian studies have reported CAM use in 56-74% of people with IBD.[49,51,52] European and Asian studies have reported the use of CAM in about half of people with IBD.[53-55] Notably, many physician providers are unaware that their patients are using CAM and only about a third of patients consult with their gastroenterologist before starting CAM.[52] A recent Crohn's and Colitis Canada survey identified access to information and research on CAM as priority areas for Canadians with IBD.[56]
The cost of travel to attend appointments is likely a significant expense for many IBD patients, although no specific Canadian data exist. Among pediatric IBD patients living in California, 25% spend US$500 annually to see their providers.[57]

Diet may be another source of considerable expense for IBD patients. Among families living in California that have a child with IBD, 34.3% spend less than US$200 per year, 31.3% spend US$200-400 per year, and 11.4% spend more than US$1,000 per year on diet.[57] In the pediatric IBD population, exclusive enteral nutrition has been shown to be an effective therapy for inducing clinical remission and contributes to dietary costs.[58] The costs of various popular elimination diets have not been well explored in IBD. The specific carbohydrate diet (SCD) is among the most popular exclusion diets adopted by patients with IBD.[59]

There are no data on comprehensive out-of-pocket expenses for IBD patients living in Canada. If the data from the US study[46] are extrapolated to Canadians with IBD, then the out-of-pocket expenses for the 146,000 Canadians living with Crohn's disease and 124,000 Canadians living with ulcerative colitis in Canada in 2018 could be as high as CAD$324 and CAD$217 million, respectively, for a total of CAD$541 million.[28]

5.8 Total Costs

The total indirect health economic burden of IBD on patients, the healthcare system, and society is significant. Based on the aforementioned cost estimates for sick days and short-term disability, premature retirement, premature death and out of pocket expenses, the total indirect health-related cost to the Canadian economy due to IBD is estimated to be close to CAD$1.29 billion in 2018, or roughly CAD$4,781 per person with IBD. The largest component of this cost is related to lost productivity, particularly premature retirement (CAD$629 million). Importantly, this estimate does not consider presenteeism costs, caregiver costs and the costs of reduced professional development, which may be substantial but could not be accurately estimated due to insufficient data. Applying the pooled estimate of US$7,189 per patient per year (CAD$9,231) in absenteeism costs from the 2014 meta-analysis to working age Canadians with IBD,[1] the estimated annual cost due to medical absenteeism may be as high as CAD$1.57 billion.

Importantly, the calculation of indirect costs in this report makes multiple assumptions, including the generalizability of non-Canadian estimates relating to lost productivity and out-of-pocket expenses to the Canadian context, and the projection of the mean wage of Canadian workers to IBD persons in the workforce. More data, specifically in the Canadian context, is needed to accurately gauge the indirect health economic impact of IBD to Canadian society.

Our gross estimate for total indirect cost differs from the estimate of CAD$1.6 billion reported in 2012,[40] reflecting new data and slightly different methodology and assumptions used to calculate indirect costs in this report. Notably, estimates of productivity losses are 40% lower in this report than in the previous report. The previous report also used a hypothetical scenario to estimate caregiver cost, which we chose to exclude from our cost estimate in favour of using only estimates substantiated by some real-world data. This further demonstrates that estimates of indirect costs are crude at this point and will undoubtedly be refined over time as more data become available.

Summary of Section 5: Indirect Costs of IBD Care

1. The total indirect economic burden of IBD in Canada is estimated to be CAD$1.29 billion in 2018, or roughly CAD$4,781 per person with IBD. This estimate comprises lost wages related to sick days and disability, premature retirement and premature death, as well as out-of-pocket costs. Losses from presenteeism, reduced professional development and caregiver burden are not included due to insufficient data on the cost impact of these factors.

2. In a meta-analysis of studies between 1994 and 2014 the annual indirect cost of absenteeism for IBD patients ranged from US$515.67 (USA) to US$14,727 (Germany) per patient per annum (pooled estimate US$7,189), after adjusting for purchasing power disparity.

3. A large U.S. survey found that, on average, IBD patients incurred an extra 4.8 days off of work and US$783 annually in excess lost wages than persons without IBD.

4. A study based on U.S. private insurance claims found that ulcerative colitis patients cost an additional US$2,164 per person per annum relating to disability days and medically-related absenteeism.

5. A prospective study from an IBD center reported weekly indirect health-related costs of US$1,133 for IBD patients with active disease, US$370.13 for IBD patients in remission, and US$191.23 for persons without IBD relating to both presenteeism and absenteeism.

6. In a survey of 744 IBD patients from Manitoba, reduced workplace productivity during the previous 14 days was reported in 37% of individuals, including a reduction of 1-2 days by 18% of patients, 3-9 days by 16% of patients, and on most days by 3% of patients.

7. The estimated average lifetime lost wages due to premature retirement is CAD$1,044,498 per person with Crohn's disease and CAD$994,760 per person with ulcerative colitis. Aggregated over all IBD retirees, this equates to roughly CAD$629 million in permanent lost wages annually due to premature retirement.

8. The lifetime indirect cost associated with premature death among IBD patients is estimated to be CAD$746,070 per decedent, or roughly CAD$33.6 million aggregated across all IBD decedents of working age.

9. In a U.S. study of caregivers of children, the average unadjusted annual work loss was 214 hours for caregivers of Crohn's disease patients and 170 hours for caregivers of children without IBD, translating to US$1,122 per caregiver in annual costs from lost productivity.

10. Canadian studies have reported complementary and alternative medicines (CAM) use in 56-74% of people with IBD. A U.S. national survey study estimated annual per-person out of pocket costs of US$1,603 for Crohn's disease patients and US$1,263 for ulcerative colitis patients, which were substantially higher than in persons without IBD.

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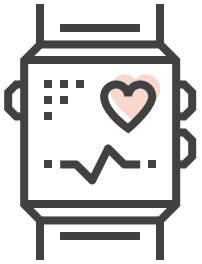
QUALITY OF LIFE IN PATIENTS WITH IBD

Quality of Life in Patients with IBD

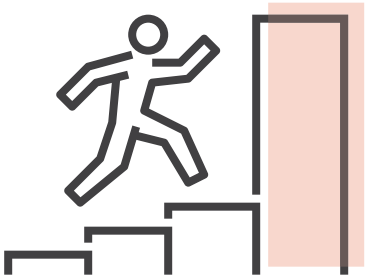
Highlights

1. Health Related Quality of Life (HRQOL) is an important measure of the global impact of IBD on a person's physical, mental and emotional well-being.

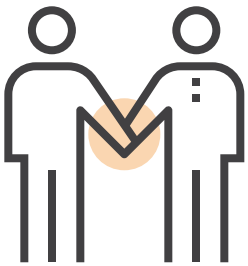


2. People living with IBD have significantly lower HRQOL when compared to that of the general population.

3. IBD often affects individuals as they pursue employment, family planning, and personal milestones.



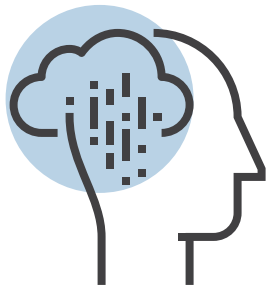
4. IBD affects the QOL of those afflicted and their caregivers.



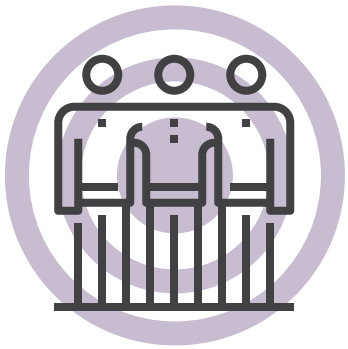
5. Access to transdisciplinary, collaborative, chronic disease models of care improves the HRQOL of people living with IBD.

Gaps in Knowledge and Future Directions

1. Patients with IBD experience emotional distress that reduces HRQOL. Clinical tools are necessary to identify the key factors causing psychological distress in patients with IBD.



2. HRQOL is reduced in individuals with IBD and their families. Studies should evaluate the cumulative burden of IBD on HRQOL in patients with IBD and their caregivers.

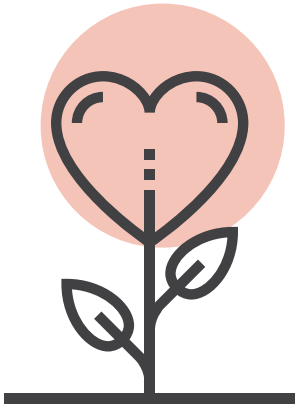


3. Patient self-perception of their IBD influences their HRQOL. Clinical studies of interventions that improve adaptive coping are needed to reduce psychosocial distress.

4. The impact of care provided by a multidisciplinary team that includes a psychologist to screen for and manage psychosocial risk and psychological distress, should be evaluated in IBD clinics.

6.0 Introduction

Quality of life (QOL) is a broad, multidimensional concept that usually includes subjective evaluations of both positive and negative aspects of life.[1,2] The Centre for Disease Control has defined QOL as "an individual's or group's perceived physical and mental health over time."[1] The concept of health related quality of life (HRQOL) and its determinants has evolved since the 1980s to encompass aspects of overall QOL that have been shown to affect either physical or mental health.[1,3,4] HRQOL questions have become an important component of public health surveillance and are considered valid future indicators of unmet needs and intervention outcomes. Self-assessed health status is a more powerful indicator of mortality and morbidity than many objective measures of health.[5,6]



HRQOL is impaired at some point in every patient with IBD, and many live chronically with impaired HRQOL. IBD affects young individuals at a time in their lives when they are most likely to be pursuing major employment, family planning, and personal milestones of critical importance. The pursuit of such critical milestones is often impeded by the unrelenting and debilitating symptoms, and the psychological distress associated with IBD.[7-10] Measuring and evaluating the disability associated with IBD, and the impact of IBD on a person's quality of life, is paramount to understanding the often hidden burden of this disease for persons living with IBD and for society as a whole.

6.1 What influences Quality of Life in People Living with IBD?

6.1.1 Compounding Factors: Disease Activity and Psychological Distress

On balance, data from most population-based studies suggest that people living with IBD have significantly lower HRQOL when compared to that of the general population; this is particularly true for those with more severe disease activity.[11-17] Disease severity remains the most significant predictor of physical and mental HRQOL.[18] Compared with individuals in the general population, the QOL domains most impacted in patients with IBD were: general health, mental health, and social functioning. These findings also hold true for children with IBD. Youth with IBD have lower HRQOL compared with their healthy peers[19-22] and higher levels of impaired school-related HRQOL than healthy or chronically ill youth.[22]

A study in which conversational interviews of persons living with Crohn's disease were conducted, demonstrated that Crohn's disease had a major impact on need fulfillment (*i.e.,* self-esteem, relationships, nutrition, hygiene, security).[23] Additionally, disease activity as well as psychological distress have been shown repeatedly to significantly impair the QOL in both children and adults living with IBD.[24-26] Patients who have had surgery also experience impaired QOL.[27] Patients with IBD experience significant psychological distress and have significant concerns related to surgery, degree of energy, and body image issues (especially concerning the need for a ostomy bag).[28] Pain is a commonly reported symptom among adult patients with IBD, which could further impair QOL.

In addition to disease severity and psychological distress, family level factors can also affect HRQOL.[29,30] In a study by Gray *et al.*, parental stress level (both that related to medical factors as well as perceived stress) was shown to mediate the relationship between disease severity and HRQOL in adolescents with IBD.[29] Higher levels of parental distress were associated with reduced HRQOL amongst adolescents with IBD.[29] Knez *et al.*, reported that parents of children with IBD report a significantly lower psychological health compared to parents of other children, and significantly lower physical health compared to parents of healthy children.[31]

Even during periods of disease remission, patients experience psychological distress which can impact their QOL.[32,33] How one perceives one's illness has been shown to have a major influence on the ability of an individual to adjust to a diagnosis of IBD. Adaptive coping mechanisms are critical in order to manage illness perceptions effectively and to reduce psychosocial distress.[34] High levels of psychological distress have been demonstrated to be associated with increased risk of disease flares.[10,35,36] The ability to work and participate in social activities is impaired by high levels of psychological distress, and leads to modifications in lifestyle as well as disruptions in social relationships and family life.[37]

Several concerns highly specific to IBD contribute to IBD-related emotional distress. These include concerns of loss of bowel control; fatigue; impairment of body image; fear of sexual inadequacy; social isolation; fear of dependency; concern about not reaching one's full potential; fear of stigmatization; and, feeling unclean.[35,36]

6.1.2 Mitigating Factors:
Clinical Remission and Value of Psychological Support

Although there is a lack of evidence that psychological interventions alter the course of IBD itself, they have been shown to improve HRQOL.[38-40] Therefore, people living with IBD require access as part of a transdisciplinary care approach, to providers with the ability to screen for, and manage, psychological distress. The Patient-Reported Outcomes Measurement Information System (PROMIS), are newly validated and reliable tools for evaluating patient-reported QOL. In addition, there are PROMIS tools which can be used to evaluate functional, gastrointestinal, and psychiatric symptom severity in ambulatory adult patients with IBD. PROMIS measures may prove to be useful tools to apply in the ambulatory setting on a broader scale for follow-up of HRQOL.[41]

Several avenues can be used to mitigate the negative impact of IBD on HRQOL.

6.1.2.1 Effective Disease Therapies

The implementation of effective disease therapies in order to decrease disease severity through the induction and maintenance of long-term clinical remission is one area of critical importance.[42] Before the availability of biologic therapies for the treatment of IBD, the use of steroids, 5-ASA, and immune modulatory therapies were not associated with long-term improvements in HRQOL. However, biologic therapies may lead to long-term improvements in HRQOL.[28,43-45] A comprehensive review by Vogelaar *et al.* revealed that long-term, sustained improvements in HRQOL are achievable in patients receiving therapy with infliximab, certolizumab, adalimumab, and natalizumab.[43] GEMINI I and II shows the positive impact of vedolizumab on HRQOL.[46]

Table 6-1:

Factors that influence QOL in people living with IBD.

	Impact on QOL		Mechanism of influence on QOL	
	Children	Adults		
IBD disease activity	Negative	Negative	Self-esteem Relationships Hygiene Security	Depressive symptoms Social isolation Psychological distress
Psychological distress	Negative	Negative	Reduced energy Impaired body image	Maladaptive coping mechanisms Social isolation
Psychological interventions	Positive	Positive	Reduction of exacerbating factors related to increased disease-related psychological distress	
Surgery	Negative	Negative	Fear of complications Need for an ostomy	Body image More severe form of disease
Pain	Negative	Unknown	Disability Depressive symptoms	Disease-related psychological distress
Parental stress	Negative	Unknown	Perceived difficulty of medical stressors	
Effective medical therapy	Positive	Positive	Induction of long-term remission	
Health information gathering from internet	Negative	Negative	Reduced certainty	
Poor sleep quality	Negative	Negative	Fatigue	Daytime dysfunction

6.1.2.2 Managing Psychological Distress

Screening for psychological distress, and the provision of patient-centered management approaches to help mitigate this distress is a critical, but often overlooked, foundational principle of the transdisciplinary care that should be provided through collaborative care programs.

6.1.2.3 Provision of Evidence-based Information

Uncertainty is another factor associated with reduced HRQOL.[47] Health information gathering through the internet by patients with Crohn's disease has been associated with reduced certainty.[47] Therefore, the provision of well-designed, evidence-supported, patient-oriented, educational tools could also help to reduce the level of uncertainty and help to improve HRQOL. Highly educated patients who are actively engaged in their healthcare are more likely to be empowered and to achieve improvements in HRQOL.

6.2 Quality of Life and Pediatric IBD

6.2.1 Unique issues to consider in or with respect to measuring/assessing QOL in children with IBD

Assessing QOL in pediatric patients with IBD requires the healthcare professional to consider two key methodological issues: whether to ask children directly,[48,49] and how to allow for varying developmental levels and ages.[50,51]

It is not always possible to obtain a self assessment of a child's QOL, whether due to age or developmental/disability limits to comprehension. In these instances, a proxy is sought. The proxy reporter of the child's QOL is most often a parent/caregiver but in some cases, may be another individual such as a teacher or physician.[49] However, using a proxy presents additional challenges. The proxies tend to have a low to modest agreement with the child's reported QOL self-assessment.[52] The degree of agreement seems to relate to the objectiveness of the dimension of QOL being assessed. Pantell & Lewis showed that parents and teachers agree fairly well in reporting on child functioning, but markedly less well for recent functional status; and certain types of subjective feelings in regard to illness, information needs, emotional states, and family functioning.[53]

Other challenges in obtaining an adequate self-reported QOL relate to the wide developmental spectrum seen across the pediatric age group. The quality of the self-report is highly dependent on the child's expressive and receptive language abilities.[50] Additionally, differences in time perception and memory related to a particular developmental stage will affect a child's ability to respond to questions based upon experiences during a specific time period.[49]

6.2.2 Pediatric IBD QOL Comparisons

Ryan *et al.* report on incorporating HRQOL screening into clinical practice and its clinical utility in predicting disease outcome and healthcare utilization.[54] This study demonstrates that youth who report lower HRQOL at baseline, on average, have increased healthcare system utilization as measured by IBD-related hospital admissions, emergency department visits, use of psychological services, telephone calls to clinicians, GI clinic visits, and referral to pain management.

Early work has also been done comparing HRQOL of pediatric IBD patients with healthy peers.[55] Not surprisingly, Haapamaki *et al.* demonstrate that children aged 7-19 with IBD have significantly lower HRQOL scores compared to age-standardized healthy peers.[55] Kunz *et al.* compared HRQOL assessments of youth with IBD to published group data of chronically ill, acutely ill, and healthy comparison groups.[22] They showed that youth with IBD have higher physical and social functioning than the chronically ill group, lower psychosocial functioning than the healthy comparison group, and lower school functioning than all published comparison groups. Additional studies are needed to ascertain whether these findings are consistent across pediatric IBD patients, those with other chronic illnesses, and healthy peers. As we gain improved understanding of the relationships between the various factors that contribute to HRQOL, we will be better positioned to design interventions that may address the modifiable factors and evaluate whether this can result in sustained improvements in HRQOL for youth with IBD.

6.3 Disability and IBD

Disability can be defined as chronic limitations that hinder the ability to engage in usual daily activities and is an objective way of understanding the impact of IBD in someone's day-to-day life.[56,57] Disability is a relatively new area of study in IBD. The World Health Organization developed international standards in the assessment of disability using the International Classification of Functioning, Disability, and Health. These tools have been used by researchers to develop generic and disease-specific instruments to evaluate disability in IBD. Ability to work was the most common IBD-related metric for disability. But this metric alone is not sufficient given it does not capture all the important aspects of the burden of this condition. Additionally, with a relapsing/remitting condition like IBD, disability may be temporary and difficult to address.[57]

Although disability studies in IBD have demonstrated increased rates of unemployment, sick leave, and disability pension among IBD patients, most patients maintain their ability to work for many years following the diagnosis of IBD. Patients with IBD have impaired productivity (presenteeism) and loss of working hours (absenteeism) compared to healthy controls, with resultant economic losses for both the individual and society (see Section 5 - Indirect Costs).

The greatest disability restrictions to QOL are described in the domains of interpersonal relationships, life activities, social participation, and mental well-being,[57,58] although there has been some discrepancy in the degree of disability between populations. These discrepancies may be related, in part, to differences between populations and cultures, as well as tools and means of assessing disability. There has been a consistent finding, however, of higher levels of disability in Crohn's disease patients compared with ulcerative colitis patients, particularly in the area of interpersonal relationships. Most patients impacted in the domain of interpersonal relationships have experienced limitations in making new friends, maintaining friendships, and in their sex life.[57] Other areas impacted to a lesser degree include education, career pursuits, family planning, and in regards to the financial burden of IBD.[59]

The stigma associated with IBD sensitizes the communication with employers and schools. How best to communicate with employers and schools regarding IBD is a voiced area of concern, which is underrepresented in the available disease-related information accessible to IBD patients. In a European study,[60] 60% of IBD patients reported feeling stressed by thinking of taking a sick leave from work due to IBD, and almost a quarter of patients had experienced unfair comments about their performance at work from colleagues or superiors. One way to reduce this burden is to facilitate open dialogue and increased awareness and to build a better understanding amongst the general population and employers of the impact of IBD on their colleagues and employees.[58]

6.4 Crohn's and Colitis Canada addresses QOL of Patients with IBD

Health charities can play an important role in filling gaps in the health system by supporting patients to live a better quality of life through both program and technological interventions.

Crohn's and Colitis Canada supports research and also offers programs to support patients to have a better QOL. Regular educational events, in-person or through webinars and social media are offered by Crohn's and Colitis Canada. In addition, the 46 chapters across Canada hold regular meetings and educational events. Patient support is available through the online Gutsy Peer Support program that matches patients to aid their discussions of disease management and quality of life. Through feedback from patients, Crohn's and Colitis Canada launched the GoHere program – a smartphone app that geo-locates businesses that provide IBD patients access to washrooms.

New technologies offer additional forms of support as indicated by the following example. Through the Crohn's and Colitis Canada funded Promoting Access and Care Through Centres of Excellence (PACE) research program, clinician-scientists are pilot testing a digital application with which patients can communicate their health status to their healthcare providers

6.5 Conclusion

IBD often begins in young individuals at a time when they are pursuing educations and/or employment, building their family, and achieving key life milestones. IBD harshly influences HRQOL and introduces disability that can impair daily activities, thus affecting interpersonal relationships, life activities, social participation, and mental well-being. The impact of IBD on HRQOL is multifaceted including the direct physical impairment from symptoms like diarrhea and abdominal pain, to psychological distress. Disease severity worsens physical and mental HRQOL. However, even in clinical remission, patients experience psychological distress. Psychological distress stems from factors such as symptoms, distorted perception of body image, fear of sexual inadequacy, social isolation, fear of dependency, concern about not reaching one's full potential, and fear of stigmatization.

HRQOL is uniquely impacted in children and adolescents with IBD. Moreover, the entire family can suffer collectively from reduced HRQOL, as parental stress is commonly experienced. Consequently, the impact of IBD on HRQOL is an important burden for persons living with IBD and for society as a whole. Fortunately, strategies are available to mitigate the negative HRQOL that many patients with IBD experience. Physical determinants of HRQOL can be addressed with appropriate medical and surgical management. Psychological distress is addressed through transdisciplinary care including a psychologist who can work with patients to develop adaptive coping mechanisms that help manage illness perceptions and reduce psychosocial distress.

Summary of Section 6: Quality of Life in Patients with IBD

1. IBD impairs HRQOL by inhibiting need fulfillment (*i.e.,* self-esteem, relationships, nutrition, hygiene, security) and causing psychological distress.

2. IBD impairs interpersonal relationships, life activities, social participation, and mental well-being.

3. Patient symptoms like diarrhea and abdominal pain reduce health related quality of life (HRQOL).

4. While disease severity is an important driver of physical and mental HRQOL, patients experience psychological distress even during clinical remission.

5. Psychological distress impairs work productivity and disrupts social activities and relationships.

6. Patients with IBD experience emotional distress relating to factors such as loss of bowel control, impairment of body image, fear of sexual inadequacy, social isolation, fear of dependency, concern about not reaching one's full potential, and fear of stigmatization.

7. Families with children with IBD have impaired QOL as a collective – for example, parental stress from medical factors and child's perceived stress.

8. Patients' perception of their illness affects their ability to adjust to a diagnosis of IBD. Adaptive coping mechanisms help manage illness perceptions and reduce psychosocial distress.

9. Biologics are associated with improvement in long-term HRQOL in people with IBD.

10. Patients with IBD should have access to transdisciplinary care including mental health practitioners to screen for and manage psychological distress.

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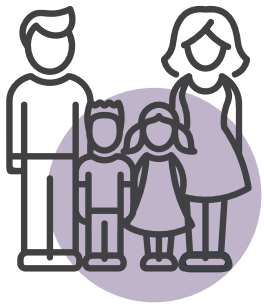
SPECIAL POPULATIONS: CHILDREN WITH IBD

Special Populations: Children with IBD

Highlights

1. In 2018, there are over 7,000 children and youth under 18 years old living with IBD in Canada, and 600-650 young children (under 16 years) diagnosed every year.

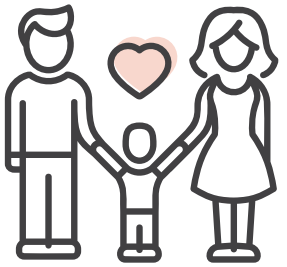


2. The number of children in Canada living with IBD is growing rapidly, increasing 50% in the first decade of the 21st century.

3. IBD is still rare in children less than five years of age, but it is occurring in such young children more often than in the past.

4. Children with IBD are different from adults. For example, delayed growth, extent of disease, and difficulties encountered during adolescence are all unique to the pediatric experience.

5. We must consider the psychosocial well-being of both children and their families given that caring for a child with IBD can affect the global functioning of families.



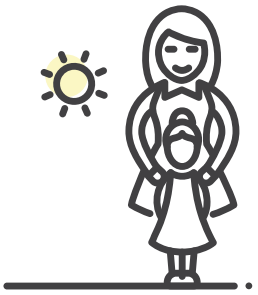
6. Treatments for children with IBD are sometimes different in children from adults, although to date, all therapies effective in adults have also been effective in children. There is great need for clinical trials of new therapies in children, so that they have equal access to emerging treatments and optimal pediatric dosing can be established.

Gaps in Knowledge and Future Research Directions

1. We have limited knowledge on what causes IBD in children and why rates are rising most rapidly in young children. We must better understand the interaction between genes, the environment, the immune system and the microbiome in order to better prevent and treat the disease.

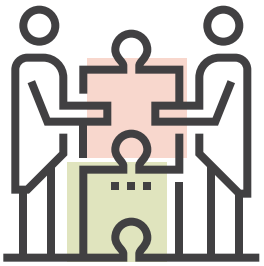
2. Treatment for infants with IBD-like illnesses and single-gene mutations is limited. Future research should work towards identifying these children and learning how best to treat them.

3. There are few clinical trials for biologics in children and most exclude very young children. Support for such trials is important to understand whether the treatments work, how they should optimally be given, and whether they are safe for young children with IBD.



4. Considering the effectiveness of dietary therapies for children with Crohn's disease (exclusive enteral nutrition), we should work to understand how diet affects intestinal inflammation and the microbiome in order to use dietary therapies to better treat IBD.

5. Health services researchers, healthcare providers, and policy-makers should work together to understand why variation in the access to treatment and medical care of children with IBD exists. We must work together to improve the quality of care provided to these children and ensure they have the highest quality of care.



6. Psychosocial implications of IBD in children and their families are important to long-term and overall well-being. Children with chronic incurable disease are at risk for mental illness associated with their disease. We should design interventions to improve the psychosocial status, mental health, and quality of life of children with IBD and their families.

7. While non-live immunizations are safe for children with IBD, we must understand how to improve their effectiveness in children who are immunosuppressed.

7.0 Introduction

While the peak onset of IBD occurs in the second or third decades of life, the frequency of new diagnoses in younger children is rising rapidly. In Canada, the fastest growing group of newly diagnosed people with IBD are children aged under five (termed Very Early Onset (VEO) IBD). These young children have not been included in clinical trials of new medications, resulting in a lack of scientific evidence of safety and effectiveness of treatments in this group. Clinical experience has shown them not to respond to usual medications used for the majority of children with IBD. Providing children with IBD with high quality care and social support also poses other challenges to care providers, families, and the health system. This section will focus on the unique challenges facing Canadian children with IBD.

7.1 Epidemiology

Approximately 10-20% of newly diagnosed IBD will occur in children under 18 years old.[1] As with adult-onset IBD, Canada has amongst the highest rates of pediatric-onset IBD in the world.[2] Recent population-based studies using provincial health administrative data demonstrated some alarming trends in Canadian children.

Data from the Ontario Crohn's and Colitis Cohort, reported a striking rise in rates of IBD in children under 18 years old. Between 1994 and 2009, the number of new diagnoses (incidence) of IBD in children <18 rose from 9.4 per 100,000 children to 13.2 per 100,000 children.[3] The rate rose most rapidly in children <10 years, in whom the number of new diagnoses increased 7.4% per year. By contrast, the rate in children 10-18 years old rose by 2.2% per year. A more recent study from the Canadian Gastro-Intestinal Epidemiology Consortium (CanGIEC) examined rates of IBD in children <16 years old from five Canadian provinces (Alberta, Manitoba, Nova Scotia, Ontario and Quebec) between 1999 and 2010.[4] This study found:

- There were nearly 3,000 children under 16 years old living with IBD in Canada, and 600-650 children are diagnosed every year.

- The number of young children in Canada living with IBD is growing rapidly, increasing 50% in the first decade of the 21st century (in children under 16 years old, rising from 33.2 per 100,000 in 2000 to 46.2 per 100,000 in 2008) (see Figure 7-1).

- Rates of new diagnoses in children <16 years were growing most rapidly in Ontario (increased 5.8% per year) and Quebec (increased 2.8% per year).

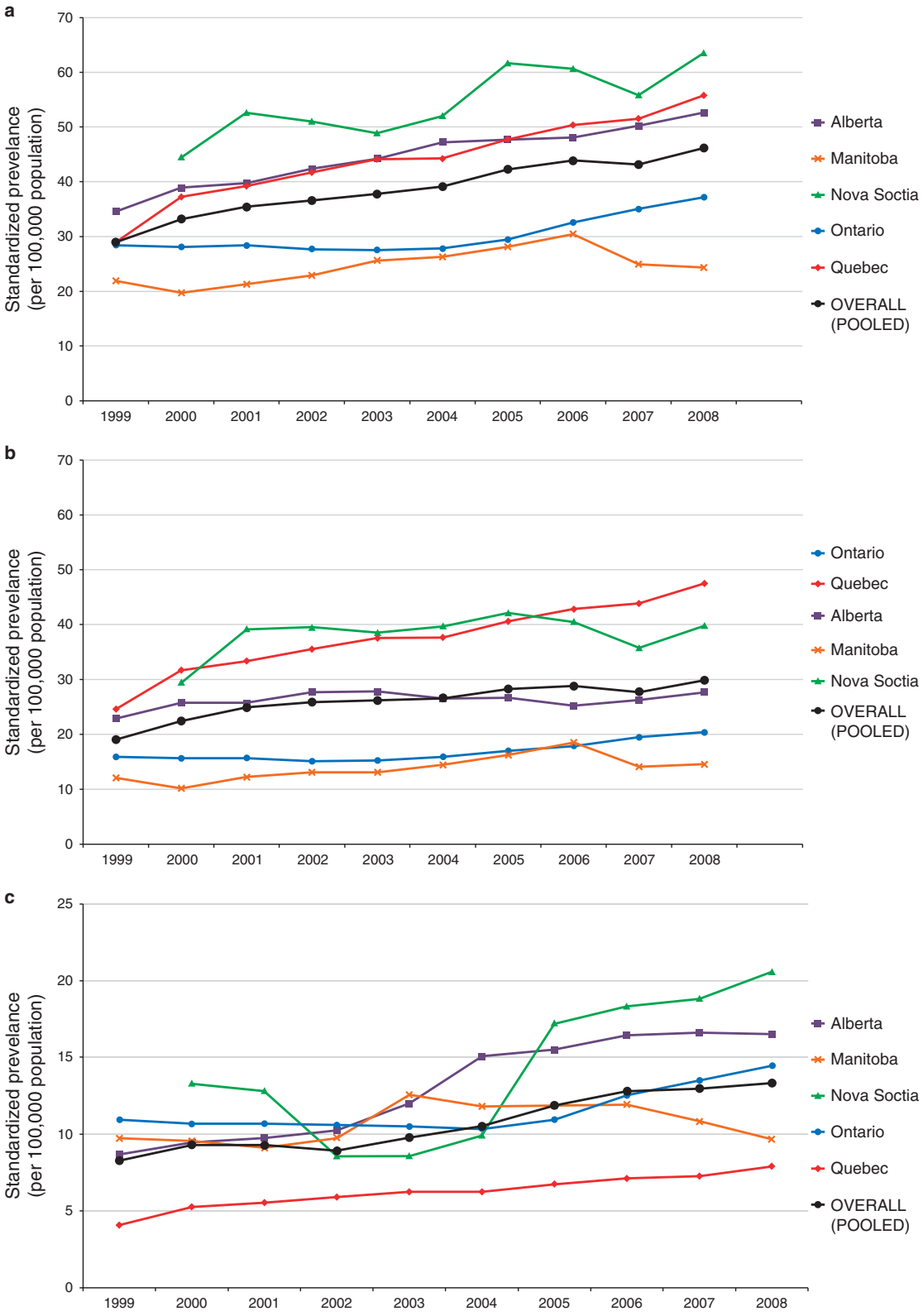


Figure 7-1: Annual standardized prevalence (per 100,000 population) of (A) IBD, (B) Crohn's disease, and (C) ulcerative colitis in Canada. Reprinted from *Am J Gastroenterol* 2017; 112:1120–1134 (Figure 5).[4]

- More children under five years of age are now being diagnosed with IBD (increased 7.2% per year nationwide).

- Nova Scotia has the highest rate of pediatric IBD, with lower rates in Quebec and Ontario. However, even Ontario and Quebec have higher rates of pediatric IBD than most countries in the world.

Another study from CanGIEC estimated the number of children and youth under 18 years living with IBD in Canada, and projected future prevalence based on past trends. This study found:

- In 2008, the prevalence of IBD in children and youth <18 years was 68 per 100,000 (in 6 Canadian provinces). This equates to 4,730 children and youth living with IBD in Canada.

- A projection model estimated that in 2018, prevalence had increased to 101 per 100,000, equating to almost 7,254 children and youth living with IBD in Canada. This represents a 53% increase in children with IBD over the last 10 years.

- In 2030, we project 13,685 children and youth with IBD living in Canada (172 per 100,000 children). This means almost double the number of children will live with IBD in 2030 compared to 2018, and almost triple the number living with IBD in 2008.

The variation in rates of IBD across the country in children is demonstrated in Figure 7-2.

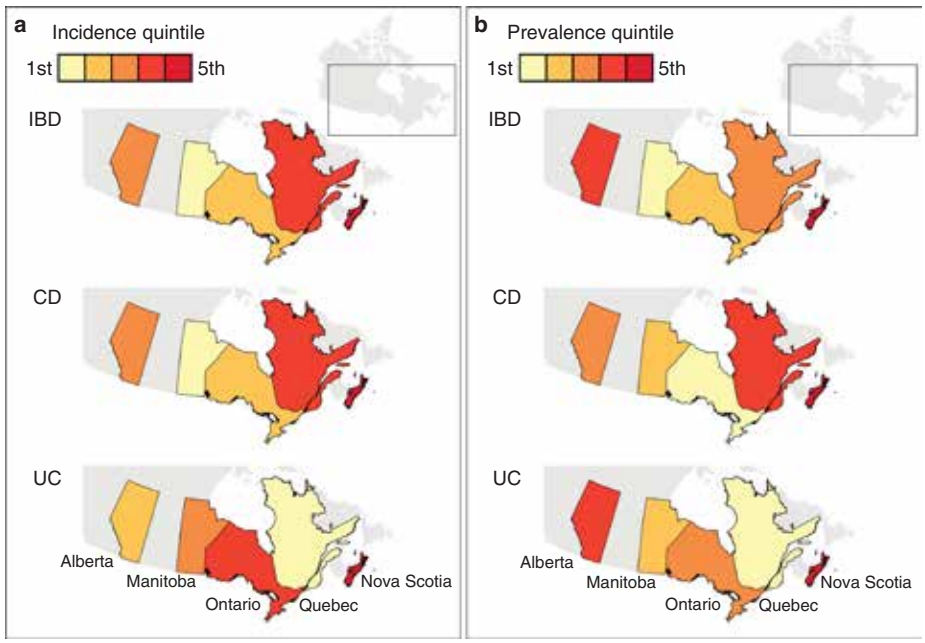


Figure 7-2: (A) Incidence of IBD (1999-2010) and (B) prevalence of IBD in Canada. Reprinted from *Am J Gastroenterol* 2017; 112:1120–1134 (Figure 1).[4]

7.2 The Pathogenesis of Childhood-onset IBD: Genetics and the Microbiome

Twin studies in Crohn's disease, which demonstrated greater concordance in monogenic twins (sharing all genes) versus dizygotic twins, provided the best initial evidence that genes were involved in causing IBD. However, just as IBD is a diverse group of disorders with complex pathogenesis, the genetic basis is similarly complex. In most patients, IBD is not monogenic (*i.e.,* Mendelian) but driven by multiple genes. Evaluation of the complete set of genetic variants (*i.e.,* genome-wide association studies (GWAS)) have defined over 230 locations of genes (disease loci) linked to IBD.[5] Interestingly, 80-90% of GWAS-identified loci exert their effect through altering how a gene is expressed rather than as an altered product of the gene.[6] However, studies using GWAS could not determine distinct differences in the genetic profiles of adolescent-onset IBD compared to adult-onset disease.[7]

Using different genetic technologies, more than 50 rare monogenic (single-gene) disorders have been identified that can present with intestinal inflammation and, therefore, mimic Crohn's disease or ulcerative colitis.[5] These monogenic disorders are so rare that they would not be identified in GWAS studies. Onset in infancy and extremely severe disease are features which warrant a search for a single gene defect. Nevertheless, monogenic disorders still account for a minority of children with IBD, even those who develop IBD before the age of six. While some monogenic disorders always present in infancy, specific disorders (e.g., XIAP deficiency) may have variable onset between neonatal period to adult-onset disease and only 30-40% of those with this gene alteration even develop IBD-like disease.[5] Many of these monogenic disorders with IBD-like disease have predominant immune based defects that do not respond to usual therapies for IBD but have been cured with allogeneic bone marrow transplantation. However, in some of the monogenic disorders resulting in epithelial defects, stem-cell transplants will not be helpful.[5]

Although genetic testing of common variants as a screening or diagnostic tool has little clinical value in the general population,[6] known genetic risk variants for Crohn's disease are associated with specific localization of disease but do not influence the disease course or predict response to therapy.[6,7] In a large study of children with Crohn's disease, early anti-TNF biologic therapy was associated with reduced rates of internal penetratinwg, but not stricturing, disease complications. A novel ileal extracellular matrix gene signature was discovered that, if present at diagnosis, was associated with future stricturing complications, regardless of exposure to early anti-TNF.[8] Genetic factors, along with environmental factors, are being shown to affect intestinal bacterial profile and function, and that individual gene variants can have specific effects.[6,9,10]

A fundamental question in determining the cause of IBD is whether the observed changes in the bacteria (*i.e.,* microbial dysbiosis of the microbiome) present in the intestinal tracts of those with IBD are a cause or a consequence of inflammation. Most work has been done on bacterial changes in the intestinal tract of IBD patients but there is also emerging evidence that fungi, viruses, and archaea (single cell microorganisms) may be playing a role as well.[10] Converging lines of evidence from mice studies[10] and human research, such as studies in which antibiotics have been linked to Crohn's disease,[11] have helped elucidate causation. The effect of antibiotics in triggering Crohn's disease is greater in children than in adults.[12] One report of children with new-onset Crohn's disease demonstrated

worse clinical disease and microbial profiles of fewer anti-inflammatory bacteria when on antibiotics at the time of their diagnosis as compared to children not on antibiotics.[12] Such findings point to the complexity of microbial communities that are involved in cause and chronicity of IBD. The products produced or suppressed by the dysbiotic environment[13] and their function on immune responses are involved in health versus disease of the lining of the intestinal tract.[10] New technologies and systems-level approaches to study the role of the intestinal microbiome are now being applied to determine interactions between the intestinal microbiota and host right at the site of disease, at the mucosa–luminal interface.[13] These technologies will allow us to move beyond description of different bacteria that can be present in IBD. We must also understand how they function and are involved in the development and chronicity of the mucosal inflammation and how they affect intestinal cell function.[8,13] It is becoming clear that changes in bacteria are not random changes but relate to community level interactions amongst the microbes and their effects on the host functioning leading to permissive dysbiotic environments.[13] Targeting the dysbiotic environment and its effect on disease will open up new treatments paradigms beyond current strategies that to a large extent currently target human inflammatory pathways. Therefore, not only does the microbiome play a role in the risk and development of IBD, but it may represent a novel therapeutic target to help treat patients with active disease.

7.3 Environmental Risk Factors of Childhood-onset IBD

With the exception of children with infantile onset disease (under two years of age), and a small number of children and adults with single-gene mutations, the genetic contribution to the risk of IBD is not enough to predict the development of IBD or the age of onset. With the new understanding of the gut microbiome as a potential source of disease, the search for environmental risk factors that alter the microbiome and increase the risk of IBD has taken on new urgency. A number of environmental risk factors have been associated with childhood-onset IBD.[14] In fact, it appears that certain environmental risk factors have a greater effect at increasing the risk of IBD in children, compared to older people.[14] In addition, since children are exposed to fewer environmental toxins in their short lives, scientists believe that we may be more successful in identifying risk factors and therefore preventing the disease in children. However, we are still very early in our ability to prevent IBD.

While smoking of cigarettes is strongly associated with Crohn's disease in adults,[15] smoking rates are very low in children. However, passive (second-hand) smoke exposure has been associated with childhood-onset IBD.[16] A small study found that exposure to passive smoke around the time of birth greatly increased the risk of later development of IBD,[17] reinforcing the recommendation that smoking near children should be avoided. When the interaction between smoking and *NOD2*, the first discovered Crohn's disease susceptibility gene, was studied, a negative interaction was found between smoking and the 1007fs variant of *NOD2*.[17] This implies that this variant protects smokers from developing IBD. However, the 1007fs variant was less prevalent in people with adult-onset Crohn's disease compared to children, while smoking prevalence increased with age.[17]

This emphasizes the potential importance of interactions between age and genetics when assessing the role of environmental risk factors on the risk of IBD.

One example of the age-related effect of environmental risk factors is air pollution. A study of UK residents found that increased levels of certain air pollutants (nitrous dioxide and particulate matter) increased the risk of IBD, but only in younger people.[18] A Canadian study found that feeding mouse pups particulate matter resulted in harmful changes to the gut microbiome[19] and an increased risk of developing IBD earlier in the mouse's life.[20] If this is true in humans, exposure to air pollutants in early life may permanently alter the gut microbiome in a way that predisposes to IBD in childhood.

Some believe that living in a more hygienic environment increases risk of IBD in children. Markers of cleaner environments such as smaller family size, availability of flush toilets, and lack of household pets have been associated with increased risk of Crohn's disease. In Canada, IBD patients tend to have a smaller number of people living in their houses when they were under five years old, and being higher in the birth order (*i.e.,* having fewer siblings early in life) resulted in increased risk of Crohn's.[21] In addition, living in an urban household has been associated with increased risk of IBD in many international studies.[22] A CanGIEC study, published in 2017, demonstrated that this effect was strongest in childhood-onset IBD; and that living in a rural household within the first five years of life was highly protective against later development of IBD.[4] In a German study, early-life exposure to farm animals reduced the risk of both Crohn's disease and ulcerative colitis.[23] One hypothesis is that early life exposure to certain bacteria, viruses, or other organisms helps to establish the gut microbiome in a way that is protective against IBD. Therefore, the cleaner environment present in the Western world and in cities may increase the risk of IBD, while reducing the risk of life-threatening infections or other diseases.

Western diet has also been associated with risk of IBD. Westernized diets are higher in animal fats and some carbohydrates, but lower in fruits, vegetables and their attendant resistant starches and omega-3 fatty acids derived from fish.[24,25] However, it is possible that breastfeeding in infancy may reduce the risk of subsequent IBD development[26] particularly during childhood.[27]

The highest rates of IBD have been reported in Canada and Northern European countries. In addition, a north-south gradient in IBD prevalence has been noted in France and the UK, with northern latitudes being associated with higher rates of IBD. This has raised interest in a possible role of vitamin D deficiency, very common amongst Canadians, and the risk of IBD.[28] There may be an association between vitamin D and the functioning of the NOD2/CARD15 gene.[29] Vitamin D may also drive inflammation through the TNF-α pathway.[30] In addition, being deficient in vitamin D during pregnancy was associated with increased risk of IBD and lupus in the offspring.[31] These associations are not yet proven, but clinical trials are underway in children to examine whether supplementation with vitamin D results in fewer flare-ups or complications of IBD.

Infections have long been suspected to trigger new IBD in children and adults. This may be through changes in the microbiome or an altered immune

response as the body tries to fight the infection. Alteration in intestinal mucosa barrier function as a consequence of dysregulated immune activation may favour the development of IBD in susceptible individuals. However, multiple Canadian studies have demonstrated that early-life antibiotic usage increase the risk of later development of IBD, particularly when they are given within the first years of life.[32-34] These findings suggest that intestinal dysbiosis may affect development of gut immune tolerance or function of the intestinal microbiome, as well as facilitating chronic intestinal mucosal inflammation. The movement toward judicious use of antibiotics and restricting their use only to children who have bacterial infections (and not viruses) may help reduce IBD risk.

7.4 How is Childhood-onset IBD Different?

While the underlying disease process and appearance of the bowel is similar between childhood- and adult-onset IBD, there are some significant differences between the two groups, resulting in unique challenges for children with IBD. Firstly, boys are more likely affected with Crohn's disease than girls. This is unexplained, and changes around the time of puberty, when rates in males and females are approximately equal. In ulcerative colitis, younger girls are slightly more likely to be diagnosed with ulcerative colitis than boys, but around puberty the ratio of males to females again becomes about equal. When children are afflicted with IBD, there are also differences in the way the IBD looks and in complications of the disease.

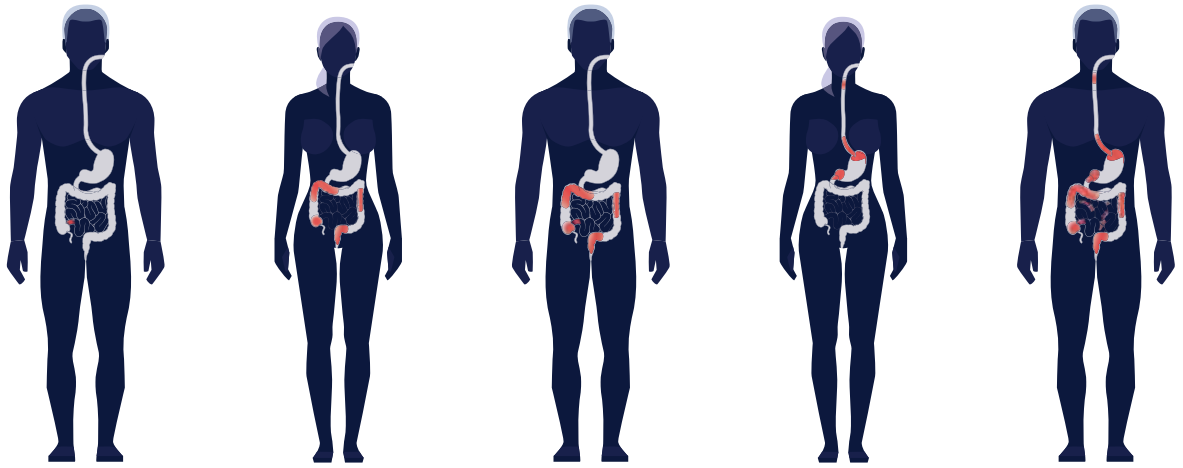


Figure 7-3: Difference in disease characteristics and location of in childhood-onset compared to adult-onset Crohn's disease. *Children with onset <10 years old are more likely to have isolated colonic disease (L2). **Children and adolescents with older age of onset (10-18 years) are more likely to have both small and large bowel affected (L3), and are ***more likely to have upper GI tract involvement (L4).
Adapted from *Gastroenterology* 2008; 135:1114-1122.[36]

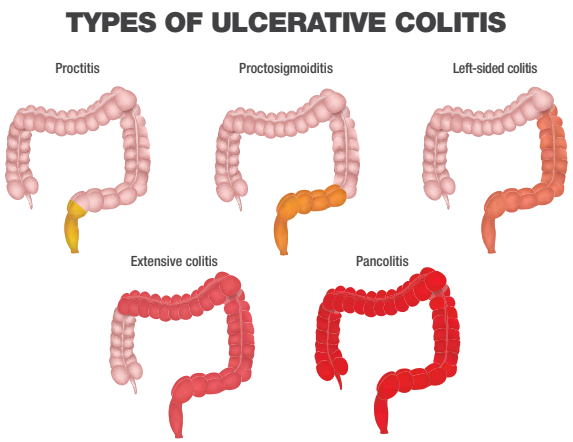
7.4.1 Disease extent and severity

Compared with adults, children with IBD are likely to present with more extensive disease (Figure 7-3).[35,36] In Crohn's disease, this means that children are more likely to have both their small and large bowels affected, whereas adults are more likely to have disease isolated to the ileum (last part of the small bowel). In addition, children may be more likely to have upper gastrointestinal tract disease (*i.e.,* disease that affects the esophagus, stomach, and duodenum), and longer segments of small bowel affected. This may also result in children with IBD being treated more aggressively early in their disease course. Children may also present with more subtle signs and symptoms early in their disease course which have been associated with delayed diagnosis. Unexplained fevers, iron deficiency anemia, poor growth or non-specific abdominal pain may be the only presenting complaints requiring pediatricians and pediatric gastroenterologists to remain vigilant.

While more of the bowel may be affected in children, they may have better overall rates of response to medications used to treat their Crohn's disease as IBD drugs are designed to halt inflammation. With time, inflammation left untreated in the bowel results in scarring of the bowel ('stricturing disease'). There are no treatments designed to reverse fibrosis and scarring of the intestinal mucosa, which may lead to many symptoms that mimic mucosal inflammation. Thus, scarred portions of the bowel are treated with surgery to remove that portion of intestine. In addition, inflammation burrows deep into the bowel wall, resulting in fistulas and abscesses in the abdomen (*i.e.,* penetrating disease), which can be potentially life-threatening. With fibrostenosis and penetrating disease taking time to develop as a result of chronic, inadequately controlled inflammation, children have lower surgical rates than adults. The risk of surgery to remove bowel in children from Ontario and Manitoba with Crohn's is 8-9% in the first year after diagnosis, 21-23% at 5 years, and 27-29% at 10 years,[37,38] significantly lower rates than in adults.[35] In addition, children with Crohn's are less likely to have complications of their disease such as fistulas and abscesses.[35] This suggests that medications are more effective at preventing severe and life-threatening complications in children. This is likely because the disease is more 'inflammatory', and less 'stricturing'.[36] This means that children, and especially children under the age of six, are less likely to need surgery to remove pieces of their bowel. This may also explain why children in clinical trials of anti-TNF biological medications and immunosuppressive treatments had higher rates of successful remission than those reported in adult studies. This is good news; Crohn's disease caught early enough (*i.e.,* during the time when the intestinal mucosa is inflamed rather than scarred) is responsive to treatment and severe complications may be prevented.

In ulcerative colitis, more than 80% of children have extensive colitis (affecting more than three-quarters of their large bowel).[36] By contrast, in a Scottish study, less than 50% of adults had extensive colitis (Figure 7-4).[36] In addition, ulcerative colitis restricted to the rectum (the last part of the colon, termed isolated proctitis) is extremely rare in children, comprising 1.4% of children, compared to 17% of adults.[36] Unfortunately, pancolitis (*i.e.,* disease affect most/all of the colon) is more severe and harder to treat successfully with medications. This means that children are more likely to be hospitalized for ulcerative colitis especially around

Figure 7-4: Difference in extent of disease in childhood-onset compared to adult-onset ulcerative colitis. Adapted from *Gastroenterology* 2008; 135:1114-1122.[36]



the time of diagnosis and may be more likely to undergo colectomy (*i.e.,* permanent surgical removal of their colon). Approximately 6% of children need a colectomy within one year of diagnosis, 12-16% at 5 years, and 15-21% at 10 years.[37,38] By comparison, in adults with ulcerative colitis, colectomy rates are 7.5%, 10.4% and 14.8% at five, 10, and 20 years respectively.[39] Population-based studies of children with ulcerative colitis in Canada[38] and the United States[40] have demonstrated stable colectomy rates in recent years, prior to the widespread use of biologics in children. However, large Canadian-run studies of the treatment of children with ulcerative colitis[41] and the availability of newer medications, has helped advance our understanding of how best to treat children with ulcerative colitis. It remains to be seen whether our improved knowledge will result in fewer colectomies.

7.4.2 Growth Failure

Impaired growth and short stature were historically a manifestation of Crohn's disease in children. Growth impairment in Crohn's disease results primarily from the direct effects of pro-inflammatory cytokines released from the intestine on the growth plates of bones. Since growth is only possible until puberty is complete, pediatric gastroenterologists are aware of the need to treat Crohn's disease aggressively in order to avoid stunting. Corticosteroid medications (a previous mainstay of treatment for Crohn's disease) are known to slow growth, and so are no longer used repetitively or for long periods of time. Their judicious use has allowed growth potential to be attained in most adolescents with IBD. The anti-TNF biologic medications are the only proven treatment to avoid growth failure in teenagers. Therefore, anti-TNF biologics should be considered as first-line treatment in growth delayed children and especially adolescents, who have a more limited time to attain their growth potential. This presents challenges in health systems that currently require children to fail traditional therapies (*i.e.,* steroids and immunosuppressives) prior to approving funding for the expensive biologic agents. In pediatric IBD, time and expertise are essential to avoid permanent life-long short stature.

7.4.3 Bone and Muscle Deficits

As with growth failure, Crohn's disease affects bone cells in children, resulting in reduced bone mineral density.[42] This bone deficit is, in part, due to loss of muscle strength in children, resulting in less healthy strain on the bone and therefore decreased bone strength.[42] It is also due to direct effects of pro-inflammatory cytokines on bone cell function. The growth period is an important time to lay down strong and healthy bones; treatment of the underlying inflammation is therefore time-sensitive. As with growth failure, steroids are known to cause decreases in bone cell mass in both children and adults. Therefore, physicians may need to avoid corticosteroids and choose to use anti-TNF biologic medications or exclusive enteral nutrition at diagnosis to treat children with very poor bone health.

7.5 Health Services Utilization and Cost of Care

Childhood-onset IBD has been recognized to have distinct challenges in diagnosis and treatment requiring the care of teams of healthcare providers who are expert in the condition. Therefore, children with IBD have been cared for increasingly by pediatric gastroenterologists and pediatric allied healthcare providers, with reduced care by adult gastroenterologists and surgeons.[43] In Ontario, this was associated with fewer surgeries in children with Crohn's disease and more use of biologic medications.[43] In addition, Manitoba children with IBD had far more physician visits in the five years before their IBD diagnosis, likely due to the difficulties making the diagnosis. This increased health services utilization spiked in the year around the diagnosis date, and then decreased. However, even five years after diagnosis, children with IBD visited physicians more than twice as often as children without IBD (Figure 7-5).[38]

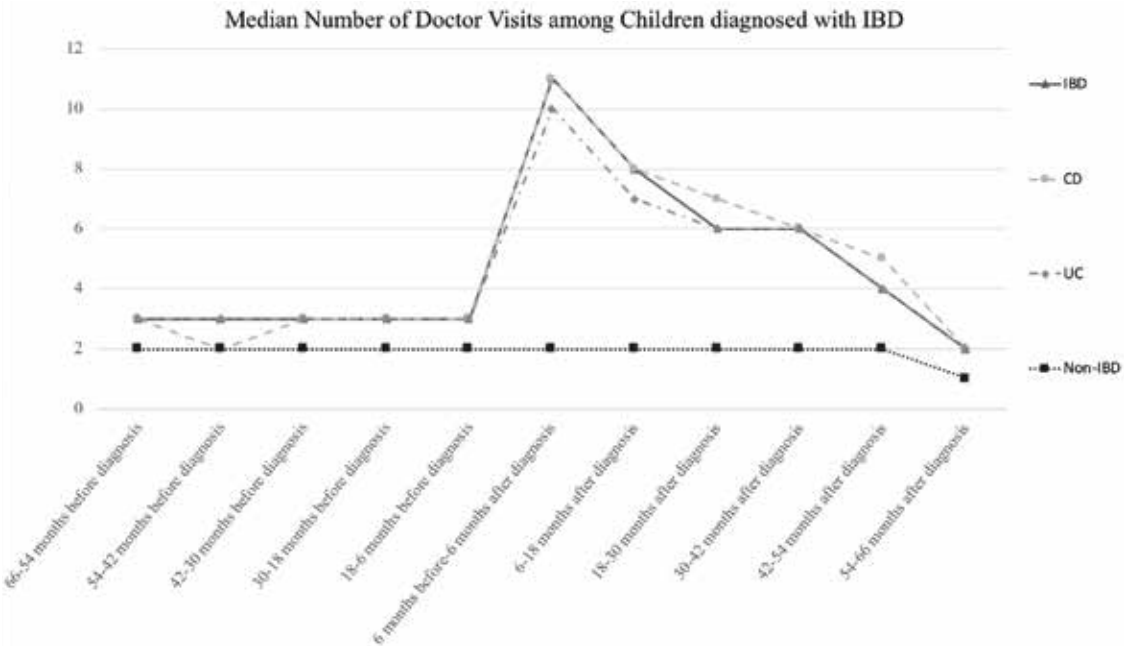


Figure 7-5: Outpatient physician visits in children with IBD in Manitoba, compared to non-IBD controls. Adapted from *Clin Gastroenterol Hepatol* 2015; 13: 1302-1309.[38]

Unfortunately, this comes at a price. An American study demonstrated that direct healthcare costs of providing care to children with IBD were 20-30% higher than adults with Crohn's disease (US $9,000-$10,000 in children vs. US $8,000 in adults per patient per year), and more than double the cost of adults with ulcerative colitis (almost US $10,000 in children vs. US $4,000-$5,000 in adults per patient per year).[44] This difference was not as great in a 2018 study from Manitoba in patients treated with anti-TNF biologics. In the year prior to anti-TNF initiation, direct costs in children <18 years were CAD$10,054 (compared with CAD$9,177 in adults aged 18-40, and CAD$8,643 in adults aged 40 and above). In the year following infliximab initiation, costs were actually lower in children (CAD$34,593) compared with adults 18-40 (CAD$39,318) and over 40 (CAD$44,050). Direct healthcare costs in children who failed the initial anti-TNF therapy were greater than in those who responded (CAD$44,391 vs. CAD$33,793).

A large Ontario study found that children with IBD were less likely to require surgery or die during a hospitalization for IBD.[45] This difference was more pronounced in patients with Crohn's disease than ulcerative colitis, with adult Crohn's patients more than twice as likely to undergo major bowel resection surgery compared with children. However, children with IBD were more likely to be re-admitted to hospital after an initial hospitalization compared with adults.[3,45] Another Ontario study examined health services utilization and surgical risk in children with VEO IBD (diagnosed before age six) compared to those diagnosed aged 6-10 years, and 10-18 years.[3] Those with VEO IBD had fewer outpatient visits, hospitalizations, emergency department visits, and required surgery less for Crohn's disease than children with disease onset at older ages (Figure 7-6).[3] This may be because their disease is different, but may also be because their disease was diagnosed earlier in life, before the inflammation had the opportunity to damage and scar the bowel and, therefore, was more responsive to medications. While increasing rates of IBD in very young children is not good news, our ability to diagnose them earlier in life and therefore treat the inflammation before complications arise is positive news.

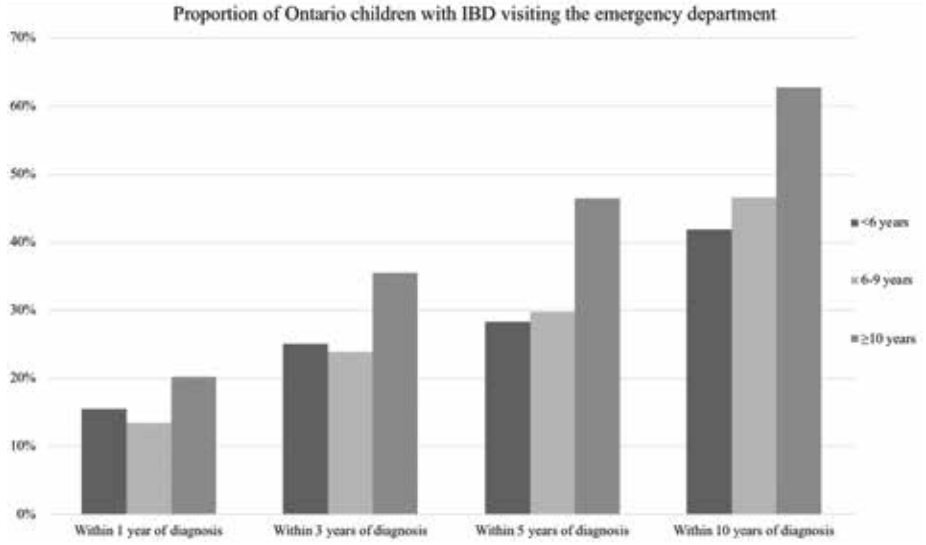


Figure 7-6: Risk of emergency department use in Ontario children with IBD. Adapted from *Gastroenterology* 2014; 147: 803-813.[3]

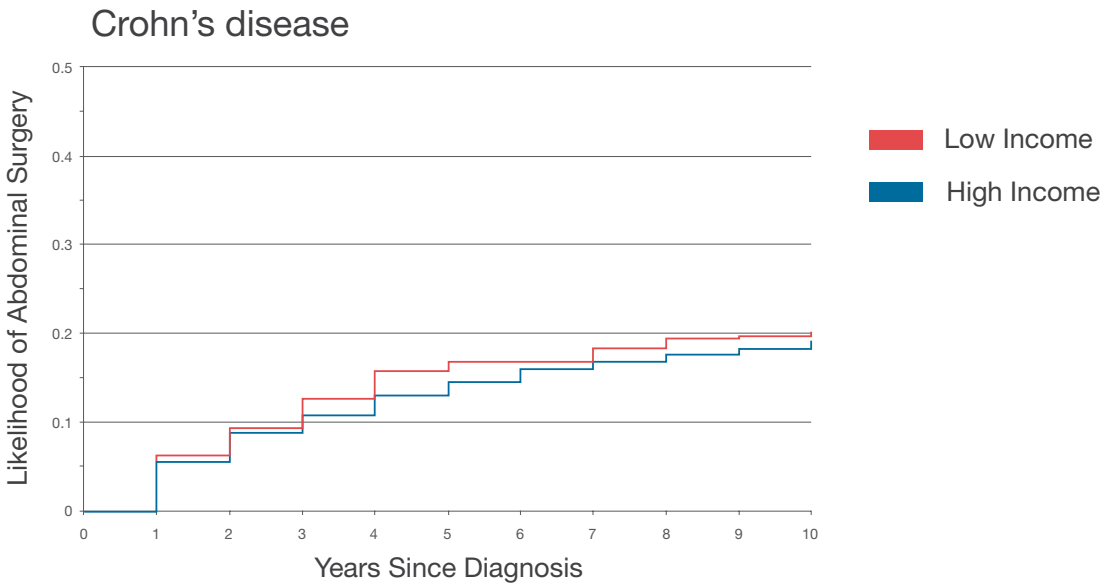


Figure 7-7: Risk of intra-abdominal surgery (resection) for Crohn's disease in high vs. low income children in Ontario. Reprinted by permission from Journal of Pediatrics 2011; 158: 960-7.[47]

In Ontario, children of lower income families had greater health services utilization for IBD and were more likely to undergo surgery for Crohn's disease (Figure 7-7).[37] This was particularly true after the year 2000 when biologics began to be used. The study authors hypothesized that lower income families on social assistance had worse access to the expensive biologic medications than higher income families with private insurance, which was also demonstrated in Canadian adults.[46] Therefore, access to newer treatments remains a significant barrier for many children.

Another significant influence on the care provided to children is the availability of multidisciplinary teams of allied healthcare professionals. While more care is being provided by pediatric gastroenterologists in specialized centres, a 2015 summit of patients and healthcare providers, convened by Crohn's and Colitis Canada, recommended that children with IBD be treated by multi-disciplinary teams consisting of specialist physicians, nurses, dietitians, social workers, and mental healthcare providers.[47] Such a multi-disciplinary team has also been endorsed by the European Crohn's and Colitis Organisation as the standard of care for children with IBD.[48] Unfortunately, the degree to which allied healthcare providers and specialists are available to care for children with IBD in

Canada varies greatly by centre.[49] In particular, the availability of social workers and mental healthcare professionals to help with the care of children with IBD is highly variable, with some Canadian centres having no social workers or psychologists dedicated to IBD care. Table 7-1 demonstrates the high degree of variability of care providers per patient across centres involved in the Canadian Children IBD Network, a Joint Partnership of the Canadian Institutes of Health Research (CIHR) and the CH.I.L.D. Foundation.

Table 7-1:

Number of IBD patients per care provider in 12 tertiary care pediatric gastroenterology centres in Canada participating in the Canadian Children IBD Network: A Joint Partnership of CIHR and the CH.I.L.D. Foundation. Reprinted by permission from *Canadian Journal of Gastroenterology and Hepatology* (Table 3).[48]

Center number	Number of patients per a physician	Number of patients per a nurse	Number of patients per a dietitian	Number of patients per a social worker	Number of patients per a psychologist
1	107	320	3200	16000	3200
2	50	500	625	1667	1667
3	31	667	1000	2000	2000
*4	120	150	1200	No social worker	No psychologist
5	111	250	250	250	No psychologist
*6	113	900	4500	No social worker	No response
7	37	184	275	2750	916
*8	182	334	286	2000	1000
9	128	287	319	718	No psychologist
*10	300	231	600	750	No psychologist
*11	530	321	1800	3000	1800
12	537	235	470	3760	626
p value	0.004	0.000	0.010	0.04	0.003

*Centres with dedicated IBD physicians.

7.6 Medications and Treatments

7.6.1 Goals of Treatment

The goal of management of pediatric IBD is multifaceted (Table 7-2). The natural course of IBD over time is one of relapsing, remitting cycles of inflammation. Thus, treatment is geared towards control of this inflammatory activity as well as the prevention of disease and treatment complications. Some differences exist in treatment options between Crohn's disease and ulcerative colitis because of the differences in location of disease and the nature of the inflammatory behavior. In general, the goals are the same:

- Control intestinal inflammation to prevent long term tissue injury and complications
- Optimize physical, pubertal and psychological growth, nutrition, and quality of life
- Minimize treatment-related toxicity

To achieve these goals, strategies to maximize treatment adherence must also be carefully considered.

Table 7-2: Treatment Goals for Pediatric IBD. Adapted from Pediatric Gastrointestinal and Liver Disease, Elsevier Health Sciences, 2015, P. 520.[50]

Controlling intestinal inflammation (achieve mucosal healing, prevent intestinal damage)
Promote physical growth and nutrition
Promote psychological growth
Improve quality of life
Minimize toxicity
Prevent disease complication
Maximize adherence

Treatment is generally broken into two phases: induction of remission (switching off the active inflammation) and maintenance of remission (keeping the inflammation switched off). Some therapies have generalized anti-inflammatory actions whilst others are targeted therapies, focused on specific elements of the body's immune response and inflammatory pathways. The choice of therapy needs to be individualized for each patient and clinical scenario and there may be more than one acceptable treatment strategy.[51]

Several important considerations set pediatric IBD treatment apart from adult IBD management.

- Firstly, there has been less research conducted in pediatric patient populations so data regarding dosing, efficacy and safety needs to be carefully interpreted in the pediatric setting. This has implications for drug availability in pediatric populations. In many cases, newer drug therapies do not have regulatory approval for use in pediatric patients or may have certain age restrictions applied. As a result, pediatric patients requiring such treatments may need special access approval which can delay therapy and may have specific healthcare resource ramifications.
- The use of placebo in the clinical trials of children with IBD was deemed unethical by an international consortium of experts, except when it is used as "add-on" therapy to standard care.[52] Drug regulatory agencies should be aware of this when considering the scientific evidence for approval of drugs for use in children with IBD.

- Children are not just little adults. The pediatric patient may metabolize drugs differently, may need different dosing and interval schedules and may have disease that behaves quite distinctly from that of adult patients. This can create problems for drug approval and reimbursement funding bodies that may enforce strict criteria around drug access and funding.

- Growth impairment and puberty delay are interrelated but unique problems in pediatric IBD that are not relevant to adults. Special cognisance is needed to ensure normalization of growth potential and appropriate pubertal development.[53] Some therapies have been associated with a failure to return patients to normal growth patterns despite their successful use in adult populations to control inflammation.

- Children and young adults, by virtue of their age at diagnosis, typically are exposed to both inflammation and treatments for longer. Therefore, issues such as cumulative dosing, monitoring, cost, and long-term risks may be unique to pediatric-onset IBD. In particular, the potential additive toxicities of combination therapies may be of concern. As many of these events are extremely rare, safety surveillance requires large patient numbers with long-term follow-up, necessitating multi-centre collaboration both nationally and internationally.

Ultimately, this highlights the important need for pediatric-focused research and post-marketing safety surveillance. However, it simultaneously raises special research ethics challenges as well as 'duration of treatment' risk versus benefit uncertainties.

7.6.2 Medication Safety in Children

All medications have the potential for side effects… but so too does untreated or poorly treated IBD! Disease complications can be far more common and severe than many treatment related side effects or adverse outcomes. Hence, one of our primary goals in determining treatment is to maximize disease control whilst minimizing the potential for medication toxicity or treatment burden.

The various classes of drug treatments are discussed in detail elsewhere in this document (see Section 2.2.2). Many are used in both children and adults with equal or similar efficacy and potential safety. However, there are some important considerations with several of these therapies that warrant specific mention. Specific to children with IBD is the ability to use exclusive enteral nutrition (EEN) as an alternative to corticosteroids in Crohn's disease to induce remission.[54] EEN can be an effective, non-pharmacologic approach to induce remission that also allows physicians to correct possible nutritional needs the child may have as a result of their inflammatory disease. Whilst the exact mechanism by which EEN works remains unclear, it is believed to alter the microbiome and induce an anti-inflammatory environment in the bowel whilst simultaneously promoting mucosal healing. This nutritional intervention has no side effects or immunosuppression as seen in many other therapies and thus is an option in the care of children and young adults. The main concern relates to the potential impact on the patient's quality of life. EEN is usually administered for 6-12 weeks and is the sole source of nutrition provided as a polymeric, or elemental formula. Taken orally in most cases, some children develop taste fatigue and will require the placement of a nasogastric tube to facilitate adequate intake. Costs, healthcare system utilization and complexity of care can

be greater than with medications. A supportive family and medical care team can minimize these challenges and thereby maximize the likelihood of successful utilization of this treatment option.

Thiopurines (azathioprine and 6-mercaptopurine) have been used in the treatment of IBD for decades as immunomodulators designed to manipulate the abnormal immune response that underpins the chronic inflammatory activity in IBD.

- The main short-term concerns relate to myelosuppression (low blood counts), hepatotoxicity (elevated liver enzymes) and cancers. Routine monitoring of blood labs is warranted during both initiation of treatment as well as in established drug therapy.

- Pancreatitis is also a concern in approximately 5% of patients and is an idiosyncratic drug reaction (dose independent event), making it more difficult to predict or prevent.[55]

- The major concern with thiopurine use is the risk of developing malignancy, in particular lymphomas and non-melanoma skin cancers. These concerns resulted in a 'black box warning' for these medications and understandably can engender significant anxiety for patients and parents.

- Lymphoma is considered about four-times more likely in IBD patients treated with thiopurines compared to those not treated with thiopurines. Longer duration of therapy is associated with increased risk.[56] While most cases of lymphomas associated with thiopurine use are classified as non-Hodgkin's lymphoma, there is also a rare and often fatal form that has been reported in younger patients.

- Hepatosplenic T-cell lymphoma (HSTCL) has primarily been reported in young adult males treated with thiopurines alone or in combination with anti-TNF therapy such as infliximab. This resulted in a 'black box warning' and a tendency for pediatric patients to be prescribed anti-TNF monotherapy or to substitute methotrexate in favor of thiopurines.[57,58]

Methotrexate, another immunomodulator agent, works in a different manner from the thiopurines and is used more in Crohn's disease than ulcerative colitis. It too can be used alone or in combination with other therapies. Toxicity is still possible with myelosuppression and hepatotoxicity still warranting routine monitoring of blood tests. However, in patients with IBD, there has been no reliable evidence that the risk of malignancy is increased with methotrexate use.[59] Methotrexate is contra-indicated in pregnancy and breastfeeding due to the risk of major fetal defects, spontaneous miscarriages and toxicity in infants. This may influence the decision to use such a medication in adolescent females and young women who have the potential to become pregnant.

Although a 'black box warning' regarding HSTCL and anti-TNF therapies such as infliximab exists, data do not support the concept that there is an increased risk of malignancy associated with anti-TNF monotherapy in children.[60] Overall, the safety profile of such therapies appears to be more favorable than that of the thiopurines.[61] There is an increased risk of infections including tuberculosis, serious bacterial infection and invasive fungal infections such that all patients, including children, should undergo screening for previous exposure to tuberculosis and Hepatitis B prior to starting anti-TNF therapies. There is the potential for patients to develop antibodies against anti-TNF therapies

which may increase the risk of infusion reactions but may also neutralize the drug leading to loss of treatment efficacy overtime. Combination therapy (anti-TNF therapies used in conjunction with thiopurines or methotrexate) has been shown to reduce this risk and improve remission rates over time. Clearly the safety of such combinations must be carefully considered. Emerging therapies targeting pathways outside that of TNF-α are being utilized increasingly in pediatric populations but data in children are still relatively limited, and pediatric-specific controlled clinical trials are needed to assess which agents best balance safety and efficacy.

7.7 Immunizations

7.7.1 Immunizations do not cause IBD

Much has been learned about the complex origins of IBD and the important roles of genetics, the environment, the microbiome and early life exposures. This has led researchers to focus on childhood infections and immunizations as potential triggers for IBD development. Despite early concerns around the risk of measles as a cause of IBD, specific studies examining this relationship have not produced any evidence to support this hypothesis. Furthermore, there is no known association between perinatal infection or measles vaccination and the development of IBD.[62-66]

Despite this, unfounded concerns about the safety of the measles-mumps-rubella (MMR) vaccine causing neurological problems in children such as autism have, at times, been prominent. This has led directly to decreased use of the vaccine internationally and in some regions in Canada. Consequent measles outbreaks in children in North America and Europe have resulted in associated deaths or permanent disability in those developing the measles infections.[62,67-69] Recent studies have further reinforced the absence of any data to support a link between IBD, measles infection, the MMR vaccine, or indeed any routine childhood vaccine administration. Similarly, there is no evidence that H1N1 (swine flu), influenza, and human papilloma virus (HPV) cause IBD.[65,67,70,71]

7.7.2 Immunizations in children with IBD are safe and important

In general, IBD does not confer any greater risk from vaccinations compared to healthy children, except in the case of live vaccines in children who are immunosuppressed. Malnutrition, active inflammatory disease and the use of immunosuppressive medications may place children with IBD at higher risk of naturally acquired infections as well as infection-related complications. However, research indicates that children with IBD vaccinated against influenza did not experience any increased IBD-related or unrelated adverse events compared to the general population.[70] There are no data to suggest increased risk of adverse events or disease severity following vaccination.[70,72-74]

Patients with IBD are at increased risk of bacterial, fungal and viral infections as well as more severe infection related complications.[75-77] For the most part, this is related to the frequent use of immune suppressing medications such as corticosteroids, azathioprine, methotrexate and anti-TNF therapies (infliximab; adalimumab). However, some infections have been shown to be a trigger for IBD flare-ups or to be associated with rarer disease related complications such as HPV infection, cervical dysplasia/cancer and anal cancer in patients with perianal disease.[77-79] Thus, protection of patients against vaccine-preventable infections is an important aspect of high quality, long term care.

Canadian children with IBD should complete the usual immunizations schedule where possible.[80] Non-live (attenuated or killed) vaccines can be given at any time, although their effectiveness may be reduced in immunosuppressed patients.[75,76,80-82] However, once a child is using immune-suppressing medications, live vaccines should not be administered due to the risk of developing the infection against which the child is being immunized. If treatment can be delayed safely, live vaccines should be administered prior to starting immunosuppressive medications. Exclusive enteral nutrition used as induction therapy (initial therapy to switch off inflammation) provides a window of time to allow catch up immunization in children prior to starting drug therapy. Once immunosuppressive therapy has been initiated, live vaccines are contraindicated until the child's immune system is back to normal.

Most guidelines recommend patients with IBD who are immunosuppressed receive both the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) every five years in addition to the yearly trivalent inactive intramuscular influenza vaccine.[83] A large Ontario study demonstrated that children with IBD were less likely to visit their doctors for IBD-related care in the years that they received their flu shot,[70] potentially because prevention of flu infection may result in less risk of IBD flare. The intra-nasal influenza preparation is a live vaccine and so should be avoided if the child is immune-suppressed.

HPV vaccination is recommended for both girls and boys with IBD,[75,76,80,81] because adults with IBD on immunosuppression may be at increased risk for the cancer-related effects of HPV.[78,84]

Travel may create special circumstances with regards to vaccination. Live vaccines, such as the yellow fever vaccine, are still contraindicated for patients on immunosuppressive therapy. Appropriate immunization information should be sought regarding the area of intended travel and discussed with a travel medicine physician and the IBD treatment team.

7.8 School Attendance and Educational Achievement

Children with IBD require frequent and regular attendance at specialized medical clinics, often in pediatric healthcare centres that are far from their homes. These visits may include physician outpatient visits, consultations with dietitians, hospitalizations, procedures, surgeries, radiology tests, or medication administration at infusion centres. In addition, children with IBD can experience fatigue and difficulty concentrating due to active inflammation, anemia, or medication side effects. In Israel, children with IBD were demonstrated to miss more school days than other children. This was more prominent in children with Crohn's disease (24 missed school days) than ulcerative colitis (21 days), or healthy children (5.1 days).[85] They were also less likely to participate in fitness classes, afterschool sports, or other afterschool activities.[85] In addition, when their disease is active, children with IBD require frequent bathroom visits while at school. For these reasons, the Canadian Digestive Health Foundation (cdhf.ca) developed an educational module entitled Blackboards and Bathrooms (https://cdhf.ca/bank/document_en/95blackboards-and-bathrooms.pdf) with the goal of informing teachers and educational administrators as to the unique challenges faced by children and teens with IBD. Policy-makers and school boards should consider these challenges when establishing educational policy. In particular, school absences for medical reasons should be excused, unlimited bathroom privileges should be provided, examination exemption may be required, and no child with a chronic disease should be subject to discrimination in the school system.

That being said, children with IBD can still achieve success in the educational system. A population-based study from Manitoba demonstrated that children with IBD achieved equal to or better Grade 12 educational outcomes than other children.[86] However, predictors of worse outcomes included lower socioeconomic status and the diagnosis of mental health problems in the year surrounding the diagnosis of IBD.[86] Therefore, those at risk should receive the proper educational and social support in order to achieve the expected success in school.

7.9 Transition from Childhood to Adulthood

Coping with life's transitions is difficult for all adolescents and young adults, and the challenge is amplified when facing a chronic disease. As adolescents with IBD age, they will demand increased autonomy and more control over healthcare treatment decisions, whilst simultaneously being at increased potential for risky behaviours which could negatively impact their health. As such, they require support to educate, inform, and guide them to take control of their disease. Multiple studies have demonstrated that the knowledge of adolescent patients is insufficient. They frequently had problems navigating the health system, such as accessing insurance programs, knowing where their pharmacy was located, obtaining information from pharmacists, and making their own appointments.[87] This lack of knowledge has been identified by adult gastroenterologists as a major factor inhibiting the smooth transition to adult care.[86] An Ontario study has demonstrated that adolescents with IBD visit the emergency department and outpatient clinics more frequently after their transfer to adult care, but are not hospitalized more frequently.[88] This may be due to adjustment from a pediatric healthcare model where nurses are readily available to support the patients by phone, or a lack of understanding of how to use the outpatient health system.

A 2015 summit of patients with IBD and healthcare providers organized by Crohn's and Colitis Canada, recommended that structured transition programs should be provided to adolescents transitioning to adult care to help educate the maturing adolescent, support adherence to medical therapy, and ensure a smooth transfer to adult care.[47] This may be facilitated by specialized, multidisciplinary IBD clinics in pediatric healthcare centres. There should be a dedicated staff person to help provide an anchor at the time of transition as well as specialist IBD nurses in the clinic. With dedicated support and a structured program, adolescents with IBD will navigate the move from pediatric to adult healthcare more easily.

7.10 Quality of Life

7.10.1 Unique Issues to consider for Pediatric IBD Quality of Life (QOL)

Assessing quality of life in pediatric patients with IBD requires consideration of several key methodological issues: whether to ask children directly;[89,90] and how to allow for varying developmental levels and ages.[91,92] Pantell *et al*. showed that parents and teachers agreed fairly well in reporting on child functioning but markedly less well for recent functional status, certain types of subjective feelings in regard to illness, information needs, emotional states, and family functioning.[93]

7.10.2 Pediatric IBD Quality of Life

Pain impairs quality of life (QOL) in pediatric Crohn's disease patients, independent of disease activity. In the absence of pain, children with active Crohn's disease reported improved QOL and significantly decreased disability and depressive symptoms when compared to children in pain during a flare. In addition, depressive symptoms were more prominent in children experiencing a disease flare.[94] Ryan *et al.* studied 112 IBD youth aged seven to 18 years of age to evaluate the clinical utility of health-related quality of life (HRQOL) screening, using the Pediatric Quality of Life Inventory, Version 4.0 (PedsQL 4.0) to predict disease outcome and healthcare utilization 12 months later.[95] On average, in youth with lower HRQOL at baseline, they noted increased healthcare utilization as measured by IBD-related hospital admissions, emergency department visits, use of psychological services, telephone calls to clinicians, GI clinic visits, and referral to pain management.

How do pediatric IBD patients fare with respect to other pediatric patients with chronic illness or their healthy peers? Generic HRQOL tools, while lacking the sensitivity to identify disease-specific challenges of a disease, can be used to evaluate HRQOL across disease groups and healthy individuals. Initial efforts to look at QOL issues between patients with IBD and those with other chronic illnesses was conducted by Ingerski *et al*.[96] Using the PedsQL tool, they studied the HRQOL across eight pediatric chronic conditions: obesity, eosinophilic gastrointestinal disorder, IBD, epilepsy, type 1 diabetes, sickle cell disease, post-renal transplantation, and cystic fibrosis.[96] They showed that youth with obesity and eosinophilic gastrointestinal disorders had lower HRQOL compared with the youth with other chronic illnesses, including IBD. However, several limitations of this work should be noted. There were a small number of patients in some of the chronic illness groups, for example, only 34 of 589 patients had

IBD). In addition, there was considerable variation of demographic and disease specific sample characteristics present across disease groups.[96] Haapamaki *et al*. compared HRQOL of 55 children with IBD, ages 7-19 years, with their healthy peers,[97] Older children with IBD had significantly lower HRQOL scores compared with age-standardized peers. Kunz *et al.* compared HRQOL assessments of youth with IBD to published group data of chronically ill, acutely ill and healthy comparison groups.[98] They showed that youth with IBD have higher physical and social functioning than the chronically ill group, lower psychosocial functioning than the healthy comparison group, and lower school functioning than all published comparison groups. Additional studies are needed to ascertain whether these findings are consistent across pediatric IBD patients, those with other chronic illnesses and healthy peers. As we gain improved understanding of the relationships between the various factors which contribute to HRQOL, we will be better positioned to design interventions that may address the modifiable factors and evaluate whether this can result in sustained improvements in HRQOL for these youth with IBD.

7.11 Caregivers

Parenting a child with a chronic illness can be very challenging and can have a negative impact on many areas of a parent's life.[98] Parents often balance a number of ongoing demands related to their child's medical plan such as managing the daily treatment responsibilities (administration of medication, special diets), attending clinic visits, and mitigating the functional limitations their child experiences as a result of having IBD.[99] In a focus group study, Akobeng *et al*. showed that 65% of parents worry about the effects of their child's IBD on the child's future, and greater than 50% expressed concerns of the bowel condition on their child's education.[100] A minority of parents worried about the consequences of their child's illness on the parent's career (15%) or the family's lifestyle (5%).[100] In a small study, Rabbet *et al.* showed that parents reported that their child's health condition was a factor in the parent's work-related difficulties (44%), impacted family plans (38%), created an increased financial burden (13%) and led to a strain on their marital relationship (6%).[101] These responsibilities and stressors imposed by the chronic illness can contribute negatively to parent and family functioning.

Family function or dysfunction can impact the HRQOL of children within the family. Adaptive family relationships are associated with positive psychological functioning,[103] while family dysfunction can lead to decreased emotional and behavioral functioning.[102] Building on data among youth with end-stage renal disease and diabetes that show there is a significant relationship between family functioning and HRQOL, a cohort of adolescents with IBD, were studied to identify which domains of family functioning may be especially problematic.[104] Youth from families with clinically elevated difficulties in problem solving, communication, and general family functioning reported lower HRQOL,

despite controlling for known impacts of disease severity and diagnosis. Further work will need to determine whether a causal link exists between family functioning and HRQOL and also, in the context of a prospective study, how this may vary over time.

Another consideration is the potential differential impact of maternal and paternal functioning on HRQOL outcomes.[105] Also, the potential interplay between the child and parent psychological status and the child's HRQOL is important.[106] Hommel *et al*. studied these issues and their data suggested that parental distress is worsened by adolescent depressive symptoms, and that these adolescents also showed lower HRQOL.[106] Gray *et al*. explored family level predictors of HRQOL by studying parenting stress as a potential mechanism through which disease activity affects HRQOL.[103] This study demonstrated the disease severity-HRQOL relation was partially mediated by parenting stress, in part because of the occurrence of medical stressors. These results would indicate that as disease severity increases, parenting stress also increases and patient HRQOL decreases. Knez *et al.* reported a significantly lower psychological health in parents of IBD children compared to parents of other children, and significantly lower physical health compared to parents of healthy children.[107] Better understanding of the relationship between family functioning and HRQOL may allow clinicians to intervene with adolescents at higher risk for impaired HRQOL, and to focus on families in need of support services or psychological intervention.[104]

7.12 Conclusions

Childhood-onset IBD is becoming increasingly common in Canada and is being diagnosed more frequently in very young children. This is particularly noteworthy due to the chronic, non-curable nature of the condition. This changing age demographic may be due to changing environmental risk factors or earlier recognition and diagnosis. Children with IBD face unique challenges due to differences in their disease characteristics, the psychosocial strain on the child and family and the process of transition from child to adult. There is increasing recognition that children with IBD should be treated in specialized, multi-disciplinary healthcare centres by physicians, nurses, dietitians, social workers, and mental health professionals with training and expertise in pediatric IBD. However, there is still variation in access to such specialists across the country and care is provided differently depending on where the child lives and regional availability of healthcare services.[49] There must be more effort to help children and their families access the best quality care and treatments for this lifelong condition.

Summary of Section 7: Special Populations: Children with IBD

1. Rates of new diagnoses in children <16 years were increasing most rapidly in Ontario (increased 5.8% per year) and Quebec (increased 2.8% per year).

2. Nova Scotia has the highest rate of pediatric IBD, with lower rates in Quebec and Ontario. However, even Ontario and Quebec have higher rates of pediatric IBD than most countries in the world.

3. IBD is caused by the interaction between genes, environmental risk factors, the microbiome, and the immune system. Since children experience shorter exposures and possibly fewer environmental risk factors, the interaction between these risk factors and genes may be stronger in with childhood-onset IBD.

4. The microbiome is mostly established in early childhood and is affected by a number of factors such as environment, diet, pregnancy/ delivery factors, and antibiotic use. Changing the microbiome to a more healthy state may prevent the disease and may also be a novel therapeutic target to treat active inflammation in children with IBD.

5. Children with IBD are different from adults. They are more likely to have extensive involvement of their intestines, especially in ulcerative colitis, and are at risk for growth impairment, osteoporosis, and psychosocial difficulties affecting their families.

6. Children with IBD may incur more direct health costs for treatment of their IBD compared to adults. However, this is not universally true for all children as the very young at diagnosis (2-6 years old) may have milder disease or respond better to medications. This may result in decreased use of the health system, fewer hospitalizations and less risk of surgery than older children and adolescents.

7. The choice of treatments for children with IBD may be different from adults. It is important to consider pediatric-specific disease considerations. Delayed growth, deficient bone development, psychosocial well-being of the child and family, disease extent, disease severity, and risk of poor outcomes during transition from pediatric to adult healthcare are all important considerations when choosing the best treatment for children and adolescents.

8. While the medications used are similar in children and adults with IBD, research to assess the effectiveness and safety of these medications in children (especially very young children) is sparse.

9. Children with IBD may be more responsive to treatment than adults since they are more likely to have inflammatory (rather than stricturing) disease. Therefore, treating the inflammation earlier in the course of disease may prevent long-term complications such as strictures, obstruction, need for surgery, and need for hospitalization.

10. Some medications used in IBD have unique or more pronounced risks in children compared with adults. For example, chronic prednisone use is associated with growth impairment and stunting in children. Anti-TNF biologics are the only medications proven to improve growth in children with Crohn's disease, and should be considered early in the course of disease in patients with severe IBD or those with marked growth impairment at the time of diagnosis.

11. Some medications are used differently, depending on the sex of the patient. For example, azathioprine (with or without biologics) is associated with hepatosplenic T-cell lymphoma (and other forms of lymphoma) in adolescent and young adult males more often than females. Methotrexate is associated with birth defects in the growing fetus and therefore should be avoided in adolescent and adult women of child-bearing age who are not using two or more forms of birth control.

12. A small group of children, typically presenting in the first two years of life, have single-gene mutations that cause an IBD-like bowel disease and also immune system dysfunction. These patients may not respond to traditional IBD medications and may require therapies such as bone marrow transplant. Canada is leading research efforts to investigate, diagnose, and treat this small group of very vulnerable children.

13. IBD (especially when it is active) can affect school attendance, social interactions, concentration, and learning. Schools should be aware of the implications of IBD and make allowances for these factors in children with active inflammation and symptoms to optimize their chances of academic and social success.

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SPECIAL POPULATIONS: IBD IN SENIORS

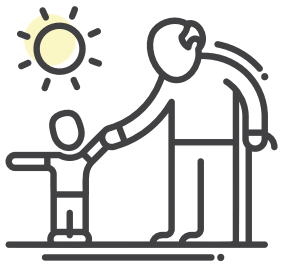
Special Populations: IBD in Seniors

Highlights

1. Approximately one out of every 160 individuals over the age of 65 in Canada is living with IBD.

2. The rising prevalence of IBD in seniors results from new diagnoses and advancing age of previously diagnosed patients with IBD.

3. Senior patients will experience greater comorbid conditions resulting from their advancing age and longer disease duration.

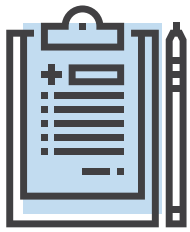


4. As the IBD population ages, the proportion of seniors with IBD will increase in gastroenterology clinics.

5. The care of seniors with IBD brings unique challenges with respect to therapeutic decision-making.

Gaps in Knowledge and Future Research Directions

1. Administrative healthcare databases are more likely to misclassify senior patients with IBD. Future research is necessary to improve the identification of senior patients with IBD in databases.



2. Gastroenterologists will need to contend with an older IBD population with greater comorbidities. Research focusing on defining the burden of comorbidities in senior IBD patients is needed for healthcare resource utilization planning.

3. The use of anti-TNF in senior patients is lower than in younger individuals with IBD. Future research should evaluate trends in using biologics in the senior population with the advent of newer biologics such as gut-selective α4β7 integrin inhibitors.

4. Polypharmacy is a challenge for senior IBD patients. Future research should focus on interventions to simplify drug regimens and administration for senior patients.

5. Senior individuals with IBD cost the healthcare system more than age-matched controls. However, research is necessary to establish the IBD-attributable cost to the healthcare system and the indirect cost to society.

8.0 Introduction

Though IBD is commonly diagnosed in young adulthood, it can present at any age. As the IBD population ages, there will be an increasing number of IBD patients who are senior (commonly defined as age 65 years or older). The care of senior IBD patients brings unique challenges with respect to diagnosis and therapeutic decision-making. The frequent coexistence of comorbid conditions may influence the choice of therapeutic strategies. The IBD clinic of the future will be populated with older patients with longer disease duration and higher risk of comorbid conditions.

8.1 Epidemiology

Approximately one out of every 160 senior individuals in Canada is affected by IBD. The rising prevalence of IBD in seniors is a result of new diagnoses made in this population, and advancing age of previously diagnosed patients with IBD with long disease duration. Epidemiologic data from Ontario suggest that the prevalence of IBD increased by 5.2% annually among seniors between 1999 and 2008, higher than that observed in non-seniors (3.9% annual increase).[1] The increase in prevalence was similarly observed in both Crohn's disease and ulcerative colitis. The incidence of IBD in Canada varies by province and the age cut-off used to define senior, but has been reported to be as high as 18.9 per 100,000 for Crohn's disease and 16.5 per 100,000 in ulcerative colitis, with the highest rate of IBD noted in Quebec.[2] In Ontario, the incidence of ulcerative colitis (12.4 per 100,000) was nearly twice that of Crohn's disease (6.6 per 100,000) in seniors. A similar predominance of ulcerative colitis among newly diagnosed IBD cases amongst seniors was also reported in Manitoba where the incidence was 16.5 per 100,000 for ulcerative colitis compared with 10.7 per 100,000 for Crohn's disease.[3]

8.2 Disease Presentation

Senior patients with longstanding IBD who were diagnosed in younger adulthood may be clinically distinct from those with senior-onset IBD. As many as 15% of IBD patients are diagnosed after age 65 years. The diagnosis of IBD in seniors can be challenging, and misdiagnosis can occur in up to 60% of the cases due to other conditions that can mimic IBD.[4] These other conditions include some that occur more frequently in the senior population such as microscopic colitis, diverticular disease, ischemic colitis, infectious colitis, and malignancy. Moreover, the presentation of IBD can be more subtle in seniors. In ulcerative colitis, rectal bleeding and abdominal pain are less common and weight loss is more commonly seen.[5] Similarly, diarrhea, rectal bleeding, abdominal pain and weight loss are all less commonly seen in senior-onset Crohn's disease than in disease presenting at younger ages.[5]

With respect to disease characteristics, seniors with Crohn's disease are more likely than their younger counterparts to have isolated colonic disease. They are also less likely to present with perianal fistulizing disease and extra-intestinal manifestations. On disease presentation, senior ulcerative colitis patients are more likely to have left-sided disease. Family history of IBD is less common amongst senior patients.[5]

IBD often follows a more benign disease course when presenting in seniors. For Crohn's disease, there is less frequent development of fibrostenotic or penetrating disease phenotype. In ulcerative colitis, there is less frequent extension of colitis (proximal to the splenic flexure) compared to younger-onset ulcerative colitis.[5,6] A large French cross-sectional study of IBD patients suggests that older age (>60 years) is not associated with worse quality of life, fatigue, or disability.[7]

8.3 Healthcare Utilization

While seniors, in general, see physicians and other healthcare providers more often, those with IBD may not see physicians more often for IBD-related reasons. Nguyen *et al*. determine that healthcare visits for IBD among Ontarians diagnosed after age 65 are significantly lower than for those diagnosed prior to age 65.[8] This observation holds true both for the first year after diagnosis and into the third year of disease. The same pattern is seen when comparing visits to the emergency department. This may be due to the lower acuity of senior-onset IBD when compared to non-senior onset IBD or may also be related to senior outpatient visits being more focused on diseases of higher morbidity, such as cardiovascular disease.

In the first year after diagnosis, the hospitalization rate with a primary diagnosis of IBD for senior-onset IBD was 357 per 1,000 person-years for Crohn's disease and 247 per 1,000 person-years for ulcerative colitis. During the fifth year following diagnosis, these rates decreased substantially to 48 and 25 per 1,000 person-year respectively. Ananthakrishnan *et al*. finds that hospitalization rates in the US are not different between senior and non-senior IBD patients. However, the case fatality rate of IBD is four times higher than among younger hospitalized patients, and the duration of the hospital stay is an average of two days longer.[9]

8.4 Surgery

Targownik *et al*. determines that persons who had ulcerative colitis diagnosed after age 65 had a 3.1% risk of requiring a colectomy within 90 days compared with 1.6% of those diagnosed under age 65 years.[10] However, among those over the age of 65 years, the risk of requiring surgery was lower over time with the colectomy rates at five years for those diagnosed over age 65 years being approximately 7% at ten years post diagnosis compared with 10% for those aged 25-64 years at diagnosis and 17% for those diagnosed under age 25 years. By contrast, Nguyen *et al.* reports that persons with senior-onset ulcerative colitis have a higher rate of IBD-related surgery with 19% of senior and 13% of younger adults undergoing IBD-related surgery within ten years of diagnosis.[11] Persons with ulcerative colitis and higher levels of comorbidity are twice as likely to require surgical management. Among persons with Crohn's disease, Nguyen *et al.* reports a rate of surgical management of 31% over ten years, which is not different from the surgical rate of persons not diagnosed as a senior.[11] In a large population-based French cohort of persons with senior-onset Crohn's disease (defined as those diagnosed over the age of 60 years), the rates of surgical management by one and ten years was found to be 18% and 32% respectively.[5]

The risk of postoperative morbidity and mortality is increased among seniors requiring intraabdominal surgery.[12] Moreover, the 30-day postoperative mortality risk is approximately tenfold higher for senior IBD patients compared with non-senior Crohn's disease (4.2% vs. 0.3%) and ulcerative colitis (6.1% vs. 0.7%) patients. Adjusted risk of postoperative complications was similarly higher. Non-fatal postoperative complications were similarly 1.4-fold and 1.7-fold higher for senior patients with Crohn's disease and ulcerative colitis respectively.[12]

8.5 Drug Utilization

Therapeutic decision making in seniors with IBD is challenging. Seniors with IBD often have comorbid conditions related to their IBD (e.g. venous thromboembolism) or as a product of aging (e.g. cardiovascular disease and cancer). Consequently, the impact of adverse events associated with IBD treatments is amplified in seniors.

Benchimol *et al*. assesses drug prescription and utilization rates among senior Ontarians with Crohn's disease and ulcerative colitis between 2006 and 2009. While use of 5-ASA was gradually decreasing, immunomodulator and corticosteroid utilization remained stable, and the use of biologic therapies rose.[13] More recent data from Manitoba show that in 2014, approximately 7% of all persons with IBD were using an immunomodulator, compared to 4% in 2004. A rapid rise in the prevalence of anti-TNF use in this population was also found. In 2010, 3.0% of Crohn's disease patients and 0.7% of ulcerative colitis patients over age 65 years were actively using anti-TNFs. By 2014, the prevalence of anti-TNF use in seniors had risen to 4.0% and 2.3% in Crohn's disease and ulcerative colitis respectively. These anti-TNF rates are lower than what has been observed for younger IBD patients. While we do not yet have any data on the utilization of vedolizumab in seniors, we anticipate that it may be more readily used because of its perceived lack of systemic immunosuppression.

8.6 Management of IBD in Seniors

Targownik *et al*. (2012) reports that within the first year of diagnosis, at most 11% of persons over age 65 years had an active dispensation for corticosteroids. However, later in the course of disease, the point prevalence of corticosteroid use ranged from 3% to 5%. Over the first five years following diagnosis, persons over 65 years have a significantly decreased risk of being dispensed corticosteroids compared with persons aged 25-64 at diagnosis (HR 0.82 95% CI 0.71-0.95).[14] These data highlight important differences in prescribing patterns among seniors with IBD compared to younger IBD patients, though it is unclear whether this is due to seniors having less severe acute flares of IBD, or a recognition on the part of clinicians of the unfavourable side effect profile of corticosteroids.

The medical and surgical management of IBD in seniors is influenced by unique challenges. Physiological changes that occur with age, including immunosenescence, decline in renal function, and the higher frequency of comorbidities, including cancer and cardiovascular disease, can alter the risk-benefit ratio of many medical therapies. Polypharmacy is an important consideration. A cohort study of 190 senior IBD patients revealed that they had, on average, nine routinely prescribed medications. Forty percent had a drug interaction that involved one of their IBD medications.[15] This finding emphasizes the importance of receiving all medications from a single pharmacy in order to check for interactions. Polypharmacy may also influence adherence. Strategies such as simplifying drug regimens (e.g., 5-ASA to once-daily regimens) and using convenience pill packaging may improve challenges faced by the senior population.

The risk of infections (*e.g.,* pneumonia, or urinary tract infections) increases with age and raises the concern of immunosuppressive therapy for IBD. Multicentre retrospective cohort data from Europe suggest that senior patients who receive anti-TNF therapy are at considerably higher risk of serious infection (11%) compared with non-senior IBD patients (2.5%) and senior control patients (0.5%).[16] Mortality is similarly higher in the senior patients taking anti-TNF compared with non-senior anti-TNF users and senior controls (10% vs. 1% and 2% respectively). Because senior IBD patients are poorly represented in clinical trials, there is sparse data on the efficacy of anti-TNF therapy in seniors. A retrospective observational study suggests that seniors are less likely than non-senior IBD patients to have a partial or complete response to anti-TNF therapy (61% vs. 83%) and are fourfold more likely to stop anti-TNF therapy.[17] Despite the risk of infection, anti-TNF therapy remains an important therapeutic option for steroid-refractory or steroid-

dependent patients. However, the less favorable risk-benefit profile is an important consideration in determining the appropriate treatment options. Gut-selective biologic therapies such as vedolizumab, which have a lower risk of infection, may be safer in seniors.

Malignancy is more frequent with age which may also impact therapeutic decisions.[18] The risk of lymphoproliferative disorders increases with age, but especially so in the presence of thiopurine use. Among senior patients (>65 years) who continued to take thiopurines, the risk of lymphoma was 5.41 per 1,000 person-years compared with 0.37 per 1,000 person-years in IBD patients younger than 50 who were taking the medication.[19, 20] Thus, the higher absolute risk of lymphoma in the senior associated with thiopurine use is an important consideration.

It is important to keep in mind that surgery remains a therapeutic option and when performed electively, is associated with considerably lower postoperative mortality and morbidity than when performed emergently.[12] A retrospective cohort study suggests that elective colectomy may be associated with greater survival than medical therapy in ulcerative colitis patients older than 50 years.[21]

8.7 Costs of Care for Seniors with IBD

Several studies have determined the costs of care among the entire IBD population. However, IBD-specific costs among seniors with IBD or senior-onset IBD are unknown. Bernstein *et al.* use population-based data to enumerate the total cost of care among all Manitobans with IBD in 2005. Persons aged between 65 and 79 were found to have mean total healthcare costs of CAD$5,298, compared with CAD$3,537 among age-matched controls. The mean difference of CA$1,761 is slightly lower than the CAD$2,070 difference between that of cases and controls in the overall population.[22] However, it is not clear whether the difference in costs between cases and controls is directly related to IBD-specific care. Van der Have *et al.* study the direct and indirect costs associated with IBD in seniors within a multi-centre Dutch cohort. The direct healthcare costs of IBD (converted to 2018 inflation-adjusted Canadian dollars) are estimated at CAD$535 per quarter year for persons over age 60 years compared with CAD$1440 per quarter year for those under age 60 years ($p<0$ .001). IBD-attributable costs were lower in those aged 70 and over when compared to those aged 60-69 (CAD$636 vs $355, $p<0.0001$). Not surprisingly, productivity losses were significantly lower among seniors (CAD$175 vs $21, $p<0.001$).[23]

8.8 Conclusion

The Canadian health system must be prepared for a rising number of senior patients living with IBD. Though risk-benefit profiles of various therapeutic interventions may differ in the senior population, it is important to keep in mind that the treatment goals remain the same and should aim for complete steroid-free remission. IBD health providers must also be prepared to work in multidisciplinary teams with other specialists in order to optimize IBD management in the context of other comorbidities.

Summary of Section 8: Special Populations: IBD in Seniors

1. Approximately 0.6% of seniors in Canada live with IBD.

2. In Ontario, the prevalence of IBD among seniors increased by 5.2% per year, which outpaced the 3.9% per year rise observed in non-seniors.

3. Approximately 15% of IBD patients are newly diagnosed after the age of 65 years.

4. The incidence of IBD in seniors ranged from 16.5 to 18.9 per 100,000 in Canada.

5. In Ontario, the diagnosis of ulcerative colitis in seniors was double that of Crohn's disease.

6. Clinical presentation of seniors with Crohn's disease is unique with a higher likelihood to present with isolated colonic disease without fistulizing disease or extra-intestinal manifestations as compared to those diagnosed at a younger age.

7. Seniors with IBD are less likely to have outpatient visits relating to their IBD as compared to younger patients with IBD.

8. Among individuals diagnosed over the age of 65 years, the 10-year risk of intestinal surgery was 7%-19% for ulcerative colitis and 31% for Crohn's disease.

9. Seniors who undergo intestinal resections for their IBD have significantly higher postoperative complications and mortality as compared to younger IBD patients undergoing surgery.

10. The use of anti-TNF agents in seniors is lower for Crohn's disease (4.0%) and ulcerative colitis (2.3%) as compared to younger individuals with IBD. However, the rate of use of biologics is increasing overtime.

11. Therapeutic decision making in seniors with IBD is challenging due to their comorbid conditions.

12. Seniors who use thiopurines have a higher risk of lymphoma (5.4 per 1,000 person-years) as compared to IBD patients younger than 50 years (0.37 per 1,000 person-years) exposed to thiopurines.

13. Newer gut-selective $\alpha 4\beta 7$ integrin inhibitors may be a safer choice for seniors due to potentially lower risk of infection and cancer.

14. Due to multiple comorbidities, seniors with IBD may struggle with polypharmacy that can lead to drug interactions and reduced medication adherence.

15. Persons aged between 65 and 79 years with IBD on average cost the healthcare system $5,298 per year, which is higher than age-matched controls.

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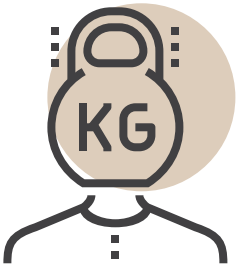
EXTRA-INTESTINAL DISEASES IN IBD

Extra-intestinal Diseases in IBD

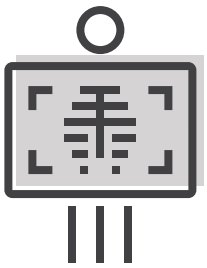
Highlights

1. The burden of extra-intestinal disease is high in patients with IBD.



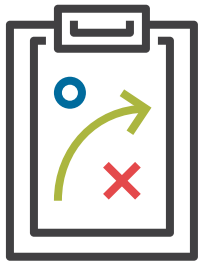
2. Immune mediated inflammatory diseases (IMID) commonly co-exist with patients with IBD and the activity of IMID can be either dependent or independent of bowel inflammation.

3. Patients with IBD can be diagnosed with co-existing diseases that affect every organ, including bones, blood, heart, liver, and others.



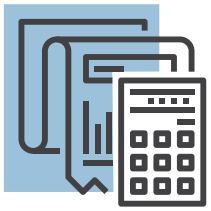
4. Patients with IBD are at increased risk of cancer, including colon cancer, caused by their bowel inflammation, cholangiocarcinoma due to primary sclerosing cholangitis, and rarely lymphoma related to immunosuppressive medications.

5. The best way to prevent or reduce the burden of many of the extra-intestinal disease is to treat the inflammation of IBD, however some extraintestinal inflammatory diseases run courses that are independent of the intestinal disease activity.



Gaps in Knowledge and Future Research Directions

1. Patients with IBD are often burdened with extra-intestinal disease. Future research should determine the collective frequency and added costs of living with extra-intestinal disease.



2. IMID are commonly co-diagnosed with IBD. Future research should focus on the pathogenesis connecting co-existing IMID with IBD.

3. Care pathways that support the investigation and mitigation of extra-intestinal disease are needed. For example, when and how ambulatory patients with IBD should receive prophylaxis against venous thromboembolic disease is unknown.

4. With an aging IBD population the burden of extra-intestinal disease should be studied in the context of comorbidities of advancing age.

5. Increasing mental health screening and access to mental healthcare should be a goal of IBD management.

9.0 Introduction

IBD is associated with a number of conditions that are extra-intestinal. Some of these conditions are also chronic immune diseases that impact on other organ systems, while others are common diseases in other organs that occur with increased frequency in persons with IBD. That IBD is associated with a number of extra-intestinal diseases, adds to the potential burden for the patient as well as to the healthcare system.

9.1 Immune Mediated Inflammatory Diseases (IMID) Classically Associated with IBD

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

Primary sclerosing cholangitis (PSC), which causes stricturing and dilations within the extrahepatic and intrahepatic biliary tree, was most common among men with ulcerative colitis in the UMIBDED study (3%).[1] In a retrospective Danish population-based study of 222 persons with IBD and PSC (2.7%), PSC-IBD patients primarily had ulcerative colitis (72%), and were diagnosed in young adulthood (median age at IBD diagnosis, 23 years).[2] Among PSC-ulcerative colitis patients, 78% had pancolitis at diagnosis. Among patients with PSC and Crohn's disease, 91% had colonic involvement. The 25-year cumulative risk of liver transplantation was high (53%). In a General Practice Research Database population-based study of primary care in the UK between 1998 and 2014, there were 250 newly diagnosed PSC patients identified.[3] Only 54% had a history of IBD. The mortality rate per 1,000 person-years was threefold higher in PSC than population controls (49.5 vs 16.1; incidence rate ratio 3.1, 95% CI 2.2-4.2).[3]

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

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

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

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

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

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

9.2 Other Immune Mediated Inflammatory Diseases (IMID) and IBD

In another study using the UMIBDED, other less commonly associated extra-intestinal diseases were reported in IBD patients.[9] The prevalence of asthma was 7.9% in ulcerative colitis and 7.1% in Crohn's disease which translates into an increased prevalence ratio (PR) compared with the general population for both ulcerative colitis (PR=1.66, 95% CI, 1.46-1.88) and Crohn's disease (PR=1.43, 95% CI 1.26-1.62). The risk of asthma was corroborated in cohorts from Quebec and Alberta.[10,11] The next most common pulmonary disease in IBD may be drug-induced pulmonary disease.[12]

Persons with IBD have an increased risk of psoriasis compared with the general population.[9] The prevalence was 1.7% in both ulcerative colitis and Crohn's disease; the PR being1.65 (95% CI 1.27-2.15) in ulcerative colitis and 1.59 (95% CI 1.24-2.05) in Crohn's disease. While the risk of psoriasis may be increased in persons with IBD and anti-TNF therapy may be very effective in the treatment of psoriasis, anti-TNF therapy for the treatment of IBD has also been associated with inducing psoriasis.[13] Antibodies to interleukin12/interleukin23, such as ustekinemab, have been shown to be effective in treating both Crohn's disease and psoriasis and, therefore, may be the optimal choice for therapy when these diseases coexist.

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

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

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

9.3 Arterial Vascular Disease and IBD

A study using the UMIBDED reported that the risk for coronary artery disease was increased with an incidence rate ratio (IRR) of 1.26 (95% CI, 1.11-1.44) in both males and females with both Crohn's disease and ulcerative colitis.[16] Researchers at the University of Miami undertook a four-year longitudinal cohort study of 356 persons with IBD and matched controls.[17] The unadjusted hazard ratio (HR) for developing coronary artery disease in the IBD group was 2.85 (95% CI, 1.82-4.46). Despite the increased risk, persons with IBD have significantly lower rates of selected traditional coronary artery disease risk factors (hypertension, diabetes, dyslipidemia, and obesity; P<0.01 for all). Adjusting for these factors, the HR for developing coronary artery disease between groups was 4.08 (95% CI 2.49-6.70).

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

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

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

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

9.4 Venous Thromboembolism

The first population-based report on the incidence of venous thromboembolism (VTE) in IBD patients was from the UMIBDED.[21] In Crohn's disease, the incidence rate of deep venous thromboembolism (DVT) was 31.4/10,000 person-years, and the incidence rate of pulmonary embolism (PE) was 10.3/10,000 person-years. In ulcerative colitis, the incidence rates were 30.0/10,000 person-years for DVT, and 19.8/10,000 person-years for PE. The IRR was 4.7 (95% CI, 3.5-6.3) for DVT and 2.9 (1.8-4.7) for PE in Crohn's disease, and 2.8 (2.1-3.7) for DVT and 3.6 (2.5-5.2) for PE in ulcerative colitis. There were no sex differences for IRR. The highest rates of DVT and PE were seen among patients over 60 years old. However, the highest IRR for these events were among patients less than 40 years, meaning that the younger adults with IBD carry an even greater increased risk for DVT and PE than their unaffected counterparts. These data translate to a rate of DVT or PE of 1 per 200 patient-years.

In a multi-centred Austrian study of 116 IBD patients who had a history of first VTE, 86 incidents were unprovoked.[22] The probability of recurrence five years after discontinuation of anticoagulation therapy was higher among patients with IBD than patients without IBD (33.4%; 95% CI, 21.8-45.0 vs 21.7%; 95% CI, 18.8-24.6; P = 0.01). After adjustment for potential confounders, IBD was found to be an independent risk factor of recurrence (HR = 2.5; 95% CI, 1.4-4.2). In a subsequent study from this Austrian group, the incidence rate of all VTE was 6.3 per 1,000 person-years which was not dissimilar from the rate reported in the earlier UMIBDED study.[23] Patients with VTE did not differ with regards to sex, underlying IBD, or disease duration. Most VTE (77.1%) were unprovoked; most (77.7%) occurred in outpatients; and, most (60.9%) occurred in patients with active disease.

In a four-centre Canadian retrospective study, patients admitted under surgeons were more likely than those admitted under gastroenterologists to receive VTE prophylaxis (84% versus 74%, P = 0.016).[24] Of note, the rate of VTE was the same for those who did and did not receive VTE prophylaxis (2.2 per 1,000 hospital-days).[24] Among the 14 VTE events, 79% had received prophylaxis, but only 36% within 24 hours of admission.[24]

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

9.5 Osteoporosis and Osteoporosis-Related Fracture in IBD

Osteoporosis increases the risk of fractures that are associated with significant morbidity, particularly those of the proximal femur (hip), vertebra, and wrist and even mortality (related to hip fractures).[25-27] A study using the UMIBDED reported that persons with IBD have a 40% higher risk of fracture than do age- and sex-matched controls without IBD; estimated at 40.8 per 10,000 person-years for IBD patients under 40, and 107 per 10,000 person-years for IBD patients aged 40-59.[28] This translates to a risk of fracture at about 1 per 100 patient-years. The proportion of seniors with IBD is also expected to rise over the next decade This is consistent with general trends in the population and the compounding prevalence effect (see Section 3), which will increase further the rates of osteoporosis-related fractures among IBD patients.[29,30]

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

9.6 Clostridium Difficile Infection

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

In a study from the University of Pittsburgh, in the year of a C. *difficile* infection, having C. *difficile* infection was significantly associated with more corticosteroid and antibiotic exposure and increased disease activity, worse quality of life, and increased healthcare utilization (all $P < 0.01$).[38] During the next year after a C. *difficile* infection, patients continued to have increased exposure to

C. *difficile* infection-targeted antibiotics (P < 0.001) and other antibiotics (P = 0.02). They also continued to have more clinic visits (P = 0.02), telephone encounters (P = 0.001), and increased healthcare financial charges (P = 0.001).

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

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

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

9.7 Mental Health

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

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

In a population-based longitudinal cohort study in Manitoba with approximately 600 persons answering surveys every 3 months for one year, a high perception of stress was associated with a flare of symptomatic IBD.[46] In a subsequent study by this group, 485 persons with IBD, answering surveys every three months for one year and submitting stool samples for fecal calprotectin, reported that a high perception of stress was associated with a flare of symptoms. However, there was only a modest association between symptoms and ulcerative colitis, and no association between symptoms and Crohn's disease.[47]

The management of stress, as well as depression and anxiety, is important for enhancing positive outcomes, reducing nonadherence to medications, and increasing quality of life.

9.8 Cancer

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

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

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

9.9 Critical Illness

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

The investigators in that study assessed predictors of ICU admission and healthcare utilization (HCU) post ICU admission.[60] Risk factors for ICU admission from the year before admission included cumulative corticosteroid use (IRR, 1.006 per 100 mg of prednisone; 95% CI, 1.004-1.008) and IBD-related surgery (IRR, 2.79; 95% CI, 1.99-3.92). Use of immunomodulatory therapies within one year, or surgery for IBD beyond one year prior, were not associated with ICU admission. In those who used corticosteroids and immunomodulatory medications in the year before ICU admission, the use of immunomodulatory medications conferred a 30% risk reduction in ICU admission (IRR, 0.70; 95% CI, 0.50-0.97). Persons with IBD who survived ICU admission had higher health services utilization in the year following ICU discharge than controls. Hence, it was concluded that corticosteroid use and surgery within the year are associated with ICU admission in IBD while immunomodulatory therapy is not.

9.10 Conclusion

The burden of extra-intestinal disease is high in patients with IBD. Extra-intestinal disease may arise in any organ system of the body. The most common and complicated extra-intestinal manifestations are other chronic IMID. Some IMID occur when IBD is active – examples include erythema nodosum and peripheral joint arthritis. Alternatively, other IMID like ankylosing spondylitis and primary sclerosing cholangitis run a course that is independent of bowel disease activity – *i.e.*, they may progress even in patients whose IBD is in remission. Recent studies have expanded the scope of IMID with associations being made between IBD and IMID such as asthma and multiple sclerosis. Moreover, patients with IBD are at higher risk of complications in other organ systems from osteoporosis to venous thromboembolism to cardiovascular disease. In addition, patients with IBD have a higher risk of cancer including colon cancer likely caused by their bowel inflammation, to cholangiocarcinoma from primary sclerosing cholangitis, to lymphoma more often arising from immunosuppression. Consequently, patients and care providers need to be vigilant in the surveillance of extra-intestinal manifestations and complications of IBD. Ultimately, the most effective means of preventing or reducing the burden of most extra-intestinal disease is to treat the underlying inflammation of IBD.

Summary of Section 9: Extra-Intestinal Diseases in IBD

1. Patients with IBD are often burdened with extra-intestinal manifestations, some of which respond to or are prevented by treating the bowel inflammation whereas others require specific treatment because they are independent of the underlying bowel inflammation.

2. Other immune mediated inflammatory diseases (IMID) can co-exist with IBD.

3. Some IMIDs run an independent course from the bowel inflammation of IBD, such as ankylosing spondylitis, iritis, and primary sclerosing cholangitis.

4. IMIDs that often have courses that match the bowel inflammation of IBD include erythema nodosum and peripheral arthritis.

5. IMIDs such as multiple sclerosis and psoriasis have been associated with IBD. However, these conditions may also emerge as complications of therapy for IBD.

6. Patients with IBD are at risk for venous thromboembolic disease, which occurs at a rate of 1 per 200 person-years.

7. Venous thromboembolic disease can be reduced by treating patients admitted to hospital with an IBD diagnosis with venous thromboembolism prophylaxis.

8. Arterial vascular disease is also increased in IBD patients, including both coronary artery disease and cerebrovascular disease.

9. Osteoporosis is more prevalent in IBD patients and translates to a 40% increased risk of fracture. While corticosteroids increase the risk of osteoporosis, patients with IBD can also develop metabolic bone disease independent of corticosteroid use.

10. Persons with IBD are more likely to be infected with clostridium difficile than community controls and often without prior antibiotic exposure.

11. Mental health comorbidity is important in IBD. Depression may antedate a diagnosis of IBD by several years as well as increase post diagnosis. High stress can exacerbate symptoms in IBD but does not necessarily increase bowel inflammation.

12. Fatigue is a common symptom in IBD and is not always explained by depression, active inflammatory disease, or other apparent factors.

13. The risk of colorectal cancer is increased twofold in Crohn's colitis and in ulcerative colitis, and tenfold in persons with primary sclerosing cholangitis with colitis.

14. Primary sclerosing cholangitis runs a course independent of IBD and can progress to cirrhosis, liver transplantation or death. Patients with IBD and primary sclerosing cholangitis are at higher risk of cholangiocarcinoma, which is often fatal.

15. The risk of lymphoma may be increased in older males with Crohn's disease, and in patients using thiopurines or anti-TNF therapy.

16. The risk for intensive care unit admission is nearly twofold higher for patients with IBD, and higher in Crohn's disease than in ulcerative colitis. Risk factors for ICU admission from the year before admission included cumulative corticosteroid use and IBD-related surgery.

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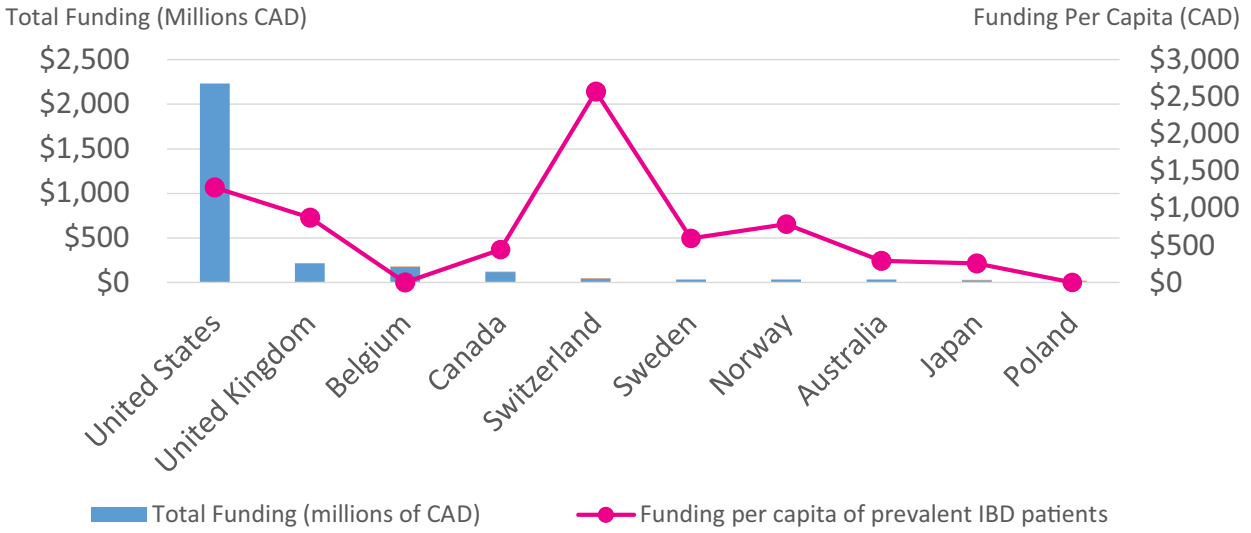
OVERVIEW OF IBD RESEARCH LANDSCAPE IN CANADA

10.0 Introduction

Health research in Canada is funded by various levels of government, health charities, foundations and industry. Crohn's and Colitis Canada and the Canadian Institutes of Health Research (CIHR), in concert with valued partners, fund the majority of health research in inflammatory bowel diseases (IBD) in Canada. The intent of this section is to provide an historical view of IBD research funding and scientist ratings in Canada between 2013 and 2017, providing international comparisons where possible.

10.1 Funding of Research

Two perspectives are provided: a look at the amount of funding of IBD research globally over the past five years; and then a look at the same time period for Canada.



	United States	United Kingdom	Belgium	Canada	Switzerland	Sweden	Norway	Australia	Japan	Poland
Total Funding (millions of CAD)	$2,227 .46	$215.30	$177.50	$119.50	$44.80	$32.24	$31.82	$28.71	$24.78	$15.83
% of World Funding	75.9%	7.3%	6.1%	4.0%	1.5%	1.1%	1.1%	1.0%	0.8%	0.5%
Funding per capita of prevalent IBD patients (CAD)[1-9]	$1,282.77	$874.27	N/A	$426.42	$2,572.64	$593.03	$785.41	$290.48	$257.51	N/A

Figure 10-1: Top 10 Countries in the World for IBD Funding (2013-2017)
*Based on country population according to: The World Bank. Population, total 2017; https://data.worldbank.org/indicator/SP.POP.TOTL. Accessed August 28, 2018. Abbreviations: CAD: Canadian dollars; IBD: inflammatory bowel disease

10.1.1 Global Funding

A global funding analysis was conducted using the *UberResearch's Dimensions* platform*. *Dimensions* is a database developed by mining primarily publicly available research funding databases found on the internet. The developers of Dimensions obtain formal permission from all funding bodies included in the platform. A comprehensive list of funders of IBD research for the period 2013-2017 included in *Dimensions* is provided in **Appendix A**.

Figure 10-1 depicts total global funding for IBD research between 2013 and 2017. During this period, the United States invested the greatest amount: over 75% ($ 2.227B) of the world's contribution. Canada ranked fourth after Belgium and the United Kingdom, investing 4% (almost $ 120M) of the total IBD funding in the world.

10.1.2 Funding in Canada

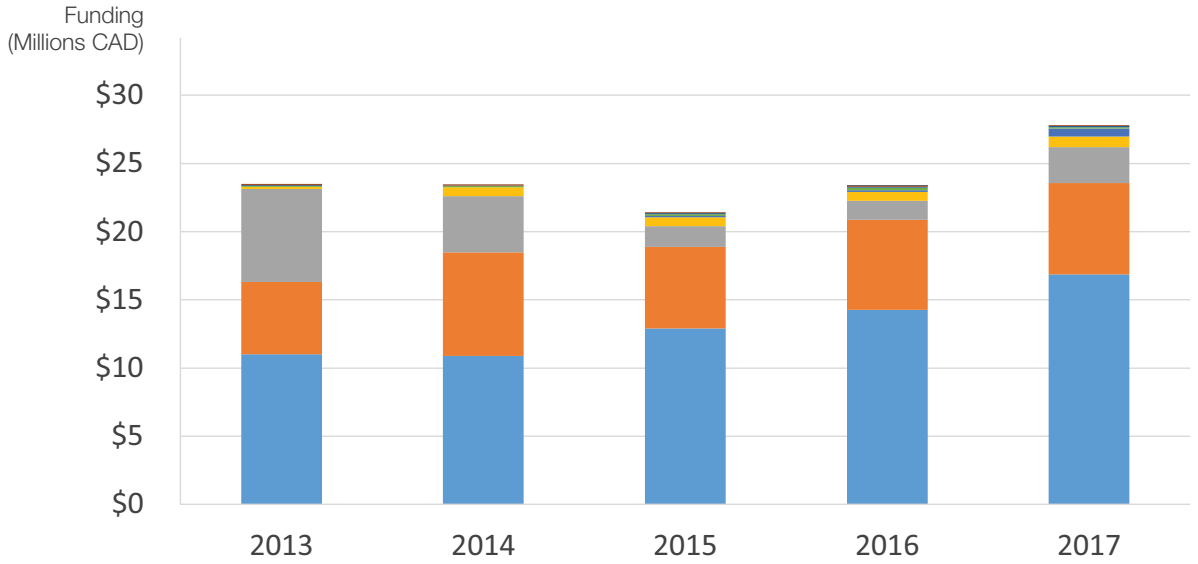
Within this overview of Canada, the activities of the top two funders, CIHR and Crohn's and Colitis Canada, are presented in more detail, together with an overview of the types of funding mechanisms used most frequently during this period.

* We thank NAPHRO, in particular the Nova Scotia Health Authority and Alberta Innovates for providing data from Dimensions

10.1.2.1 Quantifying Research Funding in Canada

To determine the extent of IBD funding in Canada, the Dimensions platform was used to identify the major funders (for methodology, please see **Appendix A**). Once major funders were identified, total funding for the period 2013-2017 was confirmed by contacting the funders individually and/or retrieving data from their websites and manually confirming the information.

Figure 10-2 depicts total funding in Canada between 2013-2017 for IBD research by federal and provincial funding agencies and by Crohn's and Colitis Canada. Total funding during this five-year period was $119.6M, with $21.4M to $27.8M in annual investments.



Funder	Year					Total by Funder
	2013	2014	2015	2016	2017	
CIHR	$11,010,425	$10,897,649	$12,893,535	$14,278,583	$16,867,707	$65,947,899
CCC	$5,283,966	$7,567,053	$6,002,125	$6,583,829	$6,694,961	$32,131,934
NAPHRO	$6,842,040	$4,128,397	$1,500,941	$1,413,121	$2,646,921	$16,531,420
Genome	$161,996	$647,985	$647,985	$647,985	$772,985	$2,878,935
CFI	$0	$0	$105,033	$125,000	$572,960	$802,993
NSERC	$43,990	$90,990	$106,500	$162,000	$102,500	$505,980
CRS	$60,000	$60,000	$120,000	$80,000	$100,000	$420,000
CCS	$112,800	$77,000	$60,000	$59,700	$39,400	$348,900
SSHRC	$0	$0	$0	$17,500	$0	$17,500
Total by Year	$23,515,217	$23,469,073	$21,436,119	$23,367,718	$27,797,434	$119,585,561

CCC: Crohn's and Colitis Canada

CCS: Canadian Cancer Society

CFI: Canada Foundation for Innovation

CIHR: Canadian Institutes of Health Research

CRS: Cancer Research Society

Genome: Genome Canada

NAPHRO: National Alliance of Provincial Health Research Organizations

NSERC: Natural Sciences and Engineering Research Council of Canada

SSHRC: Social Sciences and Humanities Research Council.

Figure 10-2. IBD Research Funding in Canada (2013-2017)

Funding data for other diseases with similar incidence and prevalence in Canada were obtained from the National Alliance of Provincial Health Research Organizations (NAPHRO), national health charities and CIHR. Funding for multiple sclerosis, Parkinson's disease and type 1 diabetes, were $94.5M, $61.9M, $98.2M, respectively, compared to $115.1M for IBD (Table 10-1). On a per capita basis, $426 were invested into IBD research for every patient in Canada. Dollar per patient funding was second to type 1 diabetes in the least amount of dollars invested among the comparative diseases.

CIHR is the largest funder, contributing almost $66M (55% of the total funding) with Crohn's and Colitis Canada ranking second, investing more than $32M (27% of total funding). NAPHRO, Genome Canada and the Canadian Foundation for Innovation (CFI) ranked third, fourth and fifth, contributing 13.8%, 2.4% and 0.7% of total funding, respectively. The funded research spans the spectrum from understanding underlying causes and mechanisms of IBD, to improving patient care and developing new therapeutic approaches. Investments made by provincial funders have been fairly consistent – and relatively small - within the analysed period (*i.e.,* in the hundreds of thousands of dollars range) with three exceptions: Research Manitoba invested an additional ~$1.3 M in 2017; a significant reduction in Ontario's investment of some $2.5M from 2013 to 2014, and a reduction by Alberta Innovates of ~$2.5M after 2014 (data not shown).

Table 10-1:

Research Funding in Canada for Comparative Diseases**

	Multiple Sclerosis	Type 1 Diabetes	Parkinson's Disease	IBD
Prevalence	117,976[10]	300,000[11]	100,000[12]	270,000[1]
Total Funding (CAD)	$94,497,700	$98,202,428	$61,921,948	$115,134,733
$ Funding Per Patient (CAD)	$801	$327	$619	$426

** Funding data for multiple sclerosis, Parkinson's disease and Type 1 diabetes were provided by NAPHRO (for all members excluding Alberta Innovates and FRQS who provided their funding information separately), CIHR, MS Society, Diabetes Canada, and Parkinson Canada. Research funding by the Juvenile Diabetes Research Foundation was included from the Foundation's annual financial reports. The NSERC and SSHRC funding databases were queried with the following terms: "multiple sclerosis", "type 1 diabetes", "diabetes", "T1D", and "Parkinson". Other potential sources of funding such as Genome Canada were not included. IBD funding was adjusted to include only the above listed funders.

10.1.2.1.1 Funding by the Canadian Institutes of Health Research

CIHR is Canada's federal funding agency for health research. CIHR's mission is to create new scientific knowledge and to enable its translation into improved health, more effective health services and products, and a strengthened Canadian health care system. CIHR supports research through investigator-initiated research funding programs (e.g. Project and Foundation Grant Programs) and priority-driven research funding programs (e.g. Programmatic Grants in Environments, Genes and Chronic Disease; Team Grants in Health Challenges in Chronic Inflammation). CIHR also provides various salary awards to train the next generation of researchers and to attract and retain highly qualified scientists in their respective fields (see Box 1: Training the Next Generation of IBD Researchers). Between 2013 and 2017, CIHR funded an average of $13M per year in research related to IBD.

BOX 1

Training the Next Generation of IBD Researchers

The CIHR/CAG/CCC/Partners Program is an on-going grants and awards program funded collaboratively by CIHR, the Canadian Association of Gastroenterology (CAG) and Crohn's and Colitis Canada. Originally launched in 1992, this program has funded research fellowships, new investigator awards, career transition awards and operating grants to support gastroenterology research, including a subset in the area of IBD. A 2012 review of this program, demonstrated the impact of long-term and collaborative investments in training and capacity building, with recipients of funding producing research publications that had greater scientific impact than publications by peers both in Canada and around the world.[13] The CIHR/CAG/CCC/Partners Program demonstrates the effectiveness of organizations collaborating across sectors to support world-class research that will ultimately improve the lives of patients with IBD.

Other examples of collaborative approaches to training the next generation of IBD researchers include partnerships between members of National Alliance of Provincial Health Research Organizations (NAPHRO) and charities such as Crohn's and Colitis Canada which have resulted in the funding of provincial fellowships, scholarships and other capacity building opportunities.

10.1.2.1.2 Funding by Crohn's and Colitis Canada

Crohn's and Colitis Canada is one of the largest non-government funders of Crohn's disease and ulcerative colitis in the world. Founded in 1974, the promise of Crohn's and Colitis Canada is to cure Crohn's disease and ulcerative colitis and improve the lives of children and adults affected by these chronic diseases. In fulfilling this promise, Crohn's and Colitis Canada invests in research to increase understanding of, improve and expand treatment options for, and ultimately, to find the cure(s) for these life-long diseases.

During the past five years (2013-2017), Crohn's and Colitis Canada invested an average of $6.4M per year to support investigator-led research projects, targeted research initiatives, fellowships and studentships to train the next generation of IBD researchers in Canada. In addition, Crohn's and Colitis Canada has held annual research conferences as part of the Meeting of the Minds education event to bring together scientists and healthcare providers to discuss the latest topics in research and IBD care.

10.1.2.2 Funding Mechanisms
10.1.2.2.1 Priority-Driven IBD Research Funding in Canada

Priority-driven funding opportunities are supported by CIHR, Crohn's and Colitis Canada and/or their partners to address specific gaps or opportunities related to IBD research. The purpose of focusing on a specific disease, theme or discipline is to address a research gap or develop Canadian research strength. A number of different priority-driven funding mechanisms have been used over the last decade, including research networks and team grants, examples of which are shared below. Where relevant, leadership of Nominated Principal Investigators and Principal Investigators is acknowledged as indicated in the CIHR Funding Decisions Database. An example of priority-driven research is profiled in Box 2.

BOX 2

Project Profile: IBD Genomic Medicine (iGenoMed) Consortium

Funded jointly by CIHR, Genome Canada, Crohn's and Colitis Canada and Genome Quebec ($9.97M), the main objective of the iGenoMed Consortium was to identify biomarkers of response to therapy and to develop predictive tests to help guide patients and their physicians in their treatment decisions. As part of the iGenoMed research project, Professors John D. Rioux and Alain Bitton, along with their colleagues across Canada and international collaborators, have produced high impact findings. These include a high-resolution map that was used to investigate which genetic variants have a causal role in IBD[14] as well as an integrative approach to the development of multi 'omic biomarkers of response to therapy.[15] In order to improve the chances of success of this new generation of predictive tests, the iGenoMed Consortium identified potential socio-economic barriers to acceptance as well as strategies to address these challenges.[16-19] These findings will help researchers identify both which genes are involved in playing a role in IBD and which medications might be successful in which patients.

10.1.2.2.1.1 Examples of Priority-Driven Research Networks

- *The Canadian Children Inflammatory Bowel Disease Network: A Joint Partnership of CIHR and the CHILD Foundation* (CIDsCaNN). Leads: Anne Griffiths, Eric Benchimol, Kevan Jacobson, Gilaad Kaplan, David Mack, Aleixo Muise, Anthony Otley, Ernest Seidman, Bruce Vallance, Thomas Walters, Christopher Waterhouse, Eytan Wine, and a team of clinical leads representing each participating centre. CIDsCaNN brings together medical doctors and scientists working across Canada with the common goals of understanding why IBD affects so many children in Canada and determining the best treatment strategies to heal bowel inflammation and allow children to grow and enjoy life normally ($5M; 2013-2018).

- *The IMAGINE (Inflammation, Microbiome, and Alimentation: Gastro-Intestinal and Neuropsychiatric Effects) Chronic Disease Network (IMAGINE SPOR).* Leads: Paul Moayyedi, Douglas Howse, Premysl Bercik, Charles Bernstein, Stephen Collins, Johannes A. Eksteen, Richard Fedorak, Gilaad Kaplan, Paul Kubes, Glenda Macqueen, Anthony Otley, John Rioux, Michael Surette, and Stephen Vanner. IMAGINE SPOR aims to transform the management of IBD and irritable bowel syndrome (IBS) and associated mental health issues. IMAGINE SPOR involves 17 hospitals/universities and 75 researchers across Canada who will study interactions between inflammation, the microbiome, diet and mental health in patients with IBD and IBS ($12.45M; 2016-2021).

- *Genetic, Environmental, Microbial (GEM).* Lead: Kenneth Croitoru. Funded by Crohn's and Colitis Canada and the Leona M Helmsley Charitable Trust, GEM is a prospective study started in 2008 to recruit healthy first-degree relatives of Crohn's patients and follow them, expecting that a proportion would develop the disease in time. An international collaboration with over 100 recruitments sites world-wide, which reached the recruitment milestones is now developing predictive biomarkers of disease ($15.8M; 2008- present).

- *Promoting Access and Care through Centres of Excellence (PACE).* Lead: Geoffrey Nguyen. A Crohn's and Colitis Canada initiative with co-funding from industry, PACE aims to address gaps in care to increase the quality of life of those living with Crohn's disease or ulcerative colitis. PACE involves five Centres of Excellence working together (Remo Panaccioni & Cynthia Seow, University of Calgary; Richard Fedorak, University of Alberta; John Marshall & Neeraj Narula, McMaster University; Alain Bitton & Waqqas Afif, McGill University) ($2.5M; 2016-present).

- *Canadian IBD Research Consortium (CIRC).* Leads: Brian Bressler, Vipul Jairath, Geoffrey Nguyen, Neeraj Narula, Laura Targownik. Although Canada has one of the highest prevalences of Crohn's disease and ulcerative colitis in the world and excellent clinician scientists, Canada is not thought of as a primary choice for clinical studies to test novel therapies. With the support of industry partners, Crohn's and Colitis Canada is addressing this gap with CIRC in bringing together a pan-Canadian multi-investigator network designed to increase clinical research activity in Canada (~$300K per year, 2017- present).

10.1.2.2.1.2 Examples of Priority-Driven Research Grants

- *Influences of Host Genome on the Human Gut Microbiome: Studies in a Healthy Cohort Carrying Crohn's Disease Risk Alleles*. Leads: Kenneth Croitoru, Denis Krause, Mark Silverberg. Emerging Team Grant: Canadian Microbiome Initiative (with CIHR and Crohn's and Colitis Canada; $2.4M; 2010-2015)

- *Influence of the Microbiome on Epigenetic Mechanisms in Inflammatory Bowel Disease (IBD)*. Lead: Cheryl Arrowsmith. Team Grant: Canadian Epigenetics, Environment and Health Research Consortium (CEEHRC) (with CIHR and Genome British Columbia; $1.5M; 2013-2018)

- *NADPH oxidase function in the pathogenesis of pediatric IBD and JIA*. Lead: John Brumell. Team Grant: Health Challenges in Chronic Inflammation Initiative (with CIHR, Crohn's and Colitis Canada and The Arthritis Society; $2.2M; 2013-2018

- *Nod-like receptors: linking innate immunity and inflammation to chronic disease*. Leads: Dana Philpott and Daniel Muruve. Team Grant: Health Challenges in Chronic Inflammation Initiative (with CIHR and Crohn's and Colitis Canada; $2.4M; 2014-2019)

- *The diet-microbiota-gut axis in pediatric IBD*. Leads: Alain Stintzi, Daniel Figeys, David Mack, Kieran O'Doherty, and Bruce Vallance. Programmatic Grants in Environments, Genes and Chronic Disease (with CIHR and Crohn's and Colitis Canada; $1.9M, 2015-2020)

- Elucidating the gene-environment interactions that drive autoimmune disease among South Asian Canadians - The GEMINI Program. Leads: Jennifer Gommerman and Kenneth Croitoru. Programmatic Grants in Environments, Genes and Chronic Disease (with CIHR and Crohn's and Colitis Canada; $2.0M, 2015-2020)

10.1.2.2.2 Investigator-Initiated IBD Research in Canada

Investigator-initiated research refers to funding competitions where the focus of the project is proposed by individual researchers and their teams. Selected projects funded by CIHR and Crohn's and Colitis Canada and partners through investigator-initiated funding which demonstrate local and Canadian leadership in international collaborations are listed below. Also listed are examples of other investigator-initiated programs demonstrating the collaborative nature of the Canadian IBD research sector:

- *Canadian Gasto-Intestinal Epidemiology Consortium (CanGIEC).* Led by Eric Benchimol at the Children's Hospital of Eastern Ontario and University of Ottawa, this pan-Canadian network of clinicians, researchers, and methodologists has been working together to provide the evidence required to improve outcomes and health care services for Canadians with IBD using population-level studies

- The interNational Early Onset Paediatric IBD Cohort Study (*NEOPICS*). Led by Aleixo Muise at the Hospital for Sick Children and University of Toronto, NEOPICS brings together international paediatric gastroenterologists and scientists from academic centres around the world to work together on identifying causes of IBD in very young children (those under 6 years of age). The goals of NEOPICS are to identify the causes of IBD in young children and infants, and to develop new treatments and cures for IBD in these patients

- *The Canadian IBD Network for Research and Growth in Quality Improvement (CINERGI)*. The CINERGI group, led by Geoffrey Nguyen at the Mount Sinai Hospital and University of Toronto, is a research network of 14 IBD specialists representing 12 Canadian academic institutions spanning seven provinces with expertise in epidemiology, clinical trials, health services research, economic analysis, and quality improvement. CINERGI is committed to improving healthcare delivery in IBD. Recent CINERGI projects include Choosing Wisely Canada for IBD and developing measures of inpatient quality indicators for inflammatory bowel disease

10.2 Output and Quality of IBD Research in Canada

10.2.1 Overview

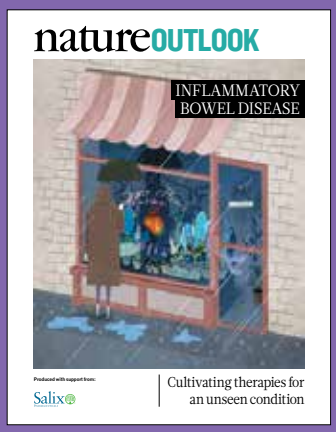
The collaborative efforts of CIHR, Crohn's and Colitis Canada and other Canadian research funders have supported the development of a strong cadre of Canadian health researchers who have world-wide impact. Indeed, IBD researchers in Canada are among the most internationally collaborative in the world[21] and Canadian researchers are among those identified as authors of the top 100 cited research manuscripts in IBD worldwide.[22] An example of impactful Canadian IBD research is detailed in Box 3.

BOX 3

International Recognition of Canadian Research Strength in IBD

The incidence of IBD is now increasing not only in North America and Europe, but also in parts of Asia, such as India and China. The increasing incidence of IBD around the world is thought to be linked not only to genetics but also to lifestyle and environmental changes. Canadian researchers are leading the way in identifying how changes in environment, such as sanitation, air quality, and diet may contribute to the development of IBD.

Two Canadian research networks, The Canadian Children Inflammatory Bowel Disease Network (CIDsCaNN) and Generational Differences in Environmental Exposure caused by Migration: Impact on Incidence of Inflammatory Disease (GEMINI) were profiled as world-wide leaders in a Nature Outlook article.[20] These research networks are among the Canadian resources that are helping us understand how environmental exposures can impact the composition of bacteria in the gut (the microbiome), and how we can treat these changes to reduce inflammation.



10.2.2 Recognition of Canadian Research Strength in IBD

A bibliometric data analysis (see **Appendix B** for methodology) conducted in 2018 demonstrates the quality of IBD research in Canada. This analysis showed that Canada ranks sixth worldwide in terms of number of IBD scientific papers published (which is equal to Canada's ranking when taking into account all scientific papers published). When productivity and impact in IBD research are combined, Canada is among the top three in the world. Table 10-2 summarizes the top five countries with the highest bibliometric indices for IBD research between 2012 and 2016. Canada consistently ranked within the top three for each of the three bibliometric measures outlined by the following:

10.2.1.1. Average Relative Impact Factor (ARIF)

This indicator is a measure of the expected impact of the research portfolio. In order to account for different citation patterns across fields and subfields, a Relative Impact Factor (RIF) is calculated by dividing the impact factor of the journal that the paper is published in by the mean impact factor of all papers in a particular subfield. The ARIF of a country is then calculated by computing the mean of the RIF of all published papers in a particular discipline for the country. An ARIF value greater than 1 indicates that the country publishes in journals cited more often than the world average.

Canada's ARIF (1.53) places Canada third internationally in IBD research after the Netherlands and United Kingdom with no statistical significance between the results of the top five countries. In terms of all scientific publications, Canada's ARIF is 1.22, which is lower than the ARIF achieved by Canadian IBD-focused researchers.

Table 10-2:

Bibliometric Data Analysis: Top Five Countries with the Greatest Impact

Nations	Total Papers	Proportion of Country's Publications in Top 10% Impact (RC) Papers	Average of Relative Citations (ARC)	Average Relative Impact Factor (ARIF)
Netherlands	562	27%	2.37	1.56
Canada	902	25%	2.19	1.53
France	730	25%	2.14	1.53
United Kingdom	1,050	25%	2.14	1.55
United States	3,865	21%	1.78	1.52
World	12,750	14%	1.27	1.15

10.2.1.2. Average of Relative Citations (ARC)

This indicator measures the observed impact of the research portfolio. It is based on the number of citations received by a published paper over a three-year period following the publication year. The number of citations received by each paper is normalized by the average number of citations received by all papers of the same subfield.

Canada's ARC value in all scientific research for the period measured was 1.42 with IBD research being 2.19. This is well above the IBD world average (1.27) and second only to the Netherlands (2.37, with the difference in score not being statistically significant). This finding means that, on average, papers dealing with IBD topics are cited 1.27 times more often than the average papers of their respective disciplinary field (for example, an IBD paper published in a journal of gastroenterology would be cited more frequently than other papers in gastroenterology). In terms of Canadian IBD papers, these are cited 2.19 times more frequently than other papers in their respective disciplines and 1.72 times more often that the world average of IBD papers. It is also important to note that Canada's ARC is significantly higher than its ARIF, indicating that the IBD research portfolio outperformed expectations over this period.

10.2.1.3. Top 10% Impact

Based on the Relative Citations (RC) measure (described above), for the period 2012-2016, 25% of Canada's published IBD papers were within the top 10% of all IBD published papers, placing Canada second in the world (behind the Netherlands) on this measure.

Although there is a time lag between research funding and publication of data, we assumed relative productivity within +/- three-year time period within a country would not vary significantly. Using this assumption, we created an average dollar investment per published paper by determining the number of published papers in the Dimensions platform that were found in the top ten bibliometric analysis and then dividing by the research investment. With these limitations, we compared Canada, the United Kingdom and the United States: Canadian funders invested $132,578 for every paper published in the top 10% impact listing. In comparison, the UK and USA invested $205,053 and $576,316, respectively. Comparative funding data are not available for the Netherlands and France in the *Dimensions* platform, precluding our ability to include these countries in this comparative analysis.

10.3 Conclusions

Investment in IBD research in Canada has resulted in the development of a strong collaborative group of researchers producing impactful, world class research. Relatively high levels of investment in all forms of research – including cure, treatment, prevention, health services and policy, and quality of life – are likely a response to the prevalence and impact on quality of life of these diseases in Canada. Historically, Canada has been the fourth largest IBD research funder in the world, investing some $119M over the period 2013-2017. With this investment, the research community has delivered an extraordinary performance. On all measures of academic productivity and influence, Canada ranks in the top two or three internationally.

Against a backdrop of generally constrained resources, the challenge ahead is two-fold: to continue to fund innovative relevant IBD research and grow the next generation of IBD researchers while at the same time, moving research findings ever more quickly into changes in health policy and practice in order to benefit affected patients and their families and, ultimately, to identify the cause(s) and find the cure(s).

Appendix A: UberResearch Methodology and List of Funding Organizations

Overview of Methodology

The core database used, Dimensions, one of the service offerings provided by Digital Science, was developed in collaboration with over 100 leading research organizations around the world and links 128 million formerly siloed documents, including $1.3 trillion in research funding, 94 million publications, 35 million patents, 399,000 clinical trials and identifies almost 4 billion connections between them. This database also makes over 986 million academic citations available for appraisal.

Grants data in Dimensions are provided directly by either funders or from public sources (Table 10-3). Funding data often comes directly from the funder organization, especially when funders are Dimensions partners, and this is provided in a variety of different ways depending on the funder's preference. New grant sources are added on a regular basis, as well as existing funder sources being updated when new data are available.

To obtain data for this analysis, the database was searched using the key words: Crohn's disease, colitis and ulcerative colitis. A full database search was conducted initially to identify all grants made internationally and then filtered for the five-year period 2013-17. Funding amounts are listed in Canadian dollars.

Table 10-3:

List of Funders of IBD Research in the Dimensions Platform by Country for the period 2013-17

Funder	Country
Australian Research Council	Australia
National Health and Medical Research Council	Australia
FWF Austrian Science Fund	Austria
Belgian Federal Science Policy Office	Belgium
European Commission	Belgium
European Research Council	Belgium
Fund for Scientific Research - FNRS	Belgium
National Council for Scientific and Technological Development	Brazil
São Paulo Research Foundation	Brazil
Alberta Innovates – Health Solutions	Canada
Canada Foundation for Innovation	Canada
Canadian Cancer Society	Canada
Canadian Institutes of Health Research	Canada
Cancer Research Society	Canada
Fonds de Recherche du Québec	Canada
Genome Canada	Canada
Michael Smith Foundation for Health Research	Canada
Ministry of Research and Innovation	Canada
Natural Sciences and Engineering Research Council	Canada
Nova Scotia Health Research Foundation	Canada
Research Manitoba	Canada
Saskatchewan Health Research Foundation	Canada
Social Sciences and Humanities Research Council	Canada
National Natural Science Foundation of China	China
Zhejiang Provincial Natural Science Foundation	China
Croatian Science Foundation	Croatia
Estonian Research Council	Estonia
Academy of Finland	Finland
Human Frontier Science Program	France
National Agency for Research	France
German Research Foundation	Germany
University Grants Committee	Hong Kong
Hungarian Scientific Research Fund	Hungary
Science Foundation Ireland	Ireland
Israel Science Foundation	Israel
Ministry of Education, Universities and Research	Italy
Japan Society for the Promotion of Science	Japan
National Research Fund Luxembourg	Luxembourg
Netherlands Organisation for Scientific Research	Netherlands

Funder	Country
Health Research Council of New Zealand	New Zealand
NordForsk	Norway
The Research Council of Norway	Norway
Ministry of Science and Higher Education	Poland
National Centre for Research and Development	Poland
National Science Center	Poland
Foundation for Science and Technology	Portugal
Russian Foundation for Basic Research	Russia
Russian Science Foundation	Russia
Ministry of Education, Science, Research and Sport of the Slovak Republic	Slovakia
Slovak Research and Development Agency	Slovakia
Slovenian Research Agency	Slovenia
Swedish Foundation for Strategic Research	Sweden
Swedish Research Council	Sweden
Swedish Research Council for Environment Agricultural Sciences and Spatial Planning	Sweden
Swedish Research Council for Health Working Life and Welfare	Sweden
VINNOVA	Sweden
Swiss National Science Foundation	Switzerland
Academy of Medical Sciences	United Kingdom
Biotechnology and Biological Sciences Research Council	United Kingdom
Cancer Research UK	United Kingdom
Department for Environment Food and Rural Affairs	United Kingdom
Engineering and Physical Sciences Research Council	United Kingdom
Innovate UK	United Kingdom
Medical Research Council	United Kingdom
National Centre for the Replacement Refinement and Reduction of Animals in Research	United Kingdom
Natural Environment Research Council	United Kingdom
NIHR Central Commissioning Facility	United Kingdom
NIHR Evaluation, Trials and Studies Coordinating Centre	United Kingdom
NIHR Trainees Coordinating Centre	United Kingdom
Royal Society	United Kingdom

Table 10-3:

List of Funders of IBD Research in the Dimensions Platform by Country for the period 2013-17*(Continued)*

Funder	Country
Scottish Government Health and Social Care Directorates	United Kingdom
Wellcome Trust	United Kingdom
Agency for Healthcare Research and Quality	United States
Agricultural Research Service	United States
Alzheimer's Drug Discovery Foundation	United States
Arnold and Mabel Beckman Foundation	United States
Arthritis Foundation	United States
Autism Speaks	United States
California HIV/AIDS Research Program	United States
California Institute for Regenerative Medicine	United States
Cancer Prevention and Research Institute of Texas	United States
Centers for Disease Control and Prevention	United States
Congressional Direct Medical Research Program	United States
Crohn's and Colitis Foundation of America	United States
Directorate for Biological Sciences	United States
Directorate for Computer & Information Science & Engineering	United States
Directorate for Engineering	United States
Directorate for Mathematical & Physical Sciences	United States
Directorate for Social, Behavioral & Economic Sciences	United States
Health Resources and Services Administration	United States
Juvenile Diabetes Research Foundation	United States
National Aeronautics and Space Administration	United States
National Cancer Institute	United States
National Center for Advancing Translational Sciences	United States
National Center for Complementary and Integrative Health	United States
National Eye Institute	United States
National Heart Lung and Blood Institute	United States

Funder	Country
National Human Genome Research Institute	United States
National Institute of Allergy and Infectious Diseases	United States
National Institute of Arthritis and Musculoskeletal and Skin Diseases	United States
National Institute of Biomedical Imaging and Bioengineering	United States
National Institute of Child Health and Human Development	United States
National Institute of Dental and Craniofacial Research	United States
National Institute of Diabetes and Digestive and Kidney Diseases	United States
National Institute of Environmental Health Sciences	United States
National Institute of Food and Agriculture	United States
National Institute of General Medical Sciences	United States
National Institute of Mental Health	United States
National Institute of Neurological Disorders and Stroke	United States
National Institute of Nursing Research	United States
National Institute on Aging	United States
National Institute On Alcohol Abuse and Alcoholism	United States
National Institute on Drug Abuse	United States
National Institutes of Health Clinical Center	United States
National Psoriasis Foundation	United States
Office of the Director	United States
Patient Centered Outcomes Research Institute	United States
Shriners Hospitals for Children	United States
United States Army	United States
United States Department of the Navy	United States
United States Department of Veterans Affairs	United States
United States National Library of Medicine	United States
University of California - Cancer Research Coordinating Committee	United States

Appendix B: Bibliometric Data

The bibliometric data used in this study are drawn from the Canadian Bibliometric Database (CBDTM) built by the Observatoire des sciences et des technologies (OST) by using Clarivate Analytic' Web of Science (WoS). The WoS includes three databases (the Science Citation Index Expanded™, the Social Sciences Citation Index™, and the Arts & Humanities Citation Index™) covering more than 12,000 journals from all fields of knowledge in 2016.

These databases do not include all documents likely to have been published by Canadian or foreign researchers, since some works are disseminated through other scientific media not indexed by the WoS (for instance, highly specialized journals, national journals, grey literature and conference proceedings not published in journals). However, the WoS databases include the researchers' scientific output most visible to Canadian and worldwide scientific communities and, therefore, is most likely to be cited.

Given that the WoS subject classification is applied to journals, and not individual papers, in order to identify more specifically papers focused on Crohn's disease and colitis, OST used the U.S. National Library of Medicine's Medical Subject Headings (MeSH) which relies on a controlled vocabulary to assign a medical topic to each paper indexed in PubMed. Table 10-4 presents the MeSH queries selected for this study, as well the number of papers retrieved in PubMed.

Table 10-4:

IBD Keywords and MeSH Queries

Search	Query	Items Found
#1	Search (Colitis Gravis [MeSH terms] AND (Review[ptyp] OR Journal Article[ptyp]) AND ("2009/01/01"[PDat] : "2016/12/31"[PDat]))	7,188
#2	Search (Crohn's disease [MeSH terms] AND (Review[ptyp] OR Journal Article[ptyp]) AND ("2009/01/01"[PDat] : "2016/12/31"[PDat]))	9,356
#3	Search (inflammatory bowel [MeSH terms] AND (Review[ptyp] OR Journal Article[ptyp]) AND ("2009/01/01"[PDat] : "2016/12/31"[PDat]))	10,914
#4	**Search #1 OR #2 OR #3**	22,647

Source: PubMe. Data retrieved on November 24th 2017.

Taken together, these three queries retrieved 22,647 papers in PubMed over the 2009-2016 period. Due to the structure of the MeSH classification, these queries also cover the following concepts and MeSH terms:

- query #1 includes papers dealing with idiopathic proctocolitis and ulcerative colitis.
- query #2 retrieves the papers dealing wwith Crohn's disease, crohn's enteritis, granulomatous colitis, granulomatous enteritis, ileocolitis, regional enteritis and terminal ileitis.

It should be noted that a given paper can bear more than one of these terms, which is why the sum of papers retrieved by each selected query is greater than the total number of distinct papers retrieved by the whole retrieval strategy.

Using authors' names, papers' titles and publication year, as well as the journal volume, number and page numbers, these PubMed papers were matched to corresponding items in the WoS to populate the bibliometric dataset from which the measurement areas identified below were calculated.

It should be noted that all PubMed records do not necessarily have a corresponding item in the WoS. Among the 22,647 papers retrieved from PubMed, 20,245 were published in a journal indexed in the WoS. Among these, 18,967 were matched to a record bearing at least one institutional address and corresponding to the document types used in the bibliometric analysis (articles, research notes and review articles because they are all considered as vehicles of new knowledge).

Details about the methodology have been published over the years.[23-25] What follows below is a synopsis of the key elements.

Indicators: For the 10 most productive countries in IBD research, the following indicators were produced, at the level of each country and each priority area.

Number of publications: The number of scientific papers with authors from a country, as identified in the authors' addresses. Although OST's database includes several types of documents, only articles, research notes and review papers are included as described above, as these are the primary means of disseminating new knowledge. This indicator is also presented as a percentage of world papers in which at least one institutional address is from the country. These numbers of publications are also compiled for Canadian institutions and sectors (university, hospitals, industries, federal government, provincial government and others).

Specialization index (SI): This is an indicator of the relative intensity of publication of a country in the priority areas identified relative to the intensity of the world in the same areas. A SI value above 1 means that a country is specialized in the priority area compared to the world average, while an index value below 1 means the opposite.

Average Relative Impact Factor (ARIF): This indicator provides a measure of the scientific impact of the journals in which a group of researchers publish. Each journal has an impact factor (IF), which is calculated annually based on the average number of citations received by the papers it published during the two previous years. The value of a journal's IF is assigned to each paper it publishes. In order to account for different citation patterns across fields and subfields (e.g., there are more citations in biomedical research than mathematics), each paper's IF is then divided by the average IF of the papers in its particular subfield in order to obtain a Relative Impact Factor (RIF). The ARIF of a given institution (or group of researchers) is computed using the average RIF of all papers belonging to it. When the ARIF is greater than 1, it means that this institution (or group of researchers) publishes in journals cited more often than the world average; when it is below 1, that the institution (or group of researchers) publishes in journals that are not cited as often as the world average. This indicator is set to non-significant when the number of publications involved is below 30.

Average of Relative Citations (ARC): This indicator is based on the number of citations received by a published paper over a three-year period following the publication year. Thus, for papers published in 2000, citations received between 2000 and 2003 are counted. Author self-citations are included. The number of citations received by each paper is normalized by the average number of citations received by all papers of the same subfield, hence taking into account the fact that citation practices are different for each specialty. When the ARC is greater than 1, it means that a paper or a group of papers scores better than the world average of its specialty; when it is below 1, those publications are not cited as often as the world average. This indicator is set to non-significant when the number of publications involved is below 30.

Top 10% impact (RC): This indicator is based on the value of the relative citation (RC). Each paper has a RC that is the number of citations it receives normalized (divided) by the average number of citations received by all papers published the same year in the same specialty. The top 10% impact (RC) is thus the papers with the RC value in the top 10% of all papers published in the same year in the same specialty.

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