

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

# Therapeutic Drug Monitoring for Patients with Inflammatory Bowel Disease: Clinical Effectiveness and Guidelines

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## Research Questions

1. What is the clinical effectiveness of therapeutic drug monitoring-guided dosing of biologic medications for patients with inflammatory bowel disease?
2. What are the evidence-based guidelines regarding the use of therapeutic drug monitoring of biologic medication levels, and associated dosage adjustments, for patients with inflammatory bowel disease?

## Key Findings

One systematic review with meta-analysis, one randomized controlled trial, and two non-randomized studies were identified regarding the clinical effectiveness of therapeutic drug monitoring-guided dosing of biologic medications for patients with inflammatory bowel disease. Additionally, three evidence-based guidelines were identified.

## Methods

A limited literature search was conducted on key resources including PubMed in Process, Medline via Ovid, Embase via Ovid, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2016 and March 22, 2018. Internet links were provided, where available.

## Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Patients of any age with inflammatory bowel disease (Crohn's disease or ulcerative colitis) receiving induction or maintenance therapy with biologic medications (adalimumab, infliximab, golimumab, ustekinumab, vedolizumab, certolizumab pegol)
<b>Interventions</b>	<ul style="list-style-type: none"> <li>• Reactive therapeutic drug monitoring (i.e., to guide treatment changes for patients with inadequate response to current treatment regimens)</li> <li>• Routine therapeutic drug monitoring (i.e., to proactively monitor response to treatment, regardless of clinical status)</li> </ul>
<b>Comparators</b>	Q1: <ul style="list-style-type: none"> <li>• No therapeutic drug monitoring</li> <li>• Empiric dose changes</li> <li>• Switching therapy</li> </ul> Q2: No comparator
<b>Outcomes</b>	Q1: Clinical benefits and harms (e.g., adequate response to therapy, remission, low disease activity, adverse events) Q2: Recommendations for the use of therapeutic drug monitoring, including defined therapeutic drug levels for biologic agents in inflammatory bowel disease patients that can be used to inform dosage adjustments

**Table 1: Selection Criteria****Study Designs**

Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

**Results**

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

One systematic review with meta-analysis, one randomized controlled trial, and two non-randomized studies were identified regarding the clinical effectiveness of therapeutic drug monitoring-guided dosing of biologic medications for patients with inflammatory bowel disease. Additionally, three evidence-based guidelines were identified. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

**Overall Summary of Findings**

One systematic review (SR) with meta-analysis (MA),<sup>1</sup> one randomized controlled trial (RCT),<sup>2</sup> and two non-randomized studies (NRS)<sup>3-5</sup> were identified regarding the clinical effectiveness of therapeutic drug monitoring-guided dosing of biologic medications for patients with inflammatory bowel disease (IBD). Detailed study characteristics are provided in Table 2.

The SR<sup>1</sup> evaluated the clinical and cost-effectiveness of therapeutic drug monitoring (TDM) of tumour necrosis factor (TNF) alpha inhibitors in patients with Crohn's disease (CD). The authors concluded that TDM was not cost-effective at their willingness to pay threshold, current tests have high rates of false positives and false negatives, and that the underlying evidence base was poor or lacking.<sup>1</sup> The authors of the RCT<sup>2</sup> concluded that TDM of infliximab for patients with active CD did not increase the proportion of patients who had corticosteroid-free clinical remission (the study's primary endpoint) when compared to adjusting infliximab doses based on clinical symptoms alone. The two NRS<sup>3-4</sup> made favourable conclusions towards use of infliximab TDM, where one study suggested TDM was associated with higher post-adjustment endoscopic remission rates, improved clinical response, fewer hospitalizations, shorter time to escalation, and higher median infliximab levels following escalation, while the other NRS<sup>4</sup> reported that TDM use was associated with lower rates of infliximab discontinuation.

Three evidence-based guideline<sup>5-7</sup> were identified regarding use of TDM of biologic medication levels, and associated dosage adjustments, for patients with IBD. One guideline,<sup>5</sup> published by the American Gastroenterological Association, made several recommendations for when TDM should be used to guide treatment decisions based on low to very low quality evidence. Conditional recommendations for the use of TDM were made for adults with active IBD treated with anti-TNF agents and adults with IBD treated with thiopurines.<sup>5</sup> The guideline by Mitrev et al.<sup>6</sup> suggested that TDM should be performed for patients undergoing treatment with anti-TNF agents upon treatment failure, following

successful induction, when contemplating a drug holiday, and periodically in clinical remission only when results would change management. The authors stated that additional research would be needed prior to recommending TDM for non-anti-TNF biological agents.<sup>6</sup> The third guideline<sup>7</sup> was published in 2016 by the National Institute for Health and Care Excellence (NICE). This guideline<sup>7</sup> suggested that although three available enzyme-linked immunosorbent assay kits (LISA-TRACKER, IDKmonitor, and Promonitor) show promise for TDM of TNF-alpha inhibitors in patients with CD, there is insufficient evidence to support their adoption into routine practice. In addition, this guideline also made recommendations for laboratories that currently utilize assay kits and where future research is needed.<sup>7</sup>

**Table 2: Summary of Included Studies on the Clinical Effectiveness of Therapeutic Drug Monitoring-Guided Dosing of Biologic Medications for Patients with IBD**

First Author, Year	Study Characteristics	Interventions	Comparators	Outcomes	Author's Conclusions
<b>Systematic Reviews and Meta-Analyses</b>					
Freeman, 2016 <sup>1</sup>	<ul style="list-style-type: none"> <li>MA performed</li> <li>72 studies included</li> <li>Patients with moderate to severe active CD treated with infliximab or adalimumab</li> <li>N=NR</li> </ul>	<ul style="list-style-type: none"> <li>Test assays for serum anti-TNF-alpha and/or of anti-drug antibody levels to inform the treatment algorithm</li> </ul>	<ul style="list-style-type: none"> <li>Standard care</li> </ul>	<ul style="list-style-type: none"> <li>Any patient-related outcome</li> <li>Test agreement</li> <li>Cost-effectiveness</li> </ul>	<ul style="list-style-type: none"> <li>Evidence on test agreement was limited with contradictory results</li> <li>MA suggested that between 20-30% of test results are likely inaccurate</li> <li>Two RCTs assessing a test-treatment regimen did not demonstrate a clinical benefit</li> <li>Four studies on cost-effectiveness suggested there was potential benefit to testing; however, these results should be viewed cautiously in view of the limited evidence</li> </ul>
<b>Randomized Controlled Trials</b>					
D'Haens, 2018 <sup>2</sup>	<ul style="list-style-type: none"> <li>Prospective, double-blind trial</li> <li>Biologic-naive adult patients with active CD</li> <li>N=122</li> </ul>	<ul style="list-style-type: none"> <li>TDM to maintain serum levels of infliximab above 3 µg/mL</li> </ul>	<ul style="list-style-type: none"> <li>Adapting dose based only on clinical symptoms alone</li> </ul>	<ul style="list-style-type: none"> <li>Sustained corticosteroid-free clinical remission</li> <li>CD activity index scores</li> <li>Levels of C-reactive protein</li> <li>Fecal levels of calprotectin</li> <li>Serum concentrations of infliximab</li> </ul>	<p><i>"In a prospective randomized exploratory trial of patients with active CD, we found increasing dose of infliximab based on a combination of symptoms, biomarkers, and serum drug concentrations does not lead to corticosteroid-free clinical remission in a larger proportion of patients than increasing dose based on symptoms alone"</i><sup>2</sup></p>

First Author, Year	Study Characteristics	Interventions	Comparators	Outcomes	Author's Conclusions
<b>Non-Randomized Studies</b>					
Kelly, 2017 <sup>3</sup>	<ul style="list-style-type: none"> <li>Retrospective review</li> <li>Primary responders to infliximab who underwent dose escalation</li> <li>N=312 dose optimizations</li> </ul>	<ul style="list-style-type: none"> <li>TDM-based decision to escalate dose</li> </ul>	<ul style="list-style-type: none"> <li>Clinical decision to escalate dose (non-TDM)</li> </ul>	<ul style="list-style-type: none"> <li>Endoscopic remission</li> <li>C-reactive protein</li> <li>IBD-specific health care utilization</li> </ul>	<ul style="list-style-type: none"> <li>Use of TDM to inform dosing escalation decisions was associated with higher post-adjustment endoscopic remission rates, improved clinical response, fewer hospitalizations, shorter time to escalation, and higher median infliximab levels following escalation</li> </ul>
Pouillon, 2017 <sup>4</sup>	<ul style="list-style-type: none"> <li>Retrospective follow-up analysis</li> <li>Patients with IBD who completed the maintenance phase of the TAXIT trial</li> <li>N=226</li> </ul>	<ul style="list-style-type: none"> <li>Trough concentration-based infliximab dosing (TDM)</li> </ul>	<ul style="list-style-type: none"> <li>Clinic-based infliximab dosing</li> </ul>	<ul style="list-style-type: none"> <li>Mucosal healing</li> <li>Continued infliximab use</li> <li>Rates of hospitalization, surgery, and steroid use</li> </ul>	<p><i>“At the end of a trial of clinic-based dosing vs trough concentration-based dosing of infliximab in patients with IBD, most patients had mucosal healing. Most patients (≥75%) in both groups continued taking infliximab for more than 3 years after the trial, but a significantly higher proportion of patients in the clinic-based dosing group discontinued infliximab in the first year after the end of the trial. Both groups had low rates of hospitalization, surgery, and steroid use”<sup>4</sup></i></p>

CD = Crohn's disease; IBD = inflammatory bowel disease; MA = meta-analysis; NR = not reported; RCT = randomized controlled trial; TAXIT = Trough Concentration Adapted Infliximab Treatment; TDM = therapeutic drug monitoring; TNF = tumour necrosis factor.

## References Summarized

### Health Technology Assessments

No literature identified.

### Systematic Reviews and Meta-Analyses

- Freeman K, Connock M, Auguste P, Taylor-Phillips S, Mistry H, Shyangdan D, et al. Clinical effectiveness and cost-effectiveness of use of therapeutic monitoring of tumour necrosis factor alpha (TNF-alpha) inhibitors versus standard care in patients with Crohn's disease: Systematic reviews and economic modelling. *Health Technol Assess.* 2016;20(83).  
[PubMed: PM27845027](https://pubmed.ncbi.nlm.nih.gov/27845027/)

## Randomized Controlled Trials

2. D'Haens G, Vermeire S, Lambrecht G, Baert F, Bossuyt P, Pariente B, et al. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, or corticosteroid-free remission in patients with active luminal Crohn's disease. *Gastroenterology*. 2018 Jan 6.  
[PubMed: PM29317275](#)

## Non-Randomized Studies

3. Kelly OB, Donnell SO, Stempak JM, Steinhart AH, Silverberg MS. therapeutic drug monitoring to guide infliximab dose adjustment is associated with better endoscopic outcomes than clinical decision making alone in active inflammatory bowel disease. *Inflamm Bowel Dis*. 2017 Jul;23(7):1202-9.  
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4. Pouillon L, Ferrante M, Van Assche G, Rutgeerts P, Noman M, Sabino J, et al. Mucosal healing and long-term outcomes of patients with inflammatory bowel diseases receiving clinic-based vs trough concentration-based dosing of infliximab. *Clin Gastroenterol Hepatol*. 2017 Dec 1.  
[PubMed: PM29203225](#)

## Guidelines and Recommendations

5. Feuerstein JD, Kupfer SS, Falck-Ytter Y, Singh S, American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on therapeutic drug monitoring in inflammatory bowel disease. *Gastroenterology*. 2017;153(3):827-34.  
[PubMed: PM28780013](#)
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## Appendix — Further Information

### Previous CADTH Reports

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9. CADTH Canadian Drug Expert Committee (CDEC). Infliximab (Inflixtra [Subsequent Entry Biologic]– Hospira HealthCare Corporation, a Pfizer Company) [Internet]. Ottawa: CADTH; 2016. [cited 2018 Apr 5]. Available from: <https://cadth.ca/infliximab-19>
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### Systematic Reviews and Meta-Analyses – Alternative Outcomes (Cost-Effectiveness)

11. Martelli L, Olivera P, Roblin X, Attar A, Peyrin-Biroulet L. Cost-effectiveness of drug monitoring of anti-TNF therapy in inflammatory bowel disease and rheumatoid arthritis: A systematic review. *J Gastroenterol*. 2017 Jan;52(1):19-25. [PubMed: PM27665099](#)

### Non-Randomized Studies

#### *Alternative Outcomes – Influence on Decision Making*

12. Selinger CP, Lenti MV, Clark T, Rafferty H, Gracie D, Ford AC, et al. Infliximab therapeutic drug monitoring changes clinical decisions in a virtual biologics clinic for inflammatory bowel disease. *Inflamm Bowel Dis*. 2017 Dec;23(12):2083-8. [PubMed: PM29140939](#)

#### *No Comparator*

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14. Gonczi L, Kurti Z, Rutka M, Vegh Z, Farkas K, Lovasz BD, et al. Drug persistence and need for dose intensification to adalimumab therapy; the importance of therapeutic drug monitoring in inflammatory bowel diseases. *BMC Gastroenterol*. 2017 Aug 8;17(1):97, 2017. [PubMed: PM28789636](#)

## Guidelines and Recommendations – Technical Review

15. Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Technical Review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. *Gastroenterology*. 2017 Sep;153(3):835-57.  
[PubMed: PM28774547](#)

## Clinical Practice Guidelines – Unspecified Methodology

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## Review Articles

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[PubMed: PM29462502](#)
19. Jalali Y, Krajcovicova A, Hlavaty T. Therapeutic drug monitoring in the treatment of inflammatory bowel disease with infliximab. *Gastroenterologie a Hepatologie*. 2018;72(1):41-6.
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[PubMed: PM28147368](#)
24. Lega S, Bramuzzo M, Dubinsky M. Therapeutic drug monitoring in pediatric IBD: Current application and future perspectives. *Curr Med Chem*. 2017 Sep 11.  
[PubMed: PM28901267](#)

25. Sheasgreen C, Nguyen GC. The evolving evidence for therapeutic drug monitoring of monoclonal antibodies in inflammatory bowel disease. *Curr Gastroenterol Rep*. 2017 May;19(5):19, 2017.  
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27. Tighe D, McNamara D. Clinical impact of immunomonitoring in the treatment of inflammatory bowel disease. *World J Gastroenterol*. 2017 Jan 21;23(3):414-25.  
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