CADTH

CADTH TECHNOLOGY REVIEW: OPTIMAL USE 360 REPORT

Appropriate Pharmacotherapy for Inflammatory Bowel Disease

Service Line:	Technology Review
Issue:	22
Publication Date:	June 2019
Report Length:	27 Pages

CADTH

Authors: Louis de Léséleuc, Danielle McGolrick

Cite as: *Appropriate pharmacotherapy for inflammatory bowel disease*. Ottawa: CADTH; 2019 Jun. CADTH Technology Review: Optimal Use 360 Report; no. 22).

Acknowledgments: Deba Hafizi, Dave Marchand, Wade Thompson, Calvin Young, Yi-Sheng Chao, Hannah Loshak, Charlene Argáez

ISSN: 2369-7385

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Background

Ulcerative colitis (UC) and Crohn disease (CD) are types of inflammatory bowel disease (IBD); the two are considered distinct from each other. According to Crohn's and Colitis Canada, as of 2018 there were approximately 270,000 Canadians living with IBD. More than 10,200 new cases of IBD are diagnosed every year (5,700 with CD and 4,500 with UC) in the country — an incidence of 0.7%. Approximately 20% to 30% of people with IBD are diagnosed before the age of 20. Canada has one of the highest incidences and prevalences of IBD in the world.[1]

Crohn disease can affect any part of the gastrointestinal tract but most commonly affects the small intestine (predominantly the ileum), ascending colon (i.e., the beginning of the large intestine), and rectum. Common gastrointestinal symptoms include abdominal pain, diarrhea, rectal bleeding, fatigue, vomiting, itchiness or irritation around the anus, flatulence, and bloating. Patients with CD may develop more severe anatomical complications with the formation of intestinal or rectal fistulae and strictures. Patients with fistulizing CD (FCD) are managed differently than those with regular luminal CD (LCD). UC affects the colon and the inflammation leads to diarrhea, pain, and bloody stools. Patients with IBD are at increased risk of developing colon cancer.

Drugs used to treat IBD include aminosalicylates, corticosteroids (CS), thiopurines (azathioprine and 6-mercaptopurine), cyclosporine, methotrexate, and biologics. Biologics used to treat IBD are shown in Table 1. Adalimumab, golimumab, and infliximab are tumour necrosis factor (TNF) antagonists; ustekinumab is an interleukin (IL)-12/IL-23 inhibitor; and vedolizumab binds to integrin alpha-4-beta-7. Drugs may be given for the induction of remission and for maintenance (i.e., prevention of relapse). Biologics or pharmacological immunomodulators (thiopurines, cyclosporine, and methotrexate) are particularly useful when steroids have failed to induce remission (CS resistance), when steroids cannot be tapered without symptom relapse (CS dependence), or to prevent relapse following steroid-induced remission and cessation of steroid use (maintenance). Two broad treatment paradigms can be used to manage IBD. Conventional "step-up" treatment usually entails the sequential use of aminosalicylates, steroids, immunomodulators, and finally biologics, while "top-down" positions biologics (sometimes combined with immunomodulators) as the preferred initial treatment.[2] Figure 1 summarizes the treatment sequences for both "step-up" and "top-down" strategies. Of note, neither biologics nor immunomodulators are indicated as first-line treatments for Crohn disease in Canada.

Table 1: Summary of Health Canada Indications for Biologics for Irritable Bowel Disease

Drug	Adult CD	Pediatric CD	Fistulizing CD	Adult UC	Pediatric UC
adalimumab	√	√	x	√	√
golimumab	x	x	x	√	x
infliximab-biosimilar	√	x	√	√	x
infliximab	√	√	√	√	√
ustekinumab	√	x	x	x	x
vedolizumab	√	x	x	√	x

CD = Crohn disease; UC = ulcerative colitis.

IBD treatment escalation is driven by a suboptimal clinical response to treatment. The assessment of the latter has traditionally relied on symptom reporting by patients. However, the research community see this method as imprecise; it has little impact on the natural history of disease and can lead to delays and suboptimal patient management.[3,4] More reliable, quantitative, and expeditious assessment methods using serum biomarkers, drug trough levels, and/or endoscopic findings are being proposed as alternatives to conventional management. These modern methods and associated decision-making schemes are collectively referred as the "treat-to-target" paradigm.[3]

Policy Issue

While biologics have shown efficacy in the treatment of IBD, their availability by Canadian public drug programs is tightly controlled because of their high cost. All Canadian drug plans require IBD patients to fulfill certain criteria before the reimbursement of biologics is granted, and renewals are also contingent on patient condition and response to treatment. In many cases, Canadian public drug programs require a moderate-to-severe luminal CD or UC patient to have failed therapy with an immunomodulator (e.g., azathioprine, 6-mecaptopurine) after a course of CS before being eligible for reimbursement of a biologic (i.e., biologics are positioned as third-line therapies). For illustrative purposes, Appendix 1 lists the Ontario Public Drug Programs (OPDP) coverage criteria for all biologics available for IBD. Table 2 summarizes these criteria and infers the resulting treatment sequence imposed in clinical practice for patients covered by these programs.

Table 2: Simplified Conceptual Treatment Sequence in Ontario Based on OPDP Biologic Coverage Criteria

	First-Line	Second-Line	Third-Line
Fistulizing CD	Antibiotics or thiopurines	Alternate first-line	Biologics
Luminal CD (moderate-to-severe)	CS[a]	Immunomodulators (thiopurines, methotrexate, cyclosporine)	Biologics
UC (moderate-to-severe)	CS[a]	Thiopurines (for CS-dependent UC) Biologics (for severe CS-resistant UC)	Biologics

CD = Crohn disease; CS = corticosteroids; OPDP = Ontario Public Drug Programs; UC = ulcerative colitis.

[a] While aminosalicylates can be given before CS for moderate-to-severe CD and UC, they are not required by policy prior to biologic initiation.

Emerging evidence suggests that using a biologic early on during the course of the disease (top-down or accelerated step-up approach) may be more effective than conventional treatment.[2] In addition, the Ontario Association of Gastroenterology argues that, in many use cases, immunomodulators (especially thiopurines) are not as effective and safe as once believed and constitute an unnecessary barrier to the optimal care of IBD patients using biologics.[5] Hence, some Canadian public drug plans are reconsidering reimbursement criteria for biologics used in IBD. Canadian jurisdictions have asked CADTH to provide summaries and assessments of the clinical evidence that would be used to support a revision of these criteria.

To help orient research, the following policy questions were submitted:

Policy Question(s)

1. Should reimbursement criteria permit biologic therapy for patients with moderate-to-severe luminal Crohn disease who have not received trials of both glucocorticoids and immunomodulators?
2. Should reimbursement criteria permit first-line biologic therapy for patients with fistulizing Crohn disease?
3. Should reimbursement criteria for biologic therapy for patients with UC include any requirements for prior immunomodulator therapy?

The purpose of this CADTH Technology Review is to summarize the evidence findings regarding drug therapy for IBD as identified by independent CADTH rapid Health Technology Assessment products designed to address the policy questions mentioned previously. It will also provide an additional perspective, including an analysis of international treatment guidelines and further discussion on implications for decision-making in order to assist the translation of current evidence into policy, practice, and future research.

Methods

To answer the policy questions stated in the previous section, CADTH developed a hierarchical, phase-wise research approach.

Phase 1: Treatment sequencing with early introduction of biologics

The policy questions posed in this project can be answered by comparing the clinical and cost-effectiveness of entire IBD treatment algorithms, whereby pharmacotherapy is escalated according to sequences specified a priori. Evidence comparing top-down algorithms that focused on early biologic initiation with conventional (step-up) treatment algorithms was searched, summarized, and assessed. The following research questions (RQ) guided this phase of research:

1. What is the clinical effectiveness and safety of early biologic treatment compared with conventional step-up treatment for luminal CD?
2. What is the cost-effectiveness of early biologic treatment compared with conventional step-up treatment for luminal CD?
3. What is the clinical effectiveness and safety of early biologic treatment compared with conventional step-up treatment for fistulizing CD?
4. What is the cost-effectiveness of early biologic treatment compared with conventional step-up treatment for fistulizing CD?
5. What is the clinical effectiveness and safety of early biologic treatment compared with conventional step-up treatment for UC?
6. What is the cost-effectiveness of early biologic treatment compared with conventional step-up treatment for UC?

As an initial exploratory step, CADTH Rapid Response Reference Lists were prepared for LCD, FCD, and UC (RQ1-2, RQ3-4, RQ5-6, respectively) in order to determine if any evidence could be found to answer these questions.[6-8] When sufficient evidence was found, the rapid review was upgraded to a peer-reviewed summary with critical appraisal.[9,10]

Please see the individual reports for detailed methods and scope. If no clinical and economic evidence was found regarding treatment sequences, research proceeded to the next phase.

Phase 2: Comparison between biologics and immunomodulators

When insufficient evidence comparing treatment sequences was found, a more focused comparison of biologics, immunomodulators, and antibiotics (the latter for FCD, only) was conducted to inform the relative place in therapy of each class. The following RQs guided this phase of research:

1. What is the clinical effectiveness and safety of biologics (with or without concomitant immunomodulators) compared with immunomodulators or antibiotics for the treatment of fistulizing CD?
2. What is the cost-effectiveness of biologics (with or without concomitant immunomodulators) compared with immunomodulators or antibiotics for the treatment of fistulizing CD?
3. What is the clinical effectiveness and safety of biologics (with or without concomitant immunomodulators) compared with immunomodulators for the treatment of UC?
4. What is the cost-effectiveness of biologics (with or without concomitant immunomodulators) compared with immunomodulators for the treatment of UC?

A Rapid Response summary with critical appraisal[10] was prepared to answer questions 1 and 2, and a peer-reviewed summary with critical appraisal[11] was commissioned for questions 3 and 4. See the reports for detailed methods and scope.

Complementary Questions

In addition to the main clinical and economic questions, CADTH conducted supplemental research to identify emerging evidence on treat-to-target approaches applied to IBD management. The following research question was addressed in a Rapid Response summary of abstracts.[12]

1. What is the clinical and cost-effectiveness of treat-to-target management compared with conventional management of IBD?

Finally, to provide a more clinical context, a review of domestic and international evidence-based clinical practice guidelines on the management of CD and UC was conducted. Information on treatment sequences and the place in therapy of various drug classes was extracted from each guideline and summarized in Table 7. The following RQ guided this portion of the project:

1. What are the evidence-based guidelines on the use of biologics in the treatment of CD (including fistulizing CD) and UC?

The methods used to search for guidelines of interest can be found in the Rapid Response Report entitled *Sequencing of Pharmacological Management of Crohn's Disease and Ulcerative Colitis: A Review of Guidelines*.[13]

Findings

Phase 1: Treatment sequencing with early introduction of biologics

The following CADTH Rapid Response reviews were commissioned to address the RQs posed in this research phase:

Early Biologic Treatment versus Conventional Step-Up Treatment for the Management of Fistulizing Crohn's Disease: Comparative Clinical Effectiveness and Cost-Effectiveness

https://www.cadth.ca/early-biologic-treatment-versus-conventional-step-treatment-management-fistulizing-crohns-disease

Early Biologic Treatment versus Conventional Treatment for the Management of Luminal Crohn's Disease: Comparative Clinical Effectiveness and Cost- Effectiveness

https://www.cadth.ca/early-biologic-treatment-versus-conventional-treatment-management-luminal-crohns-disease-comparative

Early Biologic Treatment versus Conventional Treatment for the Management of Crohn's Disease: A Review of Comparative Clinical Effectiveness and Cost-Effectiveness

https://www.cadth.ca/early-biologic-treatment-versus-conventional-treatment-management-crohns-disease-review-comparative

Early Biologic Treatment versus Conventional Step-Up Treatment for the Management of Ulcerative Colitis: Comparative Clinical Effectiveness, Cost- Effectiveness, and Guidelines

https://www.cadth.ca/early-biologic-treatment-versus-conventional-step-treatment-management-ulcerative-colitis

No evidence on early biologic sequencing was identified for FCD or UC.[6,8] As a result, the RQs were not addressed and research was moved to the next phase. For LCD, a number of potentially relevant studies were identified in the report's main section and appendix.[7] This review was therefore upgraded and a full synthesis and critical appraisal of the studies was conducted. Finally, the draft report was peer-reviewed by a clinical expert in the field of gastroenterology.[9] Findings for the latter report are summarized in Table 3 and Table 4.

Table 3: Findings of the Clinical Studies Identified in the Rapid Response Report on LCD

Study	Comparisons	Key Findings
Adults With LCD		
Khanna et al. (2015)[14] RCT N = 1,982	1. ECI algorithm: Upfront CS; anti-TNF combined with immunomodulator upon failure of remission induction with CS 2. Usual care	No significant difference between groups for remission rates or disease scores. No difference in quality of life, mortality, or rate of hospitalization.[a] Statistically significant reduction in rate of complications of CD in the ECI group.[b] Statistically significant reduction in rate of surgery for the ECI group.[b]
D'Haens et al. (2008)[15] RCT N = 133	1. Upfront infliximab combined with azathioprine; CS added if symptoms worsened 2. Usual care	Significantly higher remission rate at both 26 and 52 weeks for ECI versus conventional treatment;[b] but no significant difference at 78 and 104 weeks.[a] Significantly longer time to relapse for ECI.[b] Statistically significantly greater reduction in disease score and improvement in quality of life (10 weeks) for ECI.[b] Endoscopy score and number of ulcers lower in the ECI group.[b] No difference in surgeries or hospitalizations.[a]
Hoekman et al. (2018)[16] Long-term follow-up of RCT (8 years)[15] N = 119	1. Upfront infliximab combined with azathioprine; CS added if symptoms worsened. 2. Usual care	No difference in remission, hospitalization, or surgery rates.[a] No difference in fistula or ulcer development.[a] Statistically longer median time to flare and lower flare rates for ECI.[b] Serious infections more common in the ECI group.[c]
D'Haens (et al.), 2017[17] Prospective registry N = 2,2662	1. Infliximab within 30 days of enrolment visit 2. Conventional therapy: treatment without anti-TNF agents 3. Started with conventional therapy and switched to infliximab during follow-up	Early biologics: increased risk of serious infections and hematological conditions, with no increase in malignancy or lymphoproliferative disorders.[c]
Fan et al. (2014)[18] Prospective study N = 77	1. Upfront infliximab plus azathioprine 2. Prednisone, then azathioprine	Significantly higher proportion of mucosal healing, endoscopic remission, and deep remission for top-down ECI at week 30;[b] but not at week 54 or later [a] Significantly faster clinical remission with ECI.[b]
Ghazi et al. (2013)[19] Retrospective chart review N = 93	1. Upfront anti-TNF 2. Conventional step-up with immunomodulator	No difference in disease activity;[a] statistically greater improvement in symptoms in the anti-TNF group at 3 months;[b] but not at 6 or 12 months.[a] Statistically greater improvement in quality of life for anti-TNF at 6 months;[b] but not at 3 or 12 months.[a] No difference in the number of surgeries.[a] Higher need for hospitalization for early biologic group.[c]
Rubin et al. (2012)[20] Retrospective cohort N = 3,750	1. Upfront anti-TNF (within 30 days) 2. 5-ASA/CS/ immunomodulator, then anti-TNF 3. Immunomodulator, then anti-TNF	Significantly fewer surgeries with upfront anti-TNF.[b]
Children and Adolescents With LCD		
Kang et al. (2016)[21] Prospective study N = 76	1. Induction with infliximab within 1 month of diagnosis, then add azathioprine 2. 5-ASA/CS/AZA, then infliximab if relapse	No significant difference in clinical remission at 1 year.[a] No difference in disease activity.[a] No difference in mucosal healing at week 14;[a] but significantly higher with top-down at week 54.[b] Significantly better endoscopic response (low SES-CD score) with top-down at weeks 14 and 54.[b] No difference in adverse events between groups.[a]

Study	Comparisons	Key Findings
Lee et al. (2015)[22] Retrospective review of a prospective study N = 51	1. Upfront infliximab combined with AZA, 5-ASA, and CS 2. Conventional therapy; infliximab upon relapse	Significantly more (two-fold) patients in ECI group are relapse-free after 1 year versus step-up. Significantly fewer relapses at 2 and 3 years with ECI.[b] No difference in overall adverse events between groups.[a] More leukopenia, nausea, and vomiting in top-down.[c] More pancreatitis in step-up.[b]
Walters et al. (2014)[23] Prospective observational study N = 552	1. Early anti-TNF 2. Early immunomodulator 3. No early immunotherapy	Significantly higher remission rate with early anti-TNF versus other groups at 1 year.[b]
Lee et al. (2012)[24] Retrospective chart review N = 28	1. Upfront infliximab 2. Prednisolone and 5-ASA or AZA, then infliximab	Significantly lower relapse rate at year 2 in the top-down group;[b] but not at 1 and 3 years.[a]
Kim et al. (2011)[25] Retrospective chart review N = 29	1. Upfront infliximab 2. Prednisolone and 5-ASA or AZA, then infliximab	Significantly higher remission rate and lower disease scores with early anti-TNF versus conventional therapy at 8 weeks and 1 year.[b] Significantly greater rate of fistula closure with early anti-TNF.[b] No notable differences in safety between groups.[a]
Lee et al. (2010)[26] Retrospective chart review N = 36	1. Oral prednisolone, then 5-ASA 2. Oral prednisolone, then AZA 3. Infliximab, then infliximab plus AZA	Early infliximab better at preventing relapse (no statistical testing).[a] Fewer adverse events in early biologic group.[a]

5-ASA = 5-aminosalicylic acid; AZA = azathioprine; CD = Crohn disease; CS = corticosteroids; ECI = early combined immunosuppression; LCD = luminal Crohn disease; TNF = tumour necrosis factor; RCT = randomized controlled trial; SES-CD = Simple Endoscopic Score for Crohn Disease.

[a] No significant difference.

[b] Favours early biologic therapy

[c] Favours conventional therapy.

Table 4: Findings of the Economic Studies Identified in the Rapid Response Report on LCD

Study	Comparisons	Key Findings
Marchetti et al. (2013)[27]	1. Top-down therapy 2. Step-up therapy	Top-down therapy improved quality-adjusted life expectancy from 3.76 to 3.90 QALYs, with a cost savings of €773 compared to step-up therapy. 84% of replicates were below a threshold of €20,000/QALY for top-down. Cost-effectiveness of top-down increases over time and becomes dominant at year 5.[a]

LCD = luminal Crohn disease; QALY = quality-adjusted life-year.

[a] Favours early biologic therapy.

Phase 2: Comparison between biologics and conventional therapies for FCD and UC

The following CADTH Rapid Response Summary with Critical Appraisal reports were commissioned to address the RQs posed in this research phase:

Biologics versus Immunomodulators or Antibiotics for the Management of Fistulizing Crohn's Disease: A Review of Comparative Clinical Effectiveness and Cost-Effectiveness

https://www.cadth.ca/biologics-versus-immunomodulators-or-antibiotics-management-fistulizing-crohns-disease-review

Biologics versus Immunomodulators for the Treatment of Ulcerative Colitis: A Review of Comparative Clinical Effectiveness and Cost-Effectiveness

https://www.cadth.ca/biologics-versus-immunomodulators-treatment-ulcerative-colitis-review-comparative-clinical

Findings for the latter reports are summarized in Table 5 and Table 6.

Table 5: Findings of the Clinical Studies Identified in the Rapid Response Reports on FCD and UC

Study	Comparisons	Key Findings
Adults with FCD		
Wu et al. (2016)[28] Open-label RCT N = 42	1. Infliximab 2. Conventional treatment: methylprednisolone and azathioprine All patients received enteral nutrition	Statistically significant improvement in disease scores with infliximab compared with conventional therapy.[a] Significantly more likely to experience fistula healing with infliximab after 30 weeks of treatment (infliximab: 90.0%; conventional: 27.3%).[a] No difference in inflammatory markers.[b]
Adults with UC		
Williams et al. (2016)[29] Open-label RCT N = 270 Severe, CS-resistant UC	1. Infliximab 2. Cyclosporine	No significant difference in quality-adjusted survival, mortality, colectomy rates, time to colectomy, lengths of hospital stay after randomization, severe adverse reactions or severe adverse effects, and quality of life measures.[b] Cyclosporine associated with significantly longer log-transformed hospital stays than infliximab.[a]
Panaccione et al. (2014)[30] Double-blind RCT N = 230	1. Infliximab 2. Azathioprine 3. Infliximab plus azathioprine	Combination of intravenous infliximab and oral azathioprine significantly more effective than infliximab or azathioprine alone in corticosteroid-free remission at week 16.[a] Infliximab plus azathioprine was more effective than azathioprine in mucosal healing but similarly effective as infliximab.[a]

CD= Crohn disease; CS = corticosteroids; FCD = fistulizing Crohn disease; RCT= randomized controlled trial; UC = ulcerative colitis

[a] Favours biologic therapy.

[b] No significant difference.

Table 6: Findings of the Economic Studies Identified in the Rapid Response Report on FCD

Study	Comparisons	Key Findings
Arseneau et al.(2001)[31]	1. 6-MP and metronidazole 2. Initial infliximab induction infusions plus combination with 6-MP and metronidazole if treatment failure 3. Initial infliximab induction infusions with episodic reinfusion if treatment failure	ICER (cost/QALY) relative to 6-MP and metronidazole is $505,796 for first-line infliximab and $513,552 for infliximab episodic reinfusions (expressed as 2017 US dollars, as per Pillai et al. (2017).[32]
Lindsay et al. (2008)[33]	1. Standard care: immunomodulators and/or corticosteroids 2. Infliximab	ICER (cost/QALY) of infliximab relative to standard care is $51,397 (expressed as 2017 US dollars as per Pillai et al. (2017).[32]

6-MP = 6-mercaptopurine; FCD = fistulizing Crohn disease; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Complementary Research

Treat-to-Target

A CADTH Rapid Response summary of abstracts[12] was commissioned to address the following RQs:

1. What is the clinical effectiveness of treat-to-target management compared with conventional management of IBD?
2. What is the cost-effectiveness of treat-to-target management compared with conventional clinical management of IBD?

One randomized controlled trial (the CALM trial[34]) was identified regarding the clinical effectiveness of treat-to-target compared with conventional management of IBD. The authors of this study compared mucosal healing outcomes for patients (N = 122 per group) on a "tight control" algorithm driven by a combination of biomarkers and symptoms with patients managed with a symptoms-based clinical management algorithm. The authors observed that a significantly higher proportion of patients in the tight control group (46%) achieved the primary end point of mucosal healing by the end of the study than those in the clinical management group (30%). The authors suggested that "timely escalation with an antitumour necrosis factor therapy on the basis of clinical symptoms combined with biomarkers in patients with early Crohn's disease results in better clinical and endoscopic outcomes than symptom-driven decisions alone." [34] No economic study was identified.

Guidelines on Treatment Sequencing

Canadian and international evidence-based guidelines on the management of IBD were identified and analyzed. For the complete search methodology, please refer to the CADTH Rapid Response report entitled *Sequencing of Pharmacological Management of Crohn's Disease and Ulcerative Colitis: A Review of Guidelines*.[13] Statements on the recommended pharmacological options were extracted from the guideline documents and used to infer the relative position of drugs in the treatment sequence of IBD. Table 7 summarizes this information, organized by treatment phase (induction, maintenance) and line of therapy. Please see the referred guideline documents for more details and context.

Table 7: Summary of Recommendations for Pharmacological Therapy of Moderate-to-Severe IBD

Title, Guideline Development Group, Year of Publication	Population Relevant to the Recommendations	First-Line Pharmacotherapy for the Induction of Remission	First-Line Pharmacotherapy for the Maintenance of Remission	Second-Line Pharmacotherapy for Induction or Maintenance	Third-Line Pharmacotherapy for Induction or Maintenance
Crohn Disease					
ACG clinical guideline: management of Crohn disease in adults (2018)[35] **Grading[a,b]**	**LUMINAL CD** Adult patients	Oral corticosteroids**†† (*p148*) **Severe/Fulminant disease:** Intravenous corticosteroids*†† (*p502*)	Methotrexate*† (*p499*) Azathioprine, 6-mercaptourine**†† (*p499*) Combination anti-TNF and thiopurines**‡ (*p500*) Vedolizumab*†† (*p506*) Natalizumab*†† (*p506*)	**INDUCTION** Anti-TNF**†† (*p499*) **Severe/Fulminant disease** Anti-TNF agents**†† (*p502*)	**INDUCTION** Ustekinumab**‡ (*p502*)
	FISTULIZING CD Adult patients	Infliximab**†† (*p502*) Adalimumab, certolizumab pegol**† (*p502*) Azathioprine, 6-mercaptopurine**† (*p502*)			
Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn disease (2014)[36] **Grading[c]**	**LUMINAL CD** Patients at risk for poor outcomes unless otherwise indicated	Oral corticosteroids (EL2 – Pediatrics, EL1 – adults, 96% agreement) (*p1183*)	*For steroid-free remission:* Thiopurines (EL2 – Pediatrics, EL1 – Adults, 96% agreement) (*p1185*) Methotrexate (EL4 – Pediatrics, EL1 – Adults, 96% agreement) (*p1187*)	Anti-TNF (EL2, 100% agreement) (*p1188*)	
	FISTULIZING CD Patients at risk for poor outcomes unless otherwise indicated	Antibiotics (EL3 – pediatrics, EL1 – adults, 80% agreement) (*p1184*) **Severe fistulizing disease:** Anti-TNF + antibiotics as adjuvant (EL3, 88% agreement) (*p1184*)	Anti-TNF (EL2, 84% agreement) (*p1188*)	**INDUCTION** Anti-TNF + appropriate surgical intervention (EL2, 84% agreement) (*p1188*)	
3rd European Evidence-based Consensus on the Diagnosis and Management of	Patients with Crohn disease	Steroids with an immunomodulator (*for infrequently relapsing disease)* [EL2] (*p12*)	Thiopurines ((EL1)) or methotrexate ((EL3)) (*p19*) **For immunosuppressive-naive and**	Anti-TNF ± thiopurines (EL1) (*p12, p. 20*) Vedolizumab (EL1) (*p12*)	*When refractory to anti-TNF* Vedolizumab (EL1) (*p12*)

Title, Guideline Development Group, Year of Publication	Population Relevant to the Recommendations	First-Line Pharmacotherapy for the Induction of Remission	First-Line Pharmacotherapy for the Maintenance of Remission	Second-Line Pharmacotherapy for Induction or Maintenance	Third-Line Pharmacotherapy for Induction or Maintenance
Crohn's Disease 2016: Part 1: Diagnosis and Medical Management, ECCO (2017)[37] **Grading**[c]		**Moderate:** Budesonide [EL1], or systemic corticosteroids [EL1] (*p12*) **Severe:** Systemic corticosteroids [EL1] (*p12*)	**corticosteroid-dependent patients:** Thiopurine (EL1) Methotrexate (EL2) Anti-TNF (EL1) (*p19*) **Aggressive/severe disease:** Anti-TNF (EL5) (*p19*)		
NICE/NCGC clinical guideline (CG152): the management of Crohn disease in adults, children, and young people (2013)[38] **Grading**[d]	Adults, children, and young people with Crohn disease Note: The severity of disease for these recommendations is unclear	*For people with a first presentation or a single inflammatory exacerbation of CD in a 12-month period:* Conventional glucocorticosteroid monotherapy (prednisolone, methylprednisolone, or IV hydrocortisone) [Low-, moderate-, high-quality evidence from RCTs and original CE model] (*p197*) Conventional glucocorticosteroids in combination with azathioprine or mercaptopurine [Evidence base: very low-, low- and moderate-quality evidence from RCTs and original CE model] (p. 198), or budesonide [Very low-quality evidence from RCTs and original CE model] (*p198*) **For non-severe disease:** Budesonide [Low-quality evidence from RCTs and original cost-effectiveness model] (*p197*)	Azathioprine or mercaptopurine "particularly for those with adverse prognostic factors such as early age of onset, perianal disease, glucocorticosteroid use at presentation and severe presentations" [Low- and moderate-quality evidence from RCTs and original CE model] (*p199*)	**INDUCTION** **For non-severe disease:** 5-aminosalicylate [Very low-, low-, moderate-, high-quality evidence from RCTs] (*p198*) **MAINTENANCE** Methotrexate [Low-quality evidence from RCTs] (*p199*)	

Title, Guideline Development Group, Year of Publication	Population Relevant to the Recommendations	First-Line Pharmacotherapy for the Induction of Remission	First-Line Pharmacotherapy for the Maintenance of Remission	Second-Line Pharmacotherapy for Induction or Maintenance	Third-Line Pharmacotherapy for Induction or Maintenance
Evidence-based clinical practice guidelines for Crohn disease, integrated with formal consensus of experts in Japan, Japanese Society of Gastroenterology and Research Group of Intractable IBD (2013)[39] **Grading[e] (Recommendation grade, level of evidence; appropriateness of statements)[f]**	Patients (excluding children and elderly) with CD * designed for practice in Japan	Oral steroids (prednisolone) (B, III; 8) (*p54*) **Severe to fulminant CD:** Antimicrobials for signs of infection (C1, VI; 8) (*p54*) IV steroids (prednisolone) if infection is excluded (C1, VI; 8) (*p54*)	Azathioprine (A, I; 9) (p. 58)	**INDUCTION** Anti-TNF agent (A, II; 8) (*p54*) **Severe to fulminant CD:** Anti-TNF (C1, V; 8) (*p54*) **MAINTENANCE** *For anti-TNF induced remission:* Anti-TNF (A, II; 8) (*p58*)	
	Patients (excluding children and elderly) with Crohn disease **FISTULIZING CD**	**Fistulas:** Immunomodulators (A, I; 8) (*p56*) Anti-TNF (A, II; 9) (*p56*) **For perianal fistulas:** Anti-TNF (A, II; 8) (*p55*) Antimicrobial drugs and immunomodulators (A, I; 8) (*p55*)			
Ulcerative Colitis					
***Management of Paediatric Ulcerative Colitis, Part 2: Acute Severe Colitis— an Evidence-based Consensus Guideline From the European Crohn's and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition* (2018)[40]** **Grading[c]**	Children with acute severe ulcerative colitis (ASC)	IV methylprednisolone (EL2, EL1 – adults, 100% agreement) (*p297*)	Thiopurine (after response to IVCS) or mesalamine for rapid response to steroids and mesalamine-naive before admission (EL4, EL3 – Adults, 100% agreement) (*p303*)	**INDUCTION** Infliximab for anti-TNF-naive children [EL3, EL1 – Adults, 100% agreement) (*p300*) **MAINTENANCE** For patients who responded, continue maintenance with infliximab (EL2, EL2 – Adults, 100% agreement) (*p303*) Calcineurin inhibitors (tacrolimus and cyclosporine) (EL4, EL1 – Adults, 100% agreement) (*p300*)	

Title, Guideline Development Group, Year of Publication	Population Relevant to the Recommendations	First-Line Pharmacotherapy for the Induction of Remission	First-Line Pharmacotherapy for the Maintenance of Remission	Second-Line Pharmacotherapy for Induction or Maintenance	Third-Line Pharmacotherapy for Induction or Maintenance
Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care—an Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition **(2018)[41]** **Grading[c]**	Ambulatory children and adolescents with UC	**Systemic moderate disease:** Oral steroids (EL3, EL1 – adults, 100% agreement) Note: may also be considered for not-systemically ill severe disease (*p266*) **Severe UC:** IV steroids [EL2, EL1 – adults, 98% agreement) (*p266*)	5-ASA "Practice point" (93% agreement) *For corticosteroid-dependent or frequent (≥ 2 per year) relapses*: Thiopurines (EL3, EL1 – adults, 98% agreement) (p. 267) **Severe UC:** Thiopurines should be considered following discharge from acute severe colitis episode (EL4, EL3 – adults, 98% agreement) (*p267*)	**INDUCTION and MAINTENANCE** **For chronically active or steroid-dependent UC:** Infliximab (EL2, EL1 – adults, 100% agreement) (*p269*)	**INDUCTION and MAINTENANCE** **For chronically active or steroid-dependant UC:** Adalimumab (EL4, EL4 – adults, or golimumab (EL4, EL3 – adults), with primary non-response to infliximab (95% agreement) (*p269*) Vedolizumab as second-line biologic therapy after anti-TNF failure (EL4, EL2 adults) (95% agreement) (*p269*)
Therapeutic guidelines on ulcerative colitis: a GRADE methodology-based effort of GETECCU, GETECCU, 2013[42] **Grading[a]**	Patients with UC	**Mild-to-moderate flares:** Oral salicylates**‡ and*††/or**‡ topical salicylates *for milder flares* (*p483.e17-18, 25*) Oral steroids**†† (*p483.e19, 25*) *for moderate flares that are close to severe flares* **Severe:** IV steroids**†† (*p483.e8,13*)	**Moderate:** Azathioprine**†† (p. e29, 31)	**INDUCTION** **Moderate, steroid-resistant:** Infliximab**‡ (*p483.e23*) Adalimumab*†† (*p483.e24*) **Severe:** Cyclosporine**†† (*p483.e8,13*) Infliximab**†† (*p483.e10,13*) **MAINTENANCE** **Severe:** Infliximab, *for remission induced with infliximab*†* (*p483.e32*) *If steroid-refractory:* Azathioprine or mercaptopurine, *for remission induced with cyclosporine*†* (*p483.e34*)	**INDUCTION** Tacrolimus*† (*p483.e9*)
Ulcerative colitis: management in adults, children, and young people, NICE and the UK Royal College of Physicians (2013)[43] **Grading[g]**	Adults (18 years or older), children (11 years or younger), and young people (12 to 17 years) with UC	**Acute severe:** IV corticosteroids (*p171*) or IV cyclosporine (if IV corticosteroids not tolerated or contraindicated) (*p171*)	For all extents of disease Azathioprine or oral mercaptopurine (*p241*) Oral aminosalicylates (if azathioprine and 6-mercaptopurine not tolerated or contraindicated) (*p241*)	**INDUCTION** **Acute severe:** Combination: IV cyclosporine and IV corticosteroids (*p171-2*)	**INDUCTION** **Acute severe:** Infliximab (*p172*)

Title, Guideline Development Group, Year of Publication	Population Relevant to the Recommendations	First-Line Pharmacotherapy for the Induction of Remission	First-Line Pharmacotherapy for the Maintenance of Remission	Second-Line Pharmacotherapy for Induction or Maintenance	Third-Line Pharmacotherapy for Induction or Maintenance
***Clinical Practice Guidelines for the Medical Management of Nonhospitalized Ulcerative Colitis: The Toronto Consensus* (2015)[44]** **Grading[c]**	Patients with UC	Oral corticosteroids**† (*p1042*)	Thiopurines, *for oral corticosteroid-induced remission**† (*p1044*) Anti-TNF, *when corticosteroid-dependent*** (very low-quality evidence) (*p 1046*)	**INDUCTION** Anti-TNF**‡ combined with thiopurine or methotrexate**†† (*p1045*) **MAINTENANCE** Anti-TNF *for response to anti-TNF induction*** (very low-quality evidence) (*p1047*)	**INDUCTION** Vedolizumab** or alternative anti-TNF(very low-quality evidence) (*p1048*) Fourth-line Vedolizumab**†† (*p1048*) **MAINTENANCE** Vedolizumab *for vedolizumab-induced remission***†† (*p1049*)

ACG = American College of Gastroenterology; ASA = aminosalicylic acid; CD = Crohn disease; CE = cost-effectiveness; CS = corticosteroids; ECCO = European Crohn's and Colitis Organisation; EL = evidence level; ESPGHAN = European Society for Paediatric Gastroenterology Hepatology and Nutrition; GETECCU = the Spanish Group of Ulcerative Colitis and Crohn disease (Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa); IBD = inflammatory bowel disease; IV = intravenous; NCGC = National Clinical Guideline Centre; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trials; TNF = tumour necrosis factor; UC = ulcerative colitis.

* = conditional/weak recommendation; ** = strong recommendation; † = low level of evidence; †† = moderate level of evidence; ‡ = high level of evidence.

[a] GRADE (Grading of Recommendations Assessment, Development and Evaluation system): The level of evidence could range from "high" (implying that further research was unlikely to change the authors' confidence in the estimate of the effect), "moderate" (further research would be likely to have an impact on the confidence in the estimate of effect), "low" (further research would be expected to have an important impact on the confidence in the estimate of the effect and would be likely to change the estimate), or "very low" (any estimate of effect is very uncertain).

[b] The strength of a recommendation was graded as "strong" when the desirable effects of an intervention clearly outweigh the undesirable effects and as "conditional" when there is uncertainty about the trade-offs.

[c] Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence, where EL1 and EL4 represent a high and low level of evidence, respectively.

[d] Adaptation of GRADE system.

[e] Author-defined: Level I = SRs/MAs of RCTs, II = based on ≥ 1 RCT, III = based on non-RCT, IVa = cohort study; IVb = case-control or cross-sectional study; V = case report or series; VI = expert opinion; Recommendation grading: A = strong recommendation (high level of evidence), B = moderate recommendation (with certain level of evidence), C1 = recommendation to be done (without high level of evidence), C2 = recommendation not to be done (without a high level of evidence), D = recommendation not to be done (evidence indicates ineffective or harm).

[f] "The Assessment Committee and three external members evaluated the appropriateness of the statements of recommendation on a 1 to 9 scale (from 1 equalling ''most inappropriate'' to 9 equalling ''most appropriate'') according to the Delphi method. The final results after three Delphi rounds were reflected in the adoption of the statements of recommendation and the determination of the grades of recommendation."

[g] Recommendations were not graded, but the evidence used to generate the recommendations were assessed via GRADE and ratings ranged from "very low" to "moderate" quality (for induction) and "very low" to "low" (for maintenance).

Implications for Decision-Making

Luminal Crohn Disease

A good amount of evidence was identified on treatment sequencing for LCD in adults. While disparities in trial design preclude making definite conclusions on early biologic treatment as a clear and well-defined approach, some trends can be observed. Studies generally showed that clinical improvement is faster with a top-down approach than with conventional therapy. Higher remission rates are achieved with early biologics at early time points (three to six months), while similar rates are ultimately achieved at later time points. A faster remission may reduce the risk of complications and surgeries as seen in the REACT trial[14] and the cohort study reported by Rubin et al.[20] When accounting for the higher cost of biologics, the afforded benefits of a top-down strategy were considered cost-effective compared with conventional step-up therapy according to a UK study.[27] Most recent evidence-based guidelines now recommend anti-TNF (combined or not with immunomodulators) relatively early in the treatment course, generally following corticosteroids for moderate-to-severe CD, or upfront in fulminant or severe cases.

To further confirm the relative position of biologics in the treatment sequence of LCD, one may consider a review of the evidence featuring head-to-head comparisons between biologics and immunomodulator monotherapy. For example, studies such as the SONIC trial[45] have shown superiority of infliximab over immunomodulators in corticosteroid-free remission and mucosal healing. Findings from this trial together with sequencing evidence are consistent with the notion that biologics are more effective than other therapies at promoting healing of the inflamed gut tissue, an outcome that was suggested to be a reliable predictor of sustained disease control.[46]

Clinical evidence regarding treatment sequencing in pediatric LCD is limited to observational studies. Five of the six included studies were conducted in Korea and included fewer than 100 patients. These studies found that early biologics were significantly more effective than conventional sequencing by at least one measure (e.g., remission rate, relapse rate, endoscopic score, disease score), but results were largely inconsistent across studies, which could be explained by differences in the types of drug interventions and populations under study. A larger prospective study (the RISK study, N = 552)[23] conducted in Canada and the US found significantly higher remission rates with early anti-TNF compared with a conventional approach. The guidelines on pediatric CD identified in this report,[36,38] both from European organizations and published in 2013-2014, did not recommend early biologic initiation.

In Canada, biologics are not approved for first-line use in LCD, prior to CS. To conform to regulatory indications, early biologic algorithms would have to incorporate a step involving the induction of remission with CS. On the other hand, Health Canada-approved indications for biologics do not require an inadequate response with both CS and immunomodulators prior to the prescription of a biologic for CD.[47-50]

While early biologic use in moderate-to-severe LCD may be considered cost-effective, a policy permitting this approach would lead to more frequent biologic use, increasing the burden on drug budgets. The policy's net budget impact will depend on the number of CD patients who are managed with immunomodulators under the current model without ultimately requiring biologics, as these individuals would be offered biologics as the default option.

Fistulizing Crohn Disease

No trial on the sequencing of interventions for FCD was identified. While the REACT[14] trial included patients with fistulae, these were not analyzed in a subgroup and no FCD-specific outcomes were reported. A subsequent review of the literature found a dearth of direct or indirect comparative evidence on FCD. A single, small, clinical trial found better outcomes with infliximab compared with conventional therapy using azathioprine. No evidence comparing biologics to antibiotics was identified. Consistent with this poor yield, recent systematic reviews with broad search parameters failed to identify comparative studies on FCD.[51-54] Economic studies comparing infliximab to immunomodulators and antibiotics were dated and their findings were inconsistent. There was no evidence specifically on the pediatric population.

When taking stock of the scarcity of comparative evidence in the FCD literature, it should be noted that meta-analyses of placebo-controlled trials found no significant benefit from immunomodulators for the induction of fistula closure and no convincing evidence for the maintenance of fistula response.[52,54] Biologics, however, were found to be effective for both aspects.[55-57] These non-comparative data were outside the scope of the CADTH rapid review yet may have implications regarding the appropriateness of using immunomodulators for the management of FCD.

Evidence-based guidelines identified in this report recommend anti-TNF as a first-line option for FCD. In Canada, infliximab is the only biologic with a specific indication for the "treatment of fistulising Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment."[47] Nevertheless, other biologics (vedolizumab and adalimumab) are also reimbursed by Canadian drug plans for FCD patients of all ages, in addition to infliximab.[58] In all cases, biologics are not currently approved for the first-line treatment of FCD in Canada.[47-50]

The proportion of FCD patients who are successfully managed with immunomodulators or antibiotics without needing biologics is unknown. Consequently, the budget impact of a potential expansion of the biologic reimbursement criteria is unclear but should be relatively small given the low prevalence of FCD.[59]

Ulcerative Colitis

Unlike for LCD, no trial on drug sequencing with the early use of biologics was identified for UC, indicating that this concept is not as widespread in UC. A review of studies comparing biologics with immunomodulators in the same population identified two medium-size RCTs. The article by Williams et al. (the CONSTRUCT study)[29] reported no substantial difference between infliximab and cyclosporine regarding multiple outcomes. However, the study suffered from methodological limitations because of the absence of blinding in both patients and assessors, which may introduce bias. The relevance of these findings in the Canadian context is unclear given that cyclosporine is not recommended by a Canadian guideline on UC[44].

The study reported by Panaccione et al. (UC-SUCCESS)[30] was deemed of good quality and enrolled adult UC patients who were stabilized on, but had an inadequate response to, CS after three months — that is, CS-dependent patients. The authors found that infliximab (alone or combined with azathioprine) yielded better clinical outcomes than azathioprine monotherapy. Notably, mucosal healing was significantly better with infliximab. While these findings would lend support to changes in policy and practice toward the earlier use of

biologics (without the requirement for a trial of azathioprine), they emanate from a single trial of moderate size. More evidence may be needed to confirm these findings. A review of non-randomized studies may help complement this evidence base. This literature should also include pediatric patients, which were excluded from both comparative studies. Finally, the cost-effectiveness of using biologics instead of (or in addition to) immunomodulators in steroid-dependent UC patients should be assessed.

Most evidence-based UC guidelines recommend anti-TNF agents in cases where induction of remission has failed with CS, in line with the findings from the UC-SUCCESS trial. Guidelines still generally recommend the use of immunomodulators for the maintenance of CS-induced remission. No evidence comparing biologics to immunomodulators in the maintenance phase of steroid-induced remission was identified in the CADTH review. According to Health Canada-approved product monographs, the use of biologics for UC is indicated after "inadequate response" to a conventional drug class (CS or immunomodulators) but not necessarily the failure of both.[47-49,60]

The potential budget impact of accelerating access to biologics in UC largely rests on the number of patients who are CS-dependent and who would have benefited from immunomodulators without requiring a switch to biologics to achieve CS-free remission.

Policy Options

Condition	Option	Considerations
Adult LCD	1. Permit early biologic initiation after CS use, without the requirement for a trial of immunomodulators	Evidence suggests faster remission with fewer complications. An economic study suggests top-down is cost-effective.
	2. No change to the existing reimbursement criteria; biologics would continue to be reimbursed after trial of BOTH immunomodulators and CS	Existing criteria is not aligned with guidelines.
Pediatric LCD	1. Permit early biologic initiation after CS use, without the requirement for a trial of immunomodulators	There is weak, observational evidence to support early biologic sequence. Extrapolation of adult evidence may need validation.
	2. No change to the existing reimbursement criteria; biologics would continue to be reimbursed after trial of *both* immunomodulators and CS	
Adult FCD	1. Permit first-line biologic treatment	This is in line with guidelines but not with Health Canada-approved indications. Evidence suggests a low efficacy of immunomodulators. There is no evidence on antibiotics.
	2. No change to the existing reimbursement criteria; biologics would continue to be reimbursed after trial of *both* immunomodulators and antibiotics	
Pediatric FCD	1. Permit first-line biologic treatment	No comparative evidence was identified in the pediatric population. There is no Health Canada-approved indication for FCD in the pediatric population.
	2. No change to the existing reimbursement criteria; biologics would continue to be reimbursed after trial of *both* immunomodulators and antibiotics	
Adult UC	1. Permit early biologic initiation after CS use, without the requirement for a trial of immunomodulator if CS-dependent	A single trial suggests that azathioprine is inferior to infliximab (± azathioprine) for the induction of CS-free remission.

Condition	Option	Considerations
	2. No change to the existing reimbursement criteria; biologics would continue to be reimbursed for induction of steroid-free remission after trial of immunomodulators if CS-dependent	A single trial suggests equal benefits from cyclosporine and infliximab.
Pediatric UC	1. Permit early biologic initiation after CS use, without the requirement for a trial of immunomodulator if CS-dependent	No comparative evidence was identified in the pediatric population.
	2. No change to the existing reimbursement criteria; biologics would continue to be reimbursed for induction of steroid-free remission after trial of immunomodulators if CS-dependent	

CS = corticosteroid; FCD = fistulizing Crohn disease; LCD = luminal Crohn disease; UC = ulcerative colitis.

References

1. Crohn's and Colitis Canada. Impact of inflammatory bowel disease in Canada. Toronto (ON): Crohn's and Colitis Canada; 2018: http://crohnsandcolitis.ca/Crohns_and_Colitis/documents/reports/2018-Impact-Report-LR.pdf. Accessed 2019 Jan 29.
2. Tsui JJ, Huynh HQ. Is top-down therapy a more effective alternative to conventional step-up therapy for Crohn's disease? *Ann Gastroenterol.* 2018;31(4):413-424.
3. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol.* 2015;110(9):1324-1338.
4. Ungaro R, Colombel JF, Lissoos T, Peyrin-Biroulet L. A treat-to-target update in Ulcerative Colitis: a systematic review. *Am J Gastroenterol.* 2019 Mar.
5. Ontario Association of Gastroenterologists consensus statement on the Ontario reimbursement criteria for biologic therapies in inflammatory bowel disease. Markham (ON): Ontario Association of Gastroenterology; 2016: https://www.gastro.on.ca/sites/default/uploads/files/IBD-Consensus-Document-2016-09-08-Final.pdf. Accessed 2018 Oct 24.
6. Marchand D, Argáez C. Early biologic treatment versus conventional step-up treatment for the management of fistulizing Crohn's disease: comparative clinical effectiveness and cost-effectiveness. Ottawa (ON): CADTH; 2018 Nov: https://www.cadth.ca/sites/default/files/pdf/htis/2019/RA0985%20Early%20Biologics%20Crohn%27s%20Final.pdf. Accessed 2019 Apr 15.
7. Marchand D, Argáez C. Early biologic treatment versus conventional treatment for the management of luminal Crohn's disease: comparative clinical effectiveness and cost-effectiveness. Ottawa (ON): CADTH; 2018 Nov: https://www.cadth.ca/sites/default/files/pdf/htis/2019/RA0986%20Early%20Biologics%20Luminal%20Crohn%E2%80%99s%20Final.pdf. Accessed 2019 Apr 15.
8. Marchand D, Argáez C. Early biologic treatment versus conventional step-up treatment for the management of Ulcerative Colitis: comparative clinical effectiveness, cost-effectiveness, and guidelines. Ottawa (ON): CADTH; 2018 Nov: https://www.cadth.ca/sites/default/files/pdf/htis/2019/RA0987%20Early%20Biologics%20UC%20Final.pdf. Accessed 2019 Apr 15.
9. Thompson W, Argáez C. Early biologic treatment versus conventional treatment for the management of Crohn's disease: a review of comparative clinical effectiveness and cost-effectiveness. Ottawa (ON): CADTH; 2019 Feb: https://www.cadth.ca/sites/default/files/pdf/htis/2019/RD0050%20Early%20Biologics%20Crohn%27s%20Final.pdf. Accessed 2019 Apr 15.
10. Young C, Campbell K. Biologics versus immunomodulators or antibiotics for the management of fistulizing Crohn's disease: a review of comparative clinical effectiveness and cost-effectiveness. Ottawa (ON): CADTH; 2019 Mar: https://www.cadth.ca/sites/default/files/pdf/htis/2019/RC1107%20Fistulizing%20CD%20Final.pdf. Accessed 2019 Apr 15.
11. Chao Y-S, Loshak H. Biologics versus immunomodulators for the treatment of ulcerative colitis: a review of comparative clinical effectiveness and cost-effectiveness. Ottawa (ON): CADTH; 2019 Apr: https://cadth.ca/sites/default/files/pdf/htis/2019/RD0052%20Biologics%20UC%20Final.pdf Accessed 2019 Apr 15.
12. Hafizi D, Argáez C. Treat-to-target versus conventional management of inflammatory bowel disease: clinical effectiveness and cost-effectiveness. Ottawa (ON): CADTH; 2019 Feb: https://www.cadth.ca/sites/default/files/pdf/htis/2019/RB1311%20TtT%20IBD%20Final.pdf. Accessed 2019 Apr 15.
13. Ho C, Argáez C. Sequencing of pharmacological management of Crohn's disease and Ulcerative Colitis: a review of guidelines. Ottawa (ON): CADTH; 2019 Jan: https://www.cadth.ca/sites/default/files/pdf/htis/2019/RC1065%20Early%20Biologics%20Guidelines%20Final%20-%20revised.pdf. Accessed 2019 Apr 15.
14. Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet.* 2015;386(10006):1825-1834.
15. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet.* 2008;371(9613):660-667.
16. Hoekman DR, Stibbe JA, Baert FJ, et al. Long-term outcome of early combined immunosuppression versus conventional management in newly diagnosed Crohn's Disease. *J Crohn Colitis.* 2018;12(5):517-524.
17. D'Haens G, Reinisch W, Colombel JF, et al. Five-year safety data From ENCORE, a European observational safety registry for adults with Crohn's Disease treated with infliximab [Remicade] or conventional therapy. *J Crohn Colitis.* 2017;11(6):680-689.
18. Fan R, Zhong J, Wang ZT, Li SY, Zhou J, Tang YH. Evaluation of "top-down" treatment of early Crohn's disease by double balloon enteroscopy. *World J Gastroenterol.* 2014;20(39):14479-14487.
19. Ghazi LJ, Patil SA, Rustgi A, Flasar MH, Razeghi S, Cross RK. Step up versus early biologic therapy for Crohn's disease in clinical practice. *Inflamm Bowel Dis.* 2013;19(7):1397-1403.
20. Rubin D, Uluscu O, Sederman R. Response to biologic therapy in Crohn's disease is improved with early treatment: an analysis of health claims data. *Inflamm Bowel Dis.* 2012;18(12):2225-2231.
21. Kang B, Choi S, Kim H, Kim K, Lee Y, Choe Y. Mucosal healing in paediatric patients with moderate-to-severe luminal Crohn's Disease under combined immunosuppression: escalation versus early treatment. *J Crohn Colitis.* 2016;10(11):1279-1286.
22. Lee Y, Kang B, Lee Y, Kim M, Choe Y. Infliximab "top-down" strategy is superior to "step-up" in maintaining long-term remission in the treatment of pediatric Crohn Disease. *J Ped Gastroenterol Nutr.* 2015;60(6):737-743.

23. Walters TD, Kim MO, Denson LA, et al. Increased effectiveness of early therapy with anti-tumor necrosis factor-alpha vs an immunomodulator in children with Crohn's disease. *Gastroenterology.* 2014;146(2):383-391.

24. Lee Y, Baek S, Kim M, Lee Y, Lee Y, Choe Y. Efficacy of early infliximab treatment for pediatric Crohn's Disease: a three-year follow-up. *Ped Gastroenterol Hepatol Nutr.* 2012;15(4):243-249.

25. Kim M, Lee J, Lee J, Kim J, Choe Y. Infliximab therapy in children with Crohn's disease: a one-year evaluation of efficacy comparing 'top-down' and 'step-up' strategies. *Acta Paediatr.* 2011;100(3):451-455.

26. Lee J, Lee J, Lee H, Kim M, Choe Y. Efficacy of early treatment with infliximab in pediatric Crohn's disease. *World J Gastroenterol.* 2010;16(14):1776-1781.

27. Marchetti M, Liberato N, Di Sabatino A, Corazza G. Cost-effectiveness analysis of top-down versus step-up strategies in patients with newly diagnosed active luminal Crohn's disease. *Eur J Health Economics.* 2013;14(6):853-861.

28. Wu XL, Chen RP, Tao LP, Wu JS, Chen XR, Chen WC. Infliximab combined with enteral nutrition for managing Crohn's disease complicated with intestinal fistulas. *Gastroenterol Res Pract.* 2016;2016:5947926.

29. Williams JG, Alam MF, Alrubaiy L, et al. Comparison Of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: pragmatic randomised Trial and economic evaluation (CONSTRUCT). *Health Technol Assess.* 2016;20(44):1-320.

30. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology.* 2014;146(2):392-400.e393.

31. Arseneau KO, Cohn SM, Cominelli F, Connors AF, Jr. Cost-utility of initial medical management for Crohn's disease perianal fistulae. *Gastroenterol.* 2001;120(7):1640-1656.

32. Pillai N, Dusheiko M, Burnand B, Pittet V. A systematic review of cost-effectiveness studies comparing conventional, biological and surgical interventions for inflammatory bowel disease. *PLoS One.* 2017;12(10):e0185500.

33. Lindsay J, Punekar YS, Morris J, Chung-Faye G. Health-economic analysis: cost-effectiveness of scheduled maintenance treatment with infliximab for Crohn's disease--modelling outcomes in active luminal and fistulizing disease in adults. *Aliment Pharmacol Ther.* 2008;28(1):76-87.

34. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet.* 2018;390(10114):2779-2789.

35. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol.* 2018;113(4):481-517.

36. Ruemmele FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis.* 2014;8(10):1179-1207.

37. Gomollon F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis.* 2017;11(1):3-25.

38. Mayberry JF, Lobo A, Ford AC, Thomas A. NICE clinical guideline (CG152): the management of Crohn's disease in adults, children and young people. *Aliment Pharmacol Ther.* 2013;37(2):195-203.

39. Ueno F, Matsui T, Matsumoto T, et al. Evidence-based clinical practice guidelines for Crohn's disease, integrated with formal consensus of experts in Japan. *J Gastroenterol.* 2013;48(1):31-72.

40. Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of Paediatric Ulcerative Colitis, Part 2: Acute Severe Colitis; An Evidence-based Consensus Guideline from ECCO and ESPGHAN. *J Pediatr Gastroenterol Nutr.* 2018;30:30.

41. Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care- an Evidence-Based Guideline from ECCO and ESPGHAN. *J Pediatr Gastroenterol Nutr.* 2018;30:30.

42. Gomollon F, Garcia-Lopez S, Sicilia B, Gisbert JP, Hinojosa J, Grupo Espa~nol de Trabajo en Enfermedad de Crohn y Colitis U. Therapeutic guidelines on ulcerative colitis: a GRADE methodology based effort of GETECCU. *Gastroenterol Hepatol.* 2013;36(2):104-114.

43. National Clinical Guideline Centre. National Institute for Health and Care Excellence: Guidance. *Ulcerative colitis: management in adults, children and young people*. London: Royal College of Physicians (UK), National Clinical Guideline Centre; 2013 Jun.

44. Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology.* 2015;148(5):1035-1058.e1033.

45. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's Disease. *New England J Med.* 2010;362:1383-1395.

46. Baert F, Moortgat L, Van Assche G, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterol.* 2010;138(2):463-468; quiz e410-461.

47. Remicade (infliximab): powder for solution, sterile, lyophilized, 100 mg/vial - biological response modifier [product monograph]. Toronto (ON): Janssen Inc; 2018 May 25: https://pdf.hres.ca/dpd_pm/00045351.PDF.

48. Humira (adalimumab): 40 mg in 0.8 mL sterile solution (50 mg/mL) subcutaneous injection, 10 mg in 0.1 mL sterile solution (100 mg/mL) subcutaneous injection, 20 mg in 0.2 mL sterile solution (100 mg/mL) subcutaneous injection, 40 mg in 0.4 mL sterile solution (100 mg/mL) subcutaneous injection, 80 mg in 0.8 mL sterile solution (100 mg/mL) subcutaneous injection [product monograph]. St. Laurent (QC): AbbVie Corporation; 2018 Mar 26: https://pdf.hres.ca/dpd_pm/00044463.PDF.

49. Entyvio (vedolizumab): powder for concentrate for solution for infusion [product monograph]. Oakville (ON): Takeda Canada Inc.; 2016 Mar 15: https://pdf.hres.ca/dpd_pm/00034239.PDF.

50. Stelara (ustekinumab): solution for subcutaneous injection, 45 mg/0.5 mL, 90 mg/1.0 mL; Stelara I.V. (ustekinumab): solution for intravenous infusion, 130 mg/26 mL (5 mg/mL) [product monograph]. Toronto (ON): Janssen Inc.; 2018 Nov 09: https://pdf.hres.ca/dpd_pm/00048246.PDF.

51. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev.* 2015(10):Cd000067.

52. Chande N, Townsend CM, Parker CE, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev.* 2016;10:Cd000545.

53. McDonald JW, Wang Y, Tsoulis DJ, MacDonald JK, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. *Cochrane Database Syst Rev.* 2014(8):Cd003459.

54. Lee MJ, Parker CE, Taylor SR, et al. Efficacy of medical therapies for fistulizing Crohn's disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2018 Dec;16(12):1879-1892.

55. Panes J, Reinisch W, Rupniewska E, et al. Burden and outcomes for complex perianal fistulas in Crohn's disease: systematic review. *World J Gastroenterol.* 2018;24(42):4821-4834.

56. Fu YM, Chen M, Liao AJ. A meta-analysis of adalimumab for fistula in Crohn's disease. *Gastroenterol Res Pract.* 2017;2017:1745692.

57. Zaboli P, Abdollahi M, Mozaffari S, Nikfar S. Tumor necrosis factor-alpha antibodies in fistulizing Crohn's disease: an updated systematic review and meta-analysis. *J Res Pharm Pract,.* 2017;6(3):135-144.

58. Government of Ontario. Exceptional Access Program(EAP): EAP reimbursement criteria for frequently requested drugs. Toronto (ON): Ministry of Health and Long-Term Care, Government of Ontario; 2019 Mar: http://www.health.gov.on.ca/en/pro/programs/drugs/pdf/frequently_requested_drugs.pdf. Accessed 2019 Apr 15.

59. Schwartz D, Tagarro I, Díez M, Sandborn W. Prevalence of fistulizing Crohn's disease in the United States: estimate from a systematic literature review attempt and population-based database analysis. *Inflamm Bowel Dis.* 2019 Apr;izz056.

60. Simponi (golimumab injection): solution for subcutaneous injection, 50 mg/0.5 mL, 100 mg/1.0 mL; Simponi I.V. (golimumab for injection): solution for intravenous infusion, 50 mg/4.0 mL, tumour necrosis factor alpha (TNFα) inhibitor [product monograph]. Toronto (ON): Janssen Inc.; 2018 Nov 06: https://pdf.hres.ca/dpd_pm/00048170.PDF.

61. Government of Ontario. Ontario drug benefit formulary/Comparative drug index. 2018 Nov; https://www.formulary.health.gov.on.ca/formulary. Accessed 2019 Apr 15.

Appendix 1: Ontario Public Drug Programs Reimbursement Criteria for Inflammatory Bowel Disease Biologics

Information taken from Ontario Drug Benefit Formulary[61] for infliximab and Ontario Ministry of Health and Long-Term Care Exceptional Access Program's Reimbursement Criteria for Frequently Requested Drugs[58] for adalimumab, golimumab, and vedolizumab.

Product Name (BRAND, generic)	Dosage Form and Strength	Reimbursement Criteria	Standard Approval Duration
Perianal and Fistulizing Crohn Disease			
INFLECTRA, infliximab	100 mg/10 mL IV infusion	**Treatment of fistulizing CD** in patients who have: • actively draining perianal or enterocutaneous fistula(e) that have recurred or persisted despite a course of antibiotic therapy (ciprofloxacin and/or metronidazole) AND immunosuppressive therapy (azathioprine or 6-mercaptopurine). *Note: any intolerance(s) or contraindication(s) to treatment with required alternative(s) must be described in detail.* **Maintenance/renewal** is funded for patients who meet the Ministry initiation criteria for fistulizing Crohn disease and who have demonstrated benefit from treatment (e.g., partial resolution of fistulae and symptom improvement). The recommended dosing regimen is 5mg/kg/dose every 8 weeks.	Authorization period: 1 year
HUMIRA, adalimumab	40 mg/0.8 mL pre-filled syringe and 40 mg/0.8 mL pre-filled pen for SC injection	**For the treatment of fistulizing CD with concomitant luminal disease in patients who meet the following criteria:** • patients with actively draining perianal or enterocutaneous fistula(e) that have recurred or persisted despite a course of appropriate antibiotic therapy (e.g., ciprofloxacin and/or metronidazole) AND immunosuppressive therapy (e.g., azathioprine or 6-mercaptopurine) AND • HBI score ≥ 7. The dose that will be considered is adalimumab (HUMIRA®) 160 mg at week 0, 80 mg at week 2, followed by 40 mg every 2 weeks. **Renewal** will be considered based on the response to therapy.	Initial: 3 months

Product Name (BRAND, generic)	Dosage Form and Strength	Reimbursement Criteria	Standard Approval Duration
		The dose that will be considered on renewals is adalimumab (HUMIRA) 40 mg every two weeks. All requests for higher doses will not be approved.	Renewal: 3 months to 1 year pending fistula resolution Second renewal: 2 years for second renewal of requests with complete resolution Case-by-case duration for renewal of requests with partial resolution
ENTYVIO, vedolizumab	300 mg injection	**For the treatment of fistulizing Crohn disease with concomitant luminal disease in patients who meet the following criteria:** • patients with actively draining perianal or enterocutaneous fistula(e) that have recurred or persist despite a course of appropriate antibiotic therapy (e.g., ciprofloxacin and/or metronidazole) AND immunosuppressive therapy (e.g., AZA or 6-MP) AND • HBI score ≥ 7. **Renewal** will be considered based on the response to therapy. The dose that will be considered on renewals is 300 mg every eight weeks.	Initial Approval: 6 months at 300 mg initially administered at week 0, followed by 300 mg at week 2, 300 mg at week 6, then 300 mg every 8 weeks thereafter First renewal: 6 months to 1 year pending fistula(e) resolution Second and subsequent renewals: 2 years with complete resolution Case-by-case duration for renewal of requests with partial resolution
Luminal CD			
INFLECTRA, infliximab	100 mg/10 mL IV infusion	Treatment of **moderate-to-severe luminal CD** in patients who have: • HBI score ≥ 7; AND • Failed to respond to conventional treatment with glucocorticoids (prednisone 40 mg/day or equivalent) for at least 2 weeks or dose cannot be tapered to below prednisone 20 mg/day or equivalent; AND • Failed to respond to an immunosuppressive agent (azathioprine, 6-mercaptopurine, methotrexate, or cyclosporine) tried for at least 3 months.	Authorization period: 1 year

Product Name (BRAND, generic)	Dosage Form and Strength	Reimbursement Criteria	Standard Approval Duration
HUMIRA, adalimumab	40 mg/0.8 mL pre-filled syringe and 40 mg/0.8 mL pre-filled pen for SC injection	*Note: any intolerance(s) or contraindication(s) to treatment with required alternative(s) must be described in detail.* **Maintenance/ Renewal:** Maintenance therapy is funded for patients who meet the Ministry initiation criteria and whose disease is maintained with a 50% reduction in the HBI from pre-treatment measurement, AND improvement of symptoms (e.g., absence of bloody diarrhea, weight is stable or increased), AND the use of corticosteroids and/or other immunosuppressive therapy is reduced, being tapered, or discontinued. The planned dosing regimen for the requested biologic should be provided. The recommended doses for the treatment of CD are, as follows: • infliximab: 5 mg/kg/dose at 0, 2, and 6 weeks, then 5 mg/kg/dose every 8 weeks • adalimumab: 160 mg at week 0; 80 mg at week 2; followed by 40 mg every 2 weeks. • vedolizumab: 6 months at 300 mg initially administered at week 0, followed by 300 mg at week 2, 300 mg at week 6, then 300 mg every 8 weeks thereafter.	
ENTYVIO, vedolizumab	300 mg injection		
Ulcerative Colitis			
INFLECTRA, infliximab	100 mg/10 mL IV infusion	**Treatment of UC disease** in patients who meet the following criteria: **Induction** **1. Moderate disease** a. Mayo score between 6 and 10 (inclusive) AND b. Endoscopic subscore of 2 AND	Authorization period: 1 year

Product Name (BRAND, generic)	Dosage Form and Strength	Reimbursement Criteria	Standard Approval Duration
HUMIRA, adalimumab	40 mg/0.8 mL pre-filled syringe and 40 mg/0.8 mL pre-filled pen for SC injection	c. Stabilized with 2 weeks oral prednisone at daily doses ≥ 40 mg (or 1 week of IV equivalent) but demonstrated that the corticosteroid dose cannot be tapered despite 3 months of AZA/6MP (or where the use of immunosuppressants is contraindicated). **2. Severe disease** a. Mayo score > 10, AND b. Endoscopy subscore ≥ 2, AND c. Failed 2 weeks of oral prednisone ≥ 40 mg (or 1 week IV equivalent), OR d. Stabilized with 2 weeks of oral prednisone ≥ 40 mg (or 1 week of IV equivalent), but the prednisone dose cannot be tapered despite 3 months of AZA/6MP (or where the use of immunosuppressants is contraindicated). **Maintenance** Maintenance therapy is funded for patients who meet the Ministry initiation criteria and whose disease is maintained at a Mayo score of < 6 AND who demonstrate at least 50% reduction in the dose of prednisone compared with the starting dose following the first 6 months of treatment or be off corticosteroids after the first year of treatment.	Renewal: Adalimumab, golimumab, vedolizumab: 2 years
ENTYVIO, vedolizumab	300 mg injection		
SIMPONI, golimumab	50 mg/0.5 mL pre-filled syringe OR auto-injector, 100 mg/ mL		

6MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; CD = Crohn disease; HBI = Harvey Bradshaw Index; IV = intravenous; OPDP = Ontario Public Drug Plan; SC = subcutaneous.