ANTI-TNF ALPHA DOSE ESCALATION

DRUG PROTOCOL©

DOCUMENT SUMMARY/KEY POINTS

- The Pharmaceutical Benefits Scheme requires a 'step-up' process for patients to be approved for anti-TNFα therapy, with demonstrated failure to respond to steroids/EEN/ASA/thiopurines/methotrexate. Exception to this is the approach for patients presenting with fistulising disease and acute severe colitis.
- PBS funded anti-TNFα therapy is capped at 5 mg/kg per dose; however, this dosage recommendation is out of date. Recent evidence demonstrates that optimal anti-TNFα therapy requires the achievement of therapeutic anti-TNFα levels and escalation of the anti-TNFα dose or frequency may be required to achieve this.
- The current proposal is to simplify the access to escalated anti-TNFα therapy by following the AGA and GESA Guidelines/algorithms.

CHANGE SUMMARY

- Updated management options for acute severe colitis (ASC), specifically regarding dose escalation and treatment intensification,
- Include newer preparations of infliximab, such as subcutaneous infliximab (subcutaneous adalimumab already in use).

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st April 2024	**Review Period**: 3 years
Team Leader:	Gastroenterologist	**Area/Dept**: Gastroenterology

READ ACKNOWLEDGEMENT

- Gastroenterologists
- Prescribers of infliximab
- Pharmacists
- IBD and Gastroenterology Clinical Nurse Consultants
- Infusion Centre (Turner Ward, CHW), Medical Day Unit - C1N (SCH)

Note: Separate Practice Guidelines may be required to cover all aspects of management.

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Introduction / Background

Inflammatory bowel disease (IBD) which includes Crohn's Disease (CD), Ulcerative Colitis (UC) and Inflammatory Bowel Disease Unclassified (IBDU), is a chronic, relapsing, lifelong, inflammatory disorder affecting the gastrointestinal tract. Anti-TNFα biological therapy has been shown to be helpful in children and adults with IBD [1,2]. Although many pro-inflammatory cytokines are involved in IBD, tumour necrosis factor-α (TNFα) plays an important role in the pathogenesis of IBD.

Mechanism of Action

Infliximab and adalimumab are anti-TNFα antibodies which block the effects of TNFα by suppressing inflammation early in the cascade of cellular events that leads to features of IBD.

Repeated infusions help to maintain remission. A significant proportion of children and adult patients can lose response on long term anti-TNFα therapy. The mechanisms for this are not clearly understood and include the development of antibodies to the medicine.

Indications for Use

Infliximab and adalimumab are listed on the Pharmaceutical benefits Scheme (PBS) as Section 100 Highly Specialised Drugs for paediatric patients with refractory IBD. Indications for therapy include:

- Treatment of moderate to severe IBD to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional treatment of IBD.
- Therapy of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in Crohn's Disease.
- Treatment of acute severe colitis (ASC), where urgent escalation is required for any patient:
  i. with a Paediatric Ulcerative Colitis Activity Index (PUCAI)[3] ≥ 65;
  AND
  ii. has failed to achieve adequate response to at least 72 hours of corticosteroids.

A patient with ASC requires close monitoring by the on-call gastroenterologist. Dosing escalation and intensification is indicated as an attempt to rescue the patient from requiring a colectomy. Early and reactive use of anti-TNFα in this scenario can prevent early colectomy.[4]

Indications for dose escalation

'Dose intensification/ escalation protocol' of anti-TNFα is indicated for patients losing clinical response to standard 8 weekly 5 mg/kg IV infusions of infliximab as defined by a rise of disease activity as measured by the Paediatric Crohn's Disease Activity Index (PCDAI) or Paediatric Ulcerative Colitis Activity Index PUCAI, loss of clinical response, or evidence of low therapeutic drug levels [3]. Dose escalation may include the use of the subcutaneous form of infliximab (120mg/1ml syringe/ pen). Dose escalation of adalimumab includes escalation up to weekly double dosing. Dose escalation may be required at the time of induction treatment where there is severe intestinal inflammation and probable loss of anti-TNFα from

the gut. Studies have shown that a higher dosing regimen/ dose escalation can achieve therapeutic drug levels in this scenario, however, this has to be determined clinically as drug levels are rarely back in time.

Dose escalation and intensification in ASC is at the discretion of the treating gastroenterologist. Early and intensive use of anti-TNFα can rescue a child from a severe flare, and potentially prevent a child from a colectomy [5]. The current SCHN formulary approved dose is 10mg every 4 weeks and up to 45mg/kg within the first 2 weeks of treatment for a patient with acute severe colitis. Furthermore, newer studies with a 'treat to target' approach, using biological evaluation of inflammation, and mucosal healing suggest that dose escalation should be carried out proactively, to achieve early disease control [6].

Therapeutic Rationale

- Currently the PBS approves a dose of 5 mg/kg of infliximab, given 8 weekly as standard therapy, following an induction course given as three doses over six weeks.
- Alternatively, PBS approved adalimumab may be used as subcutaneous injection given fortnightly following an induction course, with the dose determined by the child's weight.
- Up to 30% of patients may be primary non-responders, and a significant proportion of patients have a secondary loss of response over time whilst on long term infliximab therapy, the mechanisms for which are not clearly understood and include the development of antibodies to the drug [7].
- The pharmacokinetics and pharmacodynamics of biological are potentially influenced by many factors, including disease type and severity, patient characteristics such as gender, weight, age, albumin, anti-drug antibodies and concomitant medications.
- Therapeutic drug monitoring (TDM) can be used to assess therapeutic drug levels [8]. The therapeutic range of trough levels for infliximab is 3.00-7.00 mg/L and for adalimumab is 4.9-8.0 microg/mL, however there is literature indicating that even higher levels of infliximab between 10-15 mg/L will increase drug efficacy, so higher levels may be acceptable if there Is demonstrated clinical response [9].
- Furthermore, individual patients may have factors known to be associated with higher clearance of the drug:
  - iii. low albumin level
  - iv. high inflammatory burden
  - v. higher baseline C-reactive protein
  - vi. higher baseline PCDAI and PUCAI
  - vii. higher body weight
- Development of anti-TNF antibodies may be delayed by concomitant use of immune modifiers e.g., thiopurines.
- Antibody formation and loss of response is associated with low trough levels. Studies have demonstrated that higher infliximab trough levels and the absence of antibodies are associated with clinical remission. Conversely, lower infliximab trough levels and the presence of antibodies are associated with active disease. Reports have also demonstrated that low-level anti-TNF drug antibodies may be overcome by dose

escalation and/or addition of an immunomodulator [10] and can allow for clinical improvement in disease status [11].

- Use of TDM with dose intensification for low trough levels or switching to an alternative drug in the presence of antibodies can result in a return of clinical response. This can occur within the same class of drug, e.g. switching from infliximab to adalimumab [13].
- TDM is now widely and easily available and the role of TDM in patients with primary non-response or secondary loss of response is well established.
- Dose escalation can be monitored with widely accepted therapeutic drug level monitoring for both infliximab and adalimumab.
- Drug monitoring to achieve therapeutic drug levels has become standard accepted therapy in managing inflammatory bowel disease.
- The literature supports that the achievement of therapeutic levels of anti TNF alpha levels is associated with better clinical outcomes, improved disease response and maintenance of disease remission. Higher levels of infliximab correlate with
    I. Longer duration of infliximab response
    II. Clinical remission
    III. Mucosal healing
- The safety profile of dose intensification appears to be similar to standard dosing schedules from published literature reports.
- There is evidence that the newer concept of proactive TDM with the objective of maintaining optimal anti-TNF concentrations may ultimately reduce costs and the risk of adverse events by maintaining higher remission rates [11].
- Some patients may be de-escalated successfully to standard dosing scheduling after a period of time, though the predictors of success and time periods have not been clarified and is dependent on the individual case [11].

Management of Acute Severe Colitis

- Acute severe colitis is a medical emergency, and a severe complication of IBD, which is associated with significant morbidity and a mortality rate of 1%. Optimal management includes admission to a specialist gastrointestinal unit and joint management with colorectal surgeons. Patients need to be screened for infections and thromboprophylaxis should be administered to manage the elevated risk of thromboembolism. Corticosteroids are the preferred initial medical therapy but for those who fail steroid therapy, rescue medical therapy with either infliximab or ciclosporin. More recently, escalated infliximab dosing infusions have become the preferred initial therapy, with cyclosporin or tacrolimus being considered as alternative rescue therapies.
- Administration of infliximab to patients with ASC (rescue therapy) may require higher induction doses up to 10mg/kg, shorter dosing intervals, or both, to reach target trough levels. [12] An accelerated infliximab induction strategy reduces the need for early

colectomy. An intensified infliximab dosing strategy in response to clinical or laboratory signs of breakthrough inflammation is indicated for this emergency clinical setting.

- Initial investigations include comprehensive biochemical blood panel, stool samples to exclude infection and additional investigations in anticipation of the need for rescue therapy.
- General measures such as attention to fluid status, correction of electrolyte imbalances and assessment/optimisation of nutritional status are important. High faecal calprotectin on day 3, and high CRP are associated with steroid failure. Enteral nutrition can be used as a supportive measure. Where possible, a limited, unprepared sigmoidoscopy with minimal air insufflation can performed by an experienced endoscopist to assess for severity of UC, and biopsies for CMV.
- Intravenous corticosteroids are the mainstay of early treatment for ASUC, capped at the equivalent of 60 mg methylprednisolone (equivalent to 300 mg hydrocortisone) as higher doses are associated with an increased risk of complications. Patients need to be reevaluated at day 3 to consider rescue therapy. Either calcineurin inhibitors or infliximab can be used as first line therapy. Infliximab pharmacokinetics (PK) may be altered in ASUC. There is faecal loss of infliximab, and low serum albumin noted in ASUC, is associated with low serum infliximab levels and non-response to infliximab, related to protein and drug loss from the inflamed bowel. Intensified infliximab dosing regimen might overcome the increased drug clearance and potentially improve clinical outcomes. Multiple dosing of infliximab may be better than a single dose in reducing colectomy, but up to 10mg/kg doses have been used in the published literature. Ciclosporin can be used as an additional measure for rescue therapy. Surgery may need to be considered if medical rescue therapies are not successful.
- Newer biologicals such as the selective JAK inhibitors may have a role that the treating Gastroenterologist would consider however these medications would require an IPU.

Therapeutic Drug Monitoring and Dose Escalation Protocol

1. Induction therapy as per the PBS which is 5mg/kg/dose at week 0, 2 and 6. Higher and more frequent dosing up to 45mg/ kg IV within the first 2 weeks may be required in ASUC which is covered by hospital formulary.
2. Patients with active disease or high risk factors which include corticosteroid requirement, elevated serum/stool inflammatory biomarkers, active disease at endoscopy, shorter duration of disease remission, prior surgical resection, current smoker status, male sex and those associated with severe consequences in the event of relapse, such as prior bowel resections or short gut syndrome [14] should be monitored for drug and antibody levels with proactive TDM (trough and antibody levels), at least six monthly.
3. Patients with clinical response and therapeutic drug levels should continue at the same dose.
4. Patients with supra-therapeutic levels may be considered for a dose/frequency de-escalation/reduction if there is sustained clinical response.

5. Patients with sub-therapeutic levels with no antibodies should have dose escalation (increased dose and/or increased frequency) with follow-up levels to determine and establish therapeutic levels.
6. Gastroenterologist may switch within biological class if high titre antibodies are present. Absence of clinical response, therapeutic trough levels and presence of markers of inflammation would indicate the need to consider alternative biological therapy.
7. If high titre antibodies are present with sub-therapeutic drug levels, switching within class, or out of class, may be indicated. Optimising concomitant immune modifier therapy is recommended.,
8. Treating Gastroenterologist to escalate anti-TNFα therapy as per the recommended SCHN algorithm, based on the Gastroenterology Society of Australasia, GESA [14] and the American Gastroenterology Association AGA [15].
9. Gastroenterologist to manage and record disease activity, drug, and antibody TDM, rate of escalation with clinical and TDM response to escalation, with PCDAI/PUCAI, faecal calprotectin, endoscopic and imaging assessment. Results to be recorded in Powerchart.
10. Patients at risk for accelerated infliximab clearance during induction [i.e. children <30 kg, those with extensive disease, and those with low serum albumin] may have their first proactive TDM at the second or third infusion [12].

Options for Dose Intensification/Escalation

Dose escalation and intensification as follows:

11. Infliximab may be dose escalated up to 45mg/kg IV within the first 2 weeks, with dosing intervals at the discretion of the treating gastroenterologist to reach target trough levels [12] or clinical response in ASC

Adalimumab may be dose escalated from 20 mg up to 80 mg subcutaneously, and frequency escalated up to weekly dosing.

Escalation can improve clinical response in the majority of patients, occasionally despite the presence of antibodies. As re-capturing of response is usually demonstrated in patients who achieve measurable increase in drug levels after dose intensification, TDM may be helpful to better identify patients who will respond to this intervention.

Clinical decision support tools for assessing therapeutic drug levels and escalating therapy have been developed by the American Gastroenterology Association, the GESA, and the ECCO-ESPGHAN groups [14-15].

Indications for De-Escalation

Six monthly re-assessment of suitability to ‘de-escalate’ to standard treatment dose/frequency is determined by Physician and dependent on a combination of clinical state (PCDAI and previous severity of illness) and/or imaging modalities and/or endoscopic assessment, and therapeutic drug monitoring [11].

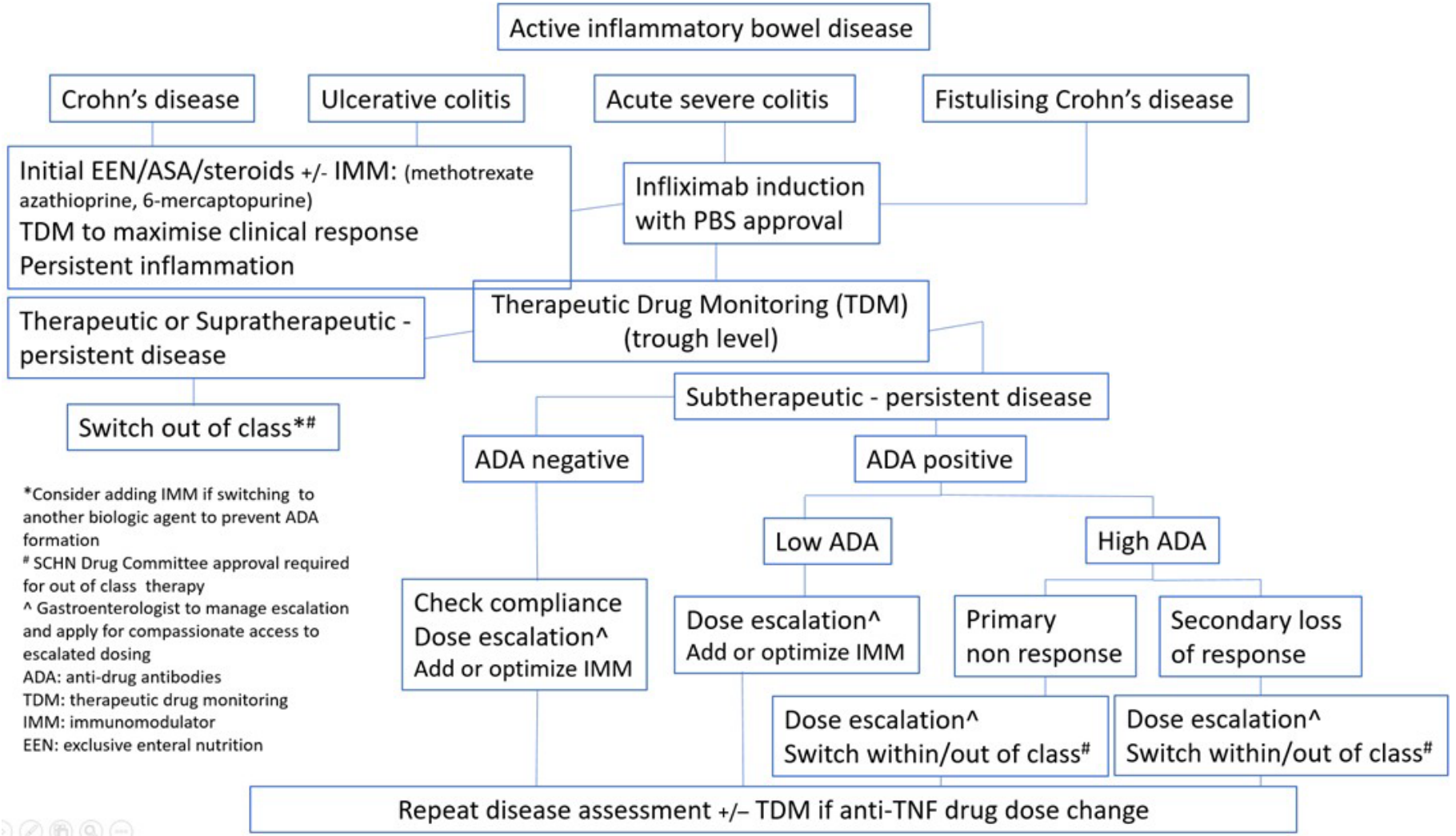
Therapeutic drug monitoring is an important tool to guide the de-escalation strategy.

Indications for Switching Within Class

Switching with the biological class of anti TNFα (e.g. from infliximab to adalimumab) may induce sustained remission in some refractory patients and is considered an acceptable approach to manage this group of patients [16-18]. Switching to the subcutaneous form of infliximab (120mg/ ml) may be considered, and dosing modified according to therapeutic drug monitoring and patient status.

Note: Patients with severe colitis/ inflammation will need dose escalation at time of induction or severe flare **before** drug levels are available.

Biological drug escalation and TDM protocol to elicit mechanisms of treatment failure and guide treatment decisions in non-responders.



Adapted from:
Mitrev N, Vande Casteele N, Seow CH, et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. Aliment Pharmacol Ther. 2017;00:1–17. https://doi.org/10.1111/apt.14368

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