Therapeutic Drug Monitoring in Inflammatory Bowel Disease

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Abbreviations used in this paper

5-ASA, 5-aminosalicylate;
6-TGN, 6-thioguanine
AGA, American Gastroenterological Association
Anti-TNF, anti-tumor necrosis factor
BMI, body mass index
CBC, complete blood count
CD, Crohn’s disease
CI, confidence interval
GRADE, Grading of Recommendations Assessment, Development and Evaluation
RCT, randomized control trial
RR, relative risk
TAXIT, Trough Concentration Adapted Infliximab Treatment
TDM, therapeutic drug monitoring
TPMT, thiopurine methyltransferase
UC, Ulcerative colitis
Introduction

This document presents the official recommendations of the American Gastroenterological Association (AGA) on therapeutic drug monitoring (TDM) in inflammatory bowel disease (IBD). The guideline was developed by the AGA's Clinical Guidelines Committee and approved by the AGA Governing Board. It is accompanied by a technical review that is a compilation of clinical evidence from which these recommendations were formulated.1

IBD is often treated with immunomodulators and/or biologics. The trough concentrations of these drugs may vary due to disease severity, phenotype, degree of inflammation, use of immunomodulator, patient gender, and body mass index (BMI) as well as variability in drug clearance through immune- and non-immune-mediated mechanisms and mechanistic failure. In order to better optimize the drug concentration and clinical improvement, TDM is used to check the drug trough concentration and assess for the presence of antibodies.2 TDM can be performed at any point of therapy in induction or maintenance therapy.2 It may be performed in a routine proactive fashion when a patient has no symptoms and is in clinical remission, or as reactive testing in response to suboptimal disease control. For the purposes of this guideline, reactive testing refers to TDM performed in patients who have active IBD defined as having active symptoms related to IBD which are confirmed with objective findings from biochemical markers, endoscopic, or radiologic findings of active inflammation or in patients who are asymptomatic clinically but have findings of objective inflammation on endoscopy or radiology.

In the event of drug failure, there are three possible causes: mechanistic failure, non-immune mediated pharmacokinetic failure, and immune-mediated pharmacokinetic failure.1 Mechanistic failure occurs when the patient is not responding despite optimal drug trough concentrations. This type of failure is likely related to the disease process being driven by inflammatory mediators that are not blocked by the particular drug. Therefore, these patients are unlikely to respond to other drugs within the same class. Non-immune-mediated pharmacokinetic failure occurs when patients do not adequately respond to therapy in the presence of sub-therapeutic trough concentrations in the absence of anti-drug antibodies. This phenomenon results from rapid drug clearance often in the setting of a high inflammatory burden. Immune-mediated pharmacokinetic failure occurs in patients who have low or undetectable trough concentrations in the presence of anti-drug antibodies. This type of drug failure results from the immune-mediated formation of neutralizing anti-drug antibodies.1 Currently, there are many commercial assays available to test trough concentrations and antibodies. In general, measurement of trough concentrations, but not of anti-drug antibodies, is relatively comparable with acceptable specificity, accuracy, and reproducibility between assays. In a comparative study, quantitative drug concentrations of infliximab with different assays was -7% to +20% of each other.3, 4 However, in another study comparing ELISA and HMSA for measuring adalimumab trough levels, considerable intra-patient variability was observed.5 Due to paucity of convincing comparative data, in case of repeated trough concentration and anti-drug antibody measurements for a patient, we suggest using the same assay. In contrast, the reporting of drug antibodies is variable between the commercial assays and there is no standardized reporting of these values. Moreover, uniform thresholds for clinically relevant antibody titers are lacking. Therefore, it may be beneficial to utilize the same assay when checking for trough concentration and anti-drug antibodies.1

This guideline was developed to inform appropriate utilization of TDM with anti-tumor necrosis factor α(anti-TNF) agents and thiopurines. Additionally, the guideline also sought to determine the role of
testing the genetic or enzymatic activity of thiopurine methyltransferase (TPMT) prior to starting a thiopurine. Due to a paucity of data at the time of publication, this guideline does not address the role of TDM in vedolizumab or ustekinumab.

The AGA process for developing clinical practice guidelines follows the standards set by the Institute of Medicine. This process is described in more detail elsewhere and was used in developing the technical review and the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to evaluate the certainty of the evidence and grade the strength of the recommendations. Understanding of this guideline and the evidence supporting the recommendations will be enhanced by reading the technical review. The guideline panel and the authors of the technical review met face to face on February 26, 2017 to discuss the findings from the technical review. The guideline authors subsequently formulated the recommendations. Although quality of evidence (Table 1) was a key factor in determining the strength of the recommendation (Table 2), the panel also assessed the balance between benefit and harm of interventions, patients’ values and preferences, and resource utilization. While cost is usually factored into the recommendation, in this situation it was not feasible to accurately assess cost given the variable costs of the commercial trough concentration and antibody testing assays throughout the United States and internationally. The recommendations, quality of evidence, and strength of the recommendations are summarized in Table 3, and accompanying clinical decision support tools are provided in Figure 1 (approach to TDM for anti-TNF agents) and 2 (approach to TDM for thiopurines).

Recommendations

1. In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes. Conditional recommendation, very low quality of evidence.  
Comment: Table 4 summarizes suggested trough concentration for anti-TNF therapy, for patients with active IBD on maintenance therapy. Of note, there may be a small subset of patients who may still respond by targeting higher target concentrations. Optimal trough concentrations for induction therapy are uncertain.

The guideline panel conditionally recommends in favor of using reactive TDM in patients with active IBD to help guide treatment changes. To answer this question, there was one randomized control trial (RCT) and three observational studies of patients with IBD who were receiving maintenance therapy with anti-TNF. The RCT included 69 patients on maintenance therapy with infliximab who developed active CD symptoms and were randomized to TDM-guided treatment changes vs. empiric dose escalation. A significant limitation of this study was an infliximab trough ≥0.5 μg/mL was considered optimal. Patients with a trough ≥0.5 μg/mL were deemed to have mechanistic drug failure and switched to an alternative non-TNF-based therapy (76% of patients). However, this trough concentration is considerably lower than the trough level of ≥ 5 μg/mL that is supported by the current evidence (Table 4). On intention to treat analysis at 12 weeks, there was no significant difference in achieving remission between the two strategies (RR, 0.78; 95% CI, 0.40-1.51). When pooling the three observational studies together, only 30% (139/464) were considered mechanistic failures (adequate trough), likely related to the higher target trough concentrations of 2.0-3.8 μg/mL for infliximab and an adalimumab trough of 4.5-4.9 μg/mL. Similar to the RCT, 19% (90/464) were deemed to have immune-mediated pharmacokinetic failure with subtherapeutic trough concentration and presence of anti-drug antibodies. However, in contrast to the 4% of patients in the RCT, 51% (235/464) were deemed to have non-immune mediated...
pharmacokinetic failure with subtherapeutic trough levels but no anti-drug antibodies.\textsuperscript{9-11} In pooling two of the studies retroactively, 45% of patients responded to empiric dose escalation.\textsuperscript{9, 10} On retrospectively applying TDM, 82% of patients with a subtherapeutic trough and no anti-drug antibodies would have responded to dose escalation (RR, 1.71; 95% CI, 1.39-2.11), while, only 8% of patients with low or undetectable trough in the presence of anti-drug antibodies would have responded (RR, 0.26; 95% CI, 0.08-0.86).\textsuperscript{9, 10}

The quality of evidence of the RCT was downgraded to very low due to a high risk of bias from a high degree of non-adherence to the protocol, indirectness resulting from the low therapeutic trough level utilized (≥0.5 μg/mL), and imprecision. Similarly, the observational studies were considered very low quality from the risk of bias related to study design and imprecision.\textsuperscript{1}

There are several issues that remain unresolved even after assessing the evidence. The best available evidence did not address the optimal timing for measuring trough concentrations. In most cases, the panel recommends that a trough level for infliximab or adalimumab be drawn as close to the next dose as possible (i.e. within 24 hours). Additionally, while the drug trough concentration is consistent across different commercial assays, assays for antibodies to the drug are not readily comparable with each other.\textsuperscript{1}

When antibodies are detected, it is unclear what antibody level is clinically meaningful. In general, low-titer antibodies may be transient and non-neutralizing. Often shortening the drug dosing interval and/or escalating the dose can optimize the trough concentration in the setting of low titer antibodies. In contrast, high titer antibodies, especially with undetectable trough concentrations, are generally persistent, and neutralizing. In the presence of high-titer anti-drug antibodies, with undetectable drug, there may be very limited benefit to attempting dose escalation of the index agent, and switching to a different drug within the same class may be more effective. Unfortunately, current data does not allow us to identify optimal anti-drug antibody cut-offs for high versus low antibodies in the current commercially available assays.\textsuperscript{1}

The above studies did not specifically address patients who were in clinical remission but had active disease on endoscopy or imaging. As treatment paradigms shift toward targeting mucosal healing, indirect evidence suggests that using reactive TDM in this situation would be reasonable.\textsuperscript{12} However, optimal target trough concentrations for achieving mucosal healing are uncertain and may be higher than those suggested for achieving clinical remission.\textsuperscript{1, 12}

Importantly, none of the aforementioned studies evaluated the use of reactive TDM during induction therapy. The benefit of applying TDM in patients with sub-optimal response to induction therapy over empiric dose escalation, is uncertain. Optimal target trough concentrations and timing of achieving maximal effectiveness of anti-TNF agents during induction therapy are unclear. Strict adherence to suggested trough thresholds for maintenance therapy in the induction phase, may result in erroneous misclassification of patients as having a mechanistic failure. During induction, empiric dose escalation may be a reasonable alternative, unless immune-mediated pharmacokinetic failure is suspected. Therefore, based on the current evidence, the ability to provide guidance regarding reactive testing during induction before response to therapy is unknown.\textsuperscript{1}

The target trough concentration is different for each of the biologic agents (Table 4).\textsuperscript{1} The studies used to derive different target trough concentrations were cross-sectional studies of patients on maintenance
therapy in various stages of response/remission. They were not specifically designed to evaluate patients who had a secondary loss of response. Based on the currently available evidence, the panel suggests target trough concentrations of $\geq 5 \mu g/mL$ for infliximab, $\geq 7.5 \mu g/mL$ for adalimumab and $\geq 20 \mu g/mL$ for certolizumab pegol in patients with active IBD to assess for mechanistic failure or pharmacokinetic failure. Data supporting these cutoffs were less robust for adalimumab than for infliximab. Additionally, it remains unclear whether higher trough levels are required to achieve therapeutic effect in UC than CD, and whether higher trough concentrations may be needed to achieve mucosal healing than clinical remission. Data on golimumab is limited and not sufficient to provide a target trough level at this time.

Based on the above evidence and target trough concentrations, the panel developed an algorithm for how patients and physicians using shared decision making may respond to reactive TDM testing (Figure 1). Initially, only the trough concentrations should be assessed. If the level is at/above the target trough, then the patient may consider switching to a different drug class given a mechanistic failure of the current agent. In the presence of sufficient trough concentrations, results of antibody testing should not guide treatment decisions. If the trough concentration is low, (below the suggested threshold, in patients with active IBD) and no antibodies present then the drug may be optimized using any of the following techniques: shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent. Typically optimizing the drug will be attempted before changing to a different drug within the class or switching to a new drug class. If there is no detectable drug trough concentration and high-titer antibodies are present, then the patient should consider switching to a different drug within the class or to a different drug class. If there is no detectable drug and low-titer antibodies are present, then one may consider trying to optimize the current drug by shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent. Alternatively, some may opt to change to a different drug within the class or switching to a new drug class. It should be noted that the reporting of drug antibodies is variable between commercial assays and there is no standardized reporting of these values. Uniform thresholds for clinically relevant antibody titers are lacking. At this time, it is unclear how antibodies affect drug efficacy when both drug trough concentration is present and antibodies are present in the assay. In cases of low trough concentrations and low or high drug antibodies, the evidence to clarify the best management is lacking. Studies are needed to determine how to best manage these findings.

2. In adult patients with clinically quiescent IBD treated with anti-TNF agents, the AGA recommends that routine proactive therapeutic drug monitoring only be used in the setting of clinical research. No recommendation, knowledge gap.

At this time, the benefit of routine proactive TDM in patients with quiescent IBD treated with anti-TNF therapy is uncertain. Therefore, because of this knowledge gap and need for further studies, no recommendation can be made regarding this question.

There were no RCTs or comparative observational studies comparing a priori proactive TDM for achieving remission and thus, indirect evidence was utilized. The single RCT on this topic was the TAXIT study by Vandee Casteele et al. in which all patients were first dose optimized to achieve an infliximab trough of 3–7 $\mu g/mL$. Once this target was reached, patients were randomized to proactive TDM vs no TDM. Once the initial dose optimization was achieved with TDM, the proportion of patients achieving remission at 1 year with proactive TDM vs no TDM was no different (RR, 1.04; 95% CI, 0.88–1.24). While this study indicates that an initial TDM for dose optimization may be beneficial, further routine
repeated TDM monitoring (e.g. before every dose of infliximab) does not show any additional benefit at 1 year. This study provided only indirect evidence to answer the question of routine TDM since all patients were initially optimized to a goal trough of 3-7 μg/mL. There was no comparator arm in this initial drug optimization phase, and therefore while the findings indicate an increase in proportion of patients in remission who had low drug levels optimized and a cost savings by dose reduction in those with a supertherapeutic drug level, the true effects of these changes long-term from routine proactive TDM remains unknown.\textsuperscript{1,24} Therefore, this study does not answer the question regarding the benefit of a one-time routine proactive TDM, or timing of drug optimization on clinical outcomes. One important finding of the TAXIT study was at 1 year, the patients in the no routine TDM group had higher rates of anti-drug antibodies and undetectable infliximab trough levels. This presumably may increase the risk of disease flares and drug failure. However, given the limited duration of follow up in the TAXIT study, the evidence to answer this is unknown. In another single-center, retrospective observational study by Vaughn et al, patients who underwent routine proactive TDM before each infliximab infusion were less likely to discontinue infliximab due to disease flares or infusion reaction compared to patients who did not undergo TDM.\textsuperscript{25}

Overall, the evidence from the TAXIT study was considered very low quality due to very serious indirectness and imprecision from the wide confidence intervals and summary estimate near unity. Similarly, evidence from Vaughn et al. was also very low quality due to the retrospective design of this study and how patients were selected for routine proactive TDM may have resulted in significant selection bias. Additionally, the limited data on direct patient-relevant clinical outcomes limits the strength of the evidence form this study and overall generalizability.\textsuperscript{1}

Post-hoc analysis from clinical trials of induction therapy of anti-TNF drugs indicates an exposure-response relationship and patients with higher trough levels between weeks 4-14 were more likely to achieve remission.\textsuperscript{1} This is further supported by the data from Vandee Casteele et al. who noted that uniform dose optimization resulted in an increase in proportion of patients in clinical remission (from 65% pre-optimization to 88% post-optimization).\textsuperscript{24} While this supports the notion that early optimization of therapy based on proactive TDM testing may be helpful, the magnitude of benefit for patient-important outcomes, long-term benefit over reactive TDM, frequency of assessments in proactive TDM are unclear.\textsuperscript{1}

Routine proactive TDM may not be without harm. Since target trough concentrations for asymptomatic patients under routine care are unclear, testing may lead to inappropriate treatment changes and therapeutic dilemmas in patients who are otherwise in clinical remission. Also, the frequency with which TDM needs to be repeated for routine proactive TDM and following a drug dosing change is also unclear. The cost associated with this is variable based on the different assay costs, as well as downstream costs of treatment changes. Further well-designed RCTs with direct patients related outcomes from routine proactive TDM compared to no TDM are still needed to answer whether routine TDM should be performed and if it is performed, how often TDM should be checked.\textsuperscript{1}

<table>
<thead>
<tr>
<th>3.</th>
<th>In adult patients with IBD being started on thiopurines, the AGA suggests routine TPMT testing (enzymatic activity or genotype) to guide thiopurine dosing. Conditional recommendation, low quality of evidence.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comment: Routine laboratory monitoring, including complete blood count (CBC), should be performed, regardless of TPMT testing results.</td>
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</table>
The guideline panel conditionally recommends routine TPMT testing prior to starting a thiopurine based on low quality evidence. While available evidence suggests that there may not be significant benefit of this strategy over empiric weight based dosing at a population level, a very small subset of patients who are homozygous for TPMT are at risk for considerable harm due to severe neutropenia and infections, if treated with empiric weight-based dosing.

There are three RCT studies comparing TPMT testing to no testing with empiric weight based thiopurine dosing. Genotype was utilized in 2 studies and enzymatic activity in one study. In these studies, patients with a normal enzyme/genotype started full dose thiopurine while those with intermediate enzymatic activity/heterozygous genotype had a 50% dose reduction. Those with low/absent enzyme activity or homozygous genotype were not given the drug or given a reduced dose at 0-10% of the initiation dose. In the 1145 patients included in the studies, only 0.17% (n=2) were homozygous. Hematologic adverse events and treatment discontinuation were used as surrogate outcomes for benefits of TPMT testing. There was no significant difference in either outcome based on TPMT testing, with the relative risk of hematologic events of 0.94 (95% CI, 0.59-1.50) and treatment discontinuation of 1.09 (95% CI, 0.94-1.27). Additionally, there was also no significant difference in clinical remission in these groups based on TPMT checking (RR 1.03; 95% CI, 0.84-1.27). However, if an individual is intermediate enzymatic activity/heterozygous genotype or homozygous genotype/low enzymatic activity, then TPMT testing to guide dosing was associated with an 89% risk reduction of hematologic adverse events. Hence, while the risk of harm from not testing a TPMT level prior to initiating therapy is minimal in most cases, there is considerable risk of harm in the 0.3% patients who are homozygous genotype or have low/absent TPMT enzymatic activity. While this risk may be mitigated by routine laboratory CBC checking, adherence to regular monitoring in clinical practice is suboptimal. It is therefore important to continue to perform routine lab monitoring with CBC and liver enzyme monitoring after starting a thiopurine regardless of the TPMT testing results.

The evidence supporting this recommendation was considered low quality due to the indirectness of the surrogate outcomes studied: hematologic adverse events and treatment discontinuation. Additionally, the evidence was further rated down for serious imprecision given the wide confidence intervals crossing unity and the low event rate.

4. In adult patients treated with thiopurines with active IBD or adverse effects thought to be due to thiopurine toxicity, the AGA suggests reactive thiopurine metabolite monitoring to guide treatment changes. Conditional recommendation, very low quality of evidence.

Comment: When measuring thiopurine metabolite monitoring in patients with active IBD-related symptoms, we suggest a target 6-thioguanine (6-TGN) cut-off between 230-450 pmol/8 x 10⁸ RBC when used as monotherapy; optimal 6-TGN cut-off when thiopurines are used in combination with anti-TNF agents is uncertain.

The panel conditionally recommends in favor of reactive testing of thiopurine metabolites in patients with active IBD based on very low quality evidence. There were no randomized control trials available to answer this question. In a retrospective observational study of 60 patients with active IBD treated with thiopurines, response to therapy was categorized based on whether patients received treatment concordant with TDM algorithm vs. treatment discordant with TDM algorithm. The TDM algorithm suggested thiopurine dose optimization, if their 6-TGN level was low (<230 pmol/8 x 10⁸ RBC) and switching to a different medication if 6-TGN level was adequate. Patients who received algorithmic-
concordant care were significantly more likely to respond to a therapeutic change as compared with patients who received algorithm-discordant care (RR, 5.15; 95% CI 1.82-14.56).\textsuperscript{30}

Overall the level of evidence was very low quality due to observational study design, imprecision from the small study size and indirectness from the study comparison groups.\textsuperscript{1}

The target 6-TGN metabolite cut-off between 230-450 pmol/8 x 10\textsuperscript{8} RBC when used as monotherapy is based on limited studies.\textsuperscript{1} 6-TGN levels ≥230 were associated with 40% higher rates of remission (RR, 1.4; 95% CI, 1.2-1.6) compared to levels <230. However, it is unclear whether this target 6-TGN concentration applies when thiopurines are used in combination with anti-TNF agents, where one of the reasons for combination therapy is to reduce the risk of immunogenicity, rather than independently targeting remission. Though lower targets have been suggested, current evidence fails to identify a target threshold.\textsuperscript{1}

Potential harms associated reactive TDM testing include the additional burden of intensified laboratory monitoring necessary with each dose adjustment and the potential for delaying alternative effective therapies in patients not responding to thiopurines.\textsuperscript{1}

\textbf{5. In adult patients with quiescent IBD treated with thiopurines, the AGA suggests against routine thiopurine metabolite monitoring. Conditional recommendation, very low quality of evidence.}

The guideline panel conditionally recommended against routine testing of thiopurine metabolites in patients with quiescent IBD. There were 2 RCT trials of 107 patients on azathioprine that investigated routine thiopurine metabolite monitoring to achieve a 6-TGN concentration of 250-400pmol/8x10\textsuperscript{8} RBC compared to standard weight-based dosing determined by TPMT testing.\textsuperscript{31, 32} There was no significant difference in the rate of achieving clinical remission (RR, 1.44; 95% CI 0.59-3.52) or serious adverse events (RR, 1.20; 95% CI 0.50-2.91) with routine thiopurine metabolite monitoring compared to standard dosing.\textsuperscript{31, 32} Of note, these studies were not performed in patients on combination therapy with anti-TNF agents and provided limited ability to optimize thiopurine therapy (only thiopurine dose escalation was permitted in patients with 6-TGN <230 and alternative strategies such adding allopurinol was not permitted). Therefore, data from these studies cannot be extrapolated to the management of thiopurines when used in combination with an anti-TNF agent.\textsuperscript{1}

The evidence supporting this recommendation was very low. Neither study achieved their recruitment target resulting in a concern for high risk of bias. Additionally, the quality of the studies was downgraded for having both serious inconsistency (I\textsuperscript{2} > 50%) and imprecision (wide confidence intervals).\textsuperscript{1}

Potential harms associated with this strategy include the additional burden of intensified laboratory monitoring necessary with each dose adjustment and the potential for delaying alternative effective therapies in patients not responding to thiopurines. Hence, based on the current evidence, the benefit of routine TDM over standard-weight based thiopurine dosing is uncertain.\textsuperscript{1}

\textbf{Summary}

These practice guideline recommendations for TDM in IBD were developed using the GRADE framework and in adherence with the standards for guideline development set forth by the Institute of Medicine for the creation of trustworthy guidelines.\textsuperscript{6, 7} The current evidence supports the use of reactive TDM to guide treatment changes in patients with active IBD on maintenance therapy who are being treated with anti-TNF agents or thiopurines. However, there is insufficient evidence to inform on the use of routine
proactive TDM with anti-TNF agents. For thiopurines, routine proactive thiopurine metabolite monitoring is not recommended in patients with quiescent IBD. Current evidence supports testing for TPMT enzyme or genotype prior to initiation of a thiopurine. However, this is not a replacement for routine lab monitoring with CBC and liver enzymes after starting therapy with a thiopurine. To further provide guidance on how to implement this guideline in practice, figure 1 and 2 provide a clinical decision support tool on when to perform TDM and how to interpret TDM when patients are taking an anti-TNF agent or a thiopurine.

There are several knowledge gaps in therapeutic drug monitoring that have been identified for which prospective observational and randomized control trials are warranted which have been highlighted in the technical review that accompanies this guideline. The exact trough targets for both induction therapy and when reactive testing is performed during maintenance therapy is unclear. Similarly, it is unclear if trough concentration targets should be different based on disease phenotype and disease state. Further studies are also needed to better clarify the difference between low and high antibodies and at which levels can antibodies before suppressed before needing to change drug therapies. Additionally, further well designed randomized control trials are needed comparing routine proactive TDM, reactive TDM, and empiric dosing changes on patient specific outcomes. Studies are also needed to assess the benefit of subsequent TDM testing and timing of when such testing should be repeated. Finally, as newer biologic agents are approved, the use of TDM to optimize these drugs will need to be evaluated.

References:


## Tables:

### Table 1. GRADE Definitions of Quality/Certainty of the Evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td>High</td>
<td>We are very confident that the true effect lies close to that of the estimate of the effect.</td>
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<tr>
<td>Moderate</td>
<td>We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>Very low</td>
<td>We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.</td>
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### Table 2. GRADE Definitions on Strength of Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Wording in the guideline</th>
<th>For the patient</th>
<th>For the clinician</th>
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<tbody>
<tr>
<td>Strong</td>
<td>“The AGA recommends.”</td>
<td>Most individuals in this situation would want the recommended course of action and only a small proportion would not.</td>
<td>Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</td>
</tr>
<tr>
<td>Conditional</td>
<td>“The AGA suggests.”</td>
<td>The majority of individuals in this situation would want the suggested course of action, but many would not.</td>
<td>Different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.</td>
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### Abbreviations
AGA American Gastroenterological Association

### Table 3. Summary of Recommendations of the AGA Clinical Guidelines for Therapeutic Drug Monitoring in Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
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<tbody>
<tr>
<td>1. In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes. Conditional recommendation, very low quality of evidence. Comment: <em>Table 4 summarizes suggested trough concentration for anti-TNF therapy, for patients with active IBD on maintenance therapy. Of note, there may be a small subset of patients who may still respond by targeting higher target concentrations. Optimal trough concentrations for induction therapy are uncertain.</em></td>
<td>Conditional Recommendation</td>
<td>Very Low Quality</td>
</tr>
<tr>
<td>2. In adult patients with clinically quiescent IBD treated with anti-TNF agents, the AGA recommends that routine proactive therapeutic drug monitoring only be used in the setting of clinical research</td>
<td>No Recommendation</td>
<td>Knowledge Gap</td>
</tr>
<tr>
<td>3. In adult patients with IBD being started on thiopurines, the AGA suggests routine TPMT testing (enzymatic activity or genotype) to guide thiopurine dosing. Comment: Routine laboratory monitoring, including CBC, should be performed, regardless of TPMT testing results.</td>
<td>Conditional Recommendation</td>
<td>Low quality</td>
</tr>
<tr>
<td>4. In adult patients treated with thiopurines with active IBD or adverse effects thought to be due to thiopurine toxicity, the AGA suggests reactive thiopurine metabolite monitoring to guide treatment changes. Comment: <em>When measuring thiopurine metabolite monitoring in patients with active IBD-related symptoms, we suggest a target 6-thioguanine (6-TGN) cut-off between 230-450 pmol/8 x 10^6 RBC when used as monotherapy; optimal 6-TGN cut-off when thiopurines are used in combination with anti-TNF agents is uncertain.</em></td>
<td>Conditional Recommendation</td>
<td>Very Low quality</td>
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<td>5. In adult patients with quiescent IBD treated with thiopurines, the AGA suggests against routine thiopurine metabolite monitoring.</td>
<td>Conditional Recommendation</td>
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</tbody>
</table>
Abbreviations: 6-TGN 6 thioguanine, AGA American Gastroenterological Association, anti-TNF anti-tumor necrosis factor, IBD inflammatory bowel disease, TPMT thiopurine methyltransferase

Table 4. Suggested target trough concentrations when applying reactive TDM in patients with active IBD on maintenance therapy with anti-TNFs.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Suggested trough concentration</th>
<th>Comments (details in accompanying technical review)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>≥ 5 µg/mL</td>
<td>6 studies (929 patients), provided data on proportion of patients NOT in remission above pre-defined infliximab thresholds (1, 3, 5, 7, 10 µg/mL). Based on these, proportion of patients not in remission decreased from 25% when using an infliximab threshold of ≥1 µg/mL, to 15% with an infliximab trough concentration of ≥3 µg/mL, to ~4% with an infliximab trough concentration of ≥7 µg/mL or ≥10 µg/mL.</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>≥ 7.5 µg/mL</td>
<td>4 studies provided data on proportion of patients not in remission above adalimumab trough concentration above 5.0 (±1) or 7.5 ±1 µg/mL. On analysis of different thresholds, proportion of patients not in remission progressively decreased from 17% when using an adalimumab threshold ≥5.0(±1) µg/mL, to 10% with an adalimumab trough concentration of ≥7.5(±1) µg/mL.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Different studies used different assays, and there is limited data on comparability of trough concentrations identified in different assays for adalimumab</td>
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<td></td>
<td></td>
<td>• It is unclear what proportion of patients on standard (40mg every other week) or escalated adalimumab dosing (40mg every week) would be able to achieve these thresholds</td>
</tr>
<tr>
<td>Certolizumab Pegol</td>
<td>≥ 20 µg/mL</td>
<td>1 study provided data from an exposure response pooled analysis from nine trials. On analysis of different thresholds, proportion of patients not in remission progressively decreased from 42% when using a certerolizumab threshold of ≥ 10 µg/mL to 26% with a certolizumab trough concentration of ≥ 20 µg/mL</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Unknown</td>
<td>There is a lack of sufficient evidence available to establish a target trough goal</td>
</tr>
</tbody>
</table>

*Of note, studies used to derive different target trough concentrations were cross-sectional studies of patients on maintenance therapy in various stages of remission/response, to identify what proportion of patients were in remission (or not in remission), above and below specific thresholds. They were not specifically designed to evaluate patients who had a secondary loss of response
Adults with IBD, treated with anti-TNF agents

Active IBD*

Reactive TDM
(check trough and anti-drug antibodies)
(very low quality evidence, weak recommendation)

Anti-TNF TROUGH ADEQUATE ?
(on maintenance therapy, for achieving clinical response/remission)?
(Infliximab ≥5µg/ml; Adalimumab ≥7.5µg/ml; Certolizumab pegol ≥20µg/ml)

Suspect mechanistic failure – Consider switching to drug of different class
(Note: target trough thresholds may be higher for achieving mucosal healing, and following induction therapy; a small proportion of patients may still achieve clinical response/remission with optimization of index therapy by targeting higher trough concentrations)

Check anti-drug antibody (ADAb) levels

Low/absent trough, NO detectable ADAbs

Consider non-immune-mediated pharmacokinetic failure – Optimize index therapy
(shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent)

Higher trough, lower ADAb

Low trough with low- or high-titer ADAbs

Approach uncertain

Absent trough, High-titer ADAbs

Consider immune-mediated pharmacokinetic failure – Switch therapy
.switching within class or outside drug class

Lower trough, higher ADAb

Clinically and endoscopically Quiescent IBD

Continue anti-TNF therapy;
NO routine proactive therapeutic drug monitoring (knowledge gap, no recommendation)

*Active IBD is defined as objective findings of active disease based on endoscopic or radiologic disease activity, with or without symptoms
Adults with IBD starting thiopurines

Check TPMT level (enzyme activity or genotype)*
(low quality evidence, weak recommendation)

- Normal genotype/
  Normal TPMT enzyme activity
  - Start at full dose

- Heterozygous genotype/
  intermediate enzyme
  - Start at reduced dose and gradually dose escalate with close lab monitoring

- Homozygous genotype/
  absent TPMT enzyme activity
  - Avoid thiopurines

Active IBD** or concern for thiopurine toxicity
(on thiopurine monotherapy)

- Reactive TDM
  (thiopurine metabolite monitoring)
  (very low quality, weak recommendation)
  - Target 6-thioguanine (6-TGN) cut-off between 230-450 pmol/8 x 10^8 RBC; 6-MMP <5700
    - NO: Increase thiopurine dose or switch to different drug class
    - YES: Consider changing to different drug class; for toxicity, consider alternative causes

Clinically and endoscopically quiescent IBD
(on thiopurine monotherapy)

- Continue thiopurines;
  NO routine proactive therapeutic drug monitoring
  (very low quality evidence, weak recommendation)

*TPMT level does not negate the need for routine lab monitoring after starting thiopurine with CBC and liver enzymes
**Active IBD is defined as objective findings of active disease based on endoscopic or radiologic disease activity, with or without symptoms