The Impact of Inflammatory Bowel Disease in Canada 2018: A Scientific Report from the Canadian Gastro-Intestinal Epidemiology Consortium to Crohn's and Colitis Canada

Eric I. Benchimol MD, PhD^{1,2,0}, Charles N. Bernstein MD^{1,3}, Alain Bitton MD^{1,4}, Sanjay K. Murthy MD, MS^{1,5}, Geoffrey C. Nguyen MD, PhD^{1,6}, Kate Lee MBA, PhD⁷, Jane Cooke-Lauder MBA, DM, CMC⁸, Shabnaz Siddiq MSc², Joseph W. Windsor PhD^{1,9}, Matthew W. Carroll BMed(Hons), MHSc^{1,10}, Stephanie Coward MSc^{1,9}, Wael El-Matary MD, MSc^{1,3}, Anne M. Griffiths MD¹¹, Jennifer L. Jones MD, MS^{1,12}, M. Ellen Kuenzig PhD^{1,2,0}, Lawrence Lee MD, PhD⁵, David R. Mack MD^{1,13}, Mina Mawani MHSc⁷, Anthony R. Otley MD, MSc^{1,14}, Harminder Singh MD, MPH^{1,3}, Laura E. Targownik MD, MSc^{1,3}, Adam V. Weizman MD, MSc⁶, Gilaad G. Kaplan MD, MPH^{1,9}

¹Canadian Gastro-Intestinal Epidemiology Consortium, Canada; ²Children's Hospital of Eastern Ontario IBD Centre, Department of Pediatrics and School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada; ³University of Manitoba IBD Clinical and Research Centre, University of Manitoba, Winnipeg, Manitoba, Canada; ⁴McGill University Health Centre IBD Centre, McGill University, Montreal, Quebec, Canada; ⁵Ottawa Hospital Research Institute, Department of Medicine and School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada; ⁶Mount Sinai Hospital Centre for IBD, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; ⁷Crohn's and Colitis Canada, Toronto, Ontario, Canada; ⁸Bataleur Enterprises Inc, Toronto, Ontario, Canada; ⁹Department of Medicine and Community Health Sciences, University of Calgary, Calgary, Alberta, Canada; ¹⁰Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada; ¹¹SickKids IBD Centre, The Hospital for Sick Children, Department of Paediatrics, University of Toronto, Ontario, Canada; ¹²Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada; ¹⁴Division of Gastroenterology and Nutrition, Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada; ¹⁴Division of Gastroenterology and Nutrition, Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada; ¹⁴Division of Gastroenterology and Nutrition, Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada;

Correspondence: Gilaad Kaplan, MD, MPH, Teaching Research and Wellness Building, 3D03-18, 3280 Hospital Drive NW, Calgary, Alberta, T2N 4Z6, Canada, e-mail ggkaplan@ucalgary.ca

Abstract

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 health care 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 health care 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. This report from Canadian clinicians and researchers to Crohn's and Colitis Canada makes recommendations aimed at the public, policy-makers, scientific funding agencies, charitable foundations and patients regarding future directions for advocacy efforts and areas to emphasize for research spending. The report also identifies gaps in knowledge in the fields of clinical, health systems and epidemiological research.

@ The Author(s) 2018. Published by Oxford University Press on behalf of the Canadian Association of Gastroenterology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

OXFORD

Received: July 24, 2018; Accepted: September 6, 2018

Keywords: Costs; Crohn's disease; Inflammatory bowel disease; Prevalence; Quality of life; Ulcerative colitis

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 5 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).

Crohn's and Colitis Canada (CCC) 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. The Canadian Gastro-Intestinal Epidemiology Consortium's overall aim is to assess the burden of IBD, provide evidence for environmental risk factors of IBD and improve the way that health care systems treat people living with IBD in Canada and abroad (see CanGIEC.ca). The CanGIEC and partnering clinician-researchers have provided this report to CCC 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.

To undertake this review, a steering committee (EB, CB, AB, GK, GN and SM) was formed, comprised of academic experts in gastroenterology and health system research. The 2018 Impact of IBD in Canada Report was created by working groups corresponding with the following sections in this report: epidemiology (EB, CB, AB, SC and GK); direct costs and health services utilization (EB, EK, LL, SM, GN, HS and LT); indirect costs of IBD care (WE, EK, LL, SM and AW); quality of life in patients with IBD (JJ, GN and AO); special populations: children with IBD (EB, MC, AG, EK, DM and AO); special populations: seniors with IBD (GN, HS and LT); and extra-intestinal disease (CB and GK). A complete overview

of the objectives, working committees and methodology of creating the report can be found in the online supplemental file, Technical Document.

THE IMPACT OF IBD IN CANADA: REPORT SUMMARY

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 1000 Canadians have 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 new cases per 100,000 people per year (13), and the lowest is in British Columbia at 18.7 per 100,000 people per year (14). 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 Asian descent and lower among those of East Asian descent (19, 20).

People with Crohn's disease face a significantly elevated risk of premature death compared with 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 codiagnosed 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 health care system for the rising burden of IBD (11).

Rising Rates of IBD in Canadian Children

There are over 7000 children under the age of 18 years old living in Canada with IBD, and the prevalence of IBD in children has risen more than 50% in the last 15 years (16, 28, 29). The rate of new diagnoses of IBD in children is rising rapidly; in particular, the number of newly diagnosed children under 5 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 (16, 28, 29). Children with IBD have different complications of IBD, respond differently to treatments and are at greater risk for some medication side effects compared with 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 health care system must be prepared for a rising number of senior patients living with IBD (16). Seniors with IBD are the fasting growing group of people living with IBD, and the Canadian health care system must be prepared to face this challenge (16). The rising prevalence of IBD in seniors is the result of new diagnoses made in this population and 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 health care providers must be prepared to work in multidisciplinary teams with other specialists to optimize IBD management in the context of the unique challenges faced by seniors with IBD (38).

Quality of Life for People with IBD

IBD often affects individuals in adolescence and early adulthood, a time when they are pursuing employment, building their family and reaching key milestones (7, 42). The impact of IBD on quality of life (QOL) is multifaceted, from direct physical impairment due to symptoms like diarrhea and abdominal pain to financial burdens associated with health care encounters, in addition 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 because 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 health care 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 health care 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 CAD in Canada in 2018. Direct medical costs are approximately \$1.28 billion CAD, 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, the 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 CAD 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 health care 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:

- Increase funding for research into preventing and treating IBD and addressing the physical, psychological, and social issues caused by IBD
- 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
- Improve recognition and funding for research into special populations of people with IBD, including children, seniors and pregnant women
- Recognize IBD is a national health priority and increase resource allocation for chronic care models that reflect the episodic nature of IBD to optimize health care delivery to this population; this is the responsibility of the federal government.
- Enact a national public health campaign and patient education programs to raise awareness and knowledge among the general public and health care professionals to facilitate earlier diagnosis and reduce social stigma associated with IBD; leadership for such a campaign could come from Crohn's and Colitis Canada.
- Introduce public and private sector programs (including laws) that foster open access to washroom facilities for people with IBD or incontinence
- Ensure timely and appropriate access to gastrointestinal specialists, allied health care professionals, endoscopy and radiology services for those who are waiting for diagnosis or treatment of IBD, particularly in rural and underserviced areas
- Enhance and harmonize public and private drug plans so that patients with IBD—no matter where they live in Canada, their age or their socioeconomic status—have

equal and better access to medically prescribed pharmaceuticals that improve a patient's health and quality of life

- 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
- 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.

ACKNOWLEDGEMENTS

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

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

References

- Kaplan GG, Ng SC. Understanding and preventing the global increase of inflammatory bowel disease. Gastroenterology 2017;152(2):313–21 e312.
- Hazlewood GS, Rezaie A, Borman M, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's Disease: A network meta-analysis. Gastroenterology 2015;148(2):344–54 e345.
- Stidham RW, Lee TC, Higgins PD, et al. Systematic review with network meta-analysis: The efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis. Aliment Pharmacol Ther 2014;39(7):660–71.
- Frolkis AD, Dykeman J, Negron ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: A systematic review and meta-analysis of population-based studies. Gastroenterology 2013;145(5):996–1006.
- Frolkis AD, Lipton DS, Fiest KM, et al. Cumulative incidence of second intestinal resection in Crohn's disease: A systematic review and meta-analysis of population-based studies. Am J Gastroenterol 2014;109(11):1739–48.
- Benchimol EI, Mack DR, Nguyen GC, et al. Incidence, outcomes, and health services burden of very early onset inflammatory bowel disease. Gastroenterology 2014;147(4):803–13 e807; quiz e814-805.
- Becker HM, Grigat D, Ghosh S, et al. Living with inflammatory bowel disease: A Crohn's and Colitis Canada survey. Can J Gastroenterol Hepatol 2015;29(2):77–84.
- Argyriou K, Kapsoritakis A, Oikonomou K, et al. Disability in patients with inflammatory bowel disease: Correlations with quality of life and patient's characteristics. Can J Gastroenterol Hepatol 2017;2017:6138105.

- Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142(1):46–54 e42; quiz e30.
- Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: A systematic review of population-based studies. Lancet (London, England) 2018;390(10114):2769–78.
- 11. Kaplan GG. The global burden of IBD: From 2015 to 2025. Nat Rev Gastroenterol Hepatol 2015;12(12):720-7.
- Coward S, Clement F, Benchimol Eric I, et al. The rising prevalence of inflammatory bowel disease in Canada: Analyzing the past to predict the future. J Can Assoc Gastroenterol 2018;1(Supp 2):A-29.
- Leddin D, Tamim H, Levy AR. Decreasing incidence of inflammatory bowel disease in Eastern Canada: A population database study. BMC Gastroenterol 2014;14:140.
- Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: A population-based study. Am J Gastroenterol 2006;101(7):1559–68.
- Benchimol EI, Kaplan GG, Otley AR, et al. Rural and urban residence during early life is associated with risk of inflammatory bowel disease: A population-based inception and birth cohort study. Am J Gastroenterol 2017;112(9):1412–22.
- Benchimol EI, Manuel DG, Guttmann A, et al. Changing age demographics of inflammatory bowel disease in Ontario, Canada: A population-based cohort study of epidemiology trends. Inflamm Bowel Dis 2014;20(10):1761–9.
- Bitton A, Vutcovici M, Patenaude V, et al. Decline in IBD incidence in Quebec: Part of the changing epidemiologic pattern in North America. Inflamm Bowel Dis 2014;20(10):1782–3.
- Bernstein CN. Review article: Changes in the epidemiology of inflammatory bowel disease-clues for aetiology. Aliment Pharmacol Ther 2017;46(10):911–9.
- Benchimol EI, Mack DR, Guttmann A, et al. Inflammatory bowel disease in immigrants to Canada and their children: A population-based cohort study. Am J Gastroenterol 2015;110(4):553–63.
- 20. Roth MP, Petersen GM, McElree C, et al. Familial empiric risk estimates of inflammatory bowel disease in Ashkenazi Jews. Gastroenterology 1989;96(4):1016–20.
- Bernstein CN, Nugent Z, Targownik LE, et al. Predictors and risks for death in a population-based study of persons with IBD in Manitoba. Gut 2015;64(9):1403–11.
- Lutgens MW, van Oijen MG, van der Heijden GJ, et al. Declining risk of colorectal cancer in inflammatory bowel disease: An updated meta-analysis of population-based cohort studies. Inflamm Bowel Dis 2013;19(4):789–99.
- Bernstein CN. Extraintestinal manifestations of inflammatory bowel disease. Curr Gastroenterol Rep 2001;3(6):477–83.
- Bernstein CN, Blanchard JF, Rawsthorne P, et al. The prevalence of extraintestinal diseases in inflammatory bowel disease: A population-based study. Am J Gastroenterol 2001;96(4):1116–22.
- Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: Improved prevalence estimates and understanding of clustering of diseases. J Autoimmun 2009;33(3–4):197–207.
- Pringsheim T, Jette N, Frolkis A, et al. The prevalence of Parkinson's disease: A systematic review and meta-analysis. Mov Disord 2014;29(13):1583–90.
- Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology 2017;88(3):296–303.
- Benchimol EI, Guttmann A, Griffiths AM, et al. Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: Evidence from health administrative data. Gut 2009;58(11):1490–7.
- Benchimol EI, Bernstein CN, Bitton A, et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: Distributed network analysis of multiple population-based provincial health administrative databases. Am J Gastroenterol 2017;112(7):1120–34.
- Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: A multicentre inception cohort study. Lancet (London, England) 2017;389(10080):1710–8.
- Haapamaki J, Roine RP, Sintonen H, et al. Health-related quality of life in paediatric patients with inflammatory bowel disease related to disease activity. J Paediatr Child Health 2011;47(11):832–7.
- van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology 2008;135(4):1114–22.
- 33. Israeli E, Ryan JD, Shafer LA, et al. Younger age at diagnosis is associated with panenteric, but not more aggressive, Crohn's disease. Clin Gastroenterol Hepatol 2014;12(1):72–9.e71.
- Benchimol EI, To T, Griffiths AM, et al. Outcomes of pediatric inflammatory bowel disease: Socioeconomic status disparity in a universal-access health care system. J Pediatr 2011;158(6):960–7 e961-964.
- 35. Herzer M, Denson LA, Baldassano RN, et al. Patient and parent psychosocial factors associated with health-related quality of life in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2011;52(3):295–9.

- Gray WN, Boyle SL, Graef DM, et al. Health-related quality of life in youth with Crohn disease: Role of disease activity and parenting stress. J Pediatr Gastroenterol Nutr 2015;60(6):749–53.
- Charpentier C, Salleron J, Savoye G, et al. Natural history of elderly-onset inflammatory bowel disease: A population-based cohort study. Gut 2014;63(3):423–32.
- Stepaniuk P, Bernstein CN, Targownik LE, et al. Characterization of inflammatory bowel disease in elderly patients: A review of epidemiology, current practices and outcomes of current management strategies. Can J Gastroenterol Hepatol 2015;29(6):327–33.
- Bollegala N, Jackson TD, Nguyen GC. Increased postoperative mortality and complications among elderly patients with inflammatory bowel diseases: An analysis of the national surgical quality improvement program cohort. Clin Gastroenterol Hepatol 2016;14(9):1274-81.
- Cottone M, Kohn A, Daperno M, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol 2011;9(1):30–5.
- Ananthakrishnan AN, McGinley EL, Binion DG. Inflammatory bowel disease in the elderly is associated with worse outcomes: A national study of hospitalizations. Inflamm Bowel Dis 2009;15(2):182–9.
- 42. Lix LM, Graff LA, Walker JR, et al. Longitudinal study of quality of life and psychological functioning for active, fluctuating, and inactive disease patterns in inflammatory bowel disease. Inflamm Bowel Dis 2008;14(11):1575–84.
- Bitton A, Sewitch MJ, Peppercorn MA, et al. Psychosocial determinants of relapse in ulcerative colitis: A longitudinal study. Am J Gastroenterol 2003;98(10): 2203–8.
- 44. Graff LA, Walker JR, Lix L, et al. The relationship of inflammatory bowel disease type and activity to psychological functioning and quality of life. Clin Gastroenterol Hepatol 2006;4(12):1491–501.
- 45. Camara RJ, Ziegler R, Begre S, et al. The role of psychological stress in inflammatory bowel disease: Quality assessment of methods of 18 prospective studies and suggestions for future research. Digestion 2009;80(2):129–39.
- Niv G, Bar Josef S, Ben Bassat O, et al. Quality of life and uncertainty in Crohn's disease. Qual Life Res 2017;26(6):1609–16.
- Panes J, O'Connor M, Peyrin-Biroulet L, et al. Improving quality of care in inflammatory bowel disease: What changes can be made today? J Crohns Colitis 2014;8(9):919–26.
- Vavricka SR, Spigaglia SM, Rogler G, et al. Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. Inflamm Bowel Dis 2012;18(3):496–505.
- Schoepfer AM, Dehlavi MA, Fournier N, et al. Diagnostic delay in Crohn's disease is associated with a complicated disease course and increased operation rate. Am J Gastroenterol 2013;108(11):1744–53; quiz 1754.
- Benchimol EI, Manuel DG, Mojaverian N, et al. Health services utilization, specialist care, and time to diagnosis with inflammatory bowel disease in immigrants to Ontario, Canada: A population-based cohort study. Inflamm Bowel Dis 2016;22(10):2482–90.
- Nguyen GC, Nugent Z, Shaw S, et al. Outcomes of patients with Crohn's disease improved from 1988 to 2008 and were associated with increased specialist care. Gastroenterology 2011;141(1):90–7.
- Benchimol EI, Bernstein CN, Nguyen GC, et al. Disparities in the care of rural and urban Canadians with inflammatory bowel disease: A population-based study (abstract). Journal of Canadian Association of Gastroenterology 2018;1(Suppl 2):51–2.
- Bernstein CN, Longobardi T, Finlayson G, et al. Direct medical cost of managing IBD patients: A Canadian population-based study. Inflamm Bowel Dis 2012;18(8):1498–508.
- Dan A, Boutros M, Nedjar H, et al. Cost of ulcerative colitis in Quebec, Canada: A retrospective cohort study. Inflamm Bowel Dis 2017;23(8):1262–71.
- 55. Burisch J, Vardi H, Pedersen N, et al. Costs and resource utilization for diagnosis and treatment during the initial year in a European inflammatory bowel disease inception cohort: An ECCO-EpiCom Study. Inflamm Bowel Dis 2015;21(1):121–31.
- 56. van der Valk ME, Mangen MJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: Results from the COIN study. Gut 2014;63(1):72–9.
- Busch K, da Silva SA, Holton M, et al. Sick leave and disability pension in inflammatory bowel disease: A systematic review. J Crohns Colitis 2014;8(11):1362–77.
- Kawalec P, Malinowski KP. Indirect health costs in ulcerative colitis and Crohn's disease: A systematic review and meta-analysis. Expert Rev Pharmacoecon Outcomes Res 2015;15(2):253–66.
- Gibson TB, Ng E, Ozminkowski RJ, et al. The direct and indirect cost burden of Crohn's disease and ulcerative colitis. J Occup Environ Med 2008;50(11): 1261–72.
- Longobardi T, Jacobs P, Wu L, et al. Work losses related to inflammatory bowel disease in Canada: Results from a national population health survey. Am J Gastroenterol 2003;98(4):844–9.