INFLIXIMAB INFUSION: ADMINISTRATION AND MANAGEMENT FOR PAEDIATRIC CROHN'S DISEASE AND ULCERATIVE COLITIS

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Infliximab is a chimeric anti-tumour necrosis factor antibody approved by the Therapeutic Goods Administration (TGA) for use in Fistulising Crohn's Disease, Refractory Luminal Crohn's disease, Moderate/Severe Ulcerative Colitis and Acute Severe Colitis. Prescribing is restricted to Gastroenterologists for:
  - Treatment of moderate to severely active Crohn's disease in children who have had an inadequate response to conventional therapy
  - Treatment of children with severe fistulising Crohn's disease.
  - Treatment of Acute Severe Ulcerative Colitis in children who have failed to achieve adequate response to 72 hours of IV Corticosteroids and have a PUCAI (Paediatric Ulcerative Colitis Activity Index) score > 45.
  - Treatment of Moderate Severe Ulcerative Colitis in children who have had inadequate response to conventional therapy.
  - Maximum dose: 10 mg/kg (dose escalation or increase in frequency of interval decisions are made in consultation with the treating Gastroenterologist).

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st October 2018	**Review Period**: 3 years
Team Leader:	CNC Inflammatory Bowel Disease	**Area/Dept**: Gastroenterology

CHANGE SUMMARY

- Introduction of fast infusion protocol for selected patients
- Grading up of infusion rates
- Use of closed system for reconstitution of medication- Infliximab is classified as hazardous

READ ACKNOWLEDGEMENT

- • Medical and nursing staff who care for patients being treated with infliximab are required to read and acknowledge the document.

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Introduction

Tumour necrosis factor alpha (TNF-α) is an important cytokine involved in promoting intestinal inflammation. In Inflammatory Bowel Disease, immune cells associated with an overactive immune system produce excess amounts of TNF-α. Controlled trials in patients with refractory Crohn's disease, Fistulising Crohn's disease and ulcerative colitis using the chimeric anti-TNF-α antibody Infliximab, have shown its efficacy in specifically binding to and neutralising TNF-α , and by reducing the ability of cells (lymphocytes) to make TNF-α.

Prescribing of Infliximab is restricted to Gastroenterologists. Infliximab is available in single-use 100 mg vials as a sterile white lyophilised powder for intravenous (IV) injection. Each vial is reconstituted with sterile water for injection and the total dose then diluted to 250 mL with 0.9% sodium chloride and given as an intravenous infusion (the final concentration should be between 0.4 – 4 mg/mL[1]). The half-life of a dose of 5 mg/kg is 9 days.

Mechanism of action

Infliximab is an antibody (anti-TNFα) that blocks the effects of TNFα resulting in decreased inflammation.

Infliximab works by suppressing inflammation early in the cascade of cellular events that leads to features of IBD [5].

Repeated infusions may help to maintain remission [6]. However, a proportion of children and adult patients can lose response on long term Infliximab therapy, the mechanisms for which are not clearly understood and include the development of antibodies to the medicine.

Infliximab is classified as a hazardous medication in The Sydney Children's Hospital Network.

Indications for Use (as indicated by the TGA)

- Treatment of moderate to severely active Crohn's disease in children who have had an inadequate response to conventional therapy.
- Treatment of children with severe fistulising Crohn's disease. Treatment of Acute Severe Ulcerative Colitis in children who have failed to achieve adequate response to 72 hours of IV Corticosteroids and have a PUCAI (Paediatric Ulcerative Colitis Activity Index) score > 45. Patients who meet the Paediatric Acute Severe Ulcerative Colitis PBS Guidelines must receive their second dose of infliximab prior to day 14 (week 2) to qualify for PBS subsidised infliximab.
- Treatment of Moderate Severe Ulcerative Colitis in children who have had an inadequate response to conventional therapy.
- Infliximab therapy is commenced with an **initial infusion** of 5 mg/kg (week 0), followed by two repeat 5 mg/kg infusions at week 2 and week 6 (known as induction). Infusions may then be given at 8 weekly intervals on an ongoing basis.
- The decision to increase the frequency or escalate the dose of the infusions outside of these parameters will be made by the treating Gastroenterologist taking into

consideration a variety of factors including PCDAI/PUCAI, infliximab level, and clinical condition.

Before Initiating Infliximab Therapy

- The family will have been counselled regarding the risks and benefits of this treatment by the attending Gastroenterologist and the Clinical Nurse Consultant.
- Patients who are identified as eligible for PBS funded Infliximab should have the appropriate paperwork completed and sent to Medicare for processing.
- The patients will have their current disease activity documented clinically by completion of the Paediatric Crohn's Disease Activity Index Form or Paediatric Ulcerative Colitis Activity Index form by the Gastroenterology Team prior to the commencement of therapy.(Electronic form available at CHW via powerchart) in adhoc charting.
- A workup for TB will be performed as appropriate. To include at least one of the following CXR/Mantoux/ Interferon Gamma Release Assay (IGRA) testing.
- The immunisation status of the patient will be checked prior to commencement of treatment.
- MMR serology will be checked. If no evidence that patient has received 2 doses of MMR containing vaccine, or if non-immune to 1 component, then the recommendation is to vaccinate prior to commencement of treatment providing the patient is well enough to wait 1 month before commencing Infliximab therapy.
- All live vaccines are **contraindicated** once Infliximab therapy is commenced (i.e. MMR, Varicella, BCG, oral Typhoid, Yellow Fever). Live vaccines should be avoided if they are going to further delay urgent treatment.
- A referral to the Specialist Immunisation team at CHW or SCH will be completed if there are specific concerns.
- Live vaccines are contraindicated in individuals until 3-6 months after all immunomodulatory therapy is discontinued.
- Laboratory investigations should be attended prior to the initiation of Infliximab therapy and must include: FBC, EUC, Albumin, LFT's, ESR, CRP. Consideration for re/testing for HIV, Hepatitis B and EBV serology should be made by the treating Gastroenterologist.

Nurse Education and Accreditation

- As Infliximab is classified as a hazardous drug, nurses are required to achieve their Hazardous Drug Accreditation before administering Infliximab.
- PPE is required. Gowns, gloves, goggles, mask are required + a closed infusion system.

Before Commencing the Infliximab Infusion

- Ensure patient is afebrile, without respiratory symptoms or signs of an active abscess. Discuss concerns with the Gastroenterologist prior to commencing infusion.
- To ensure the patient receives adequate dosing, the Infliximab dose should be reviewed regularly to ensure that it corresponds to either:

  A) The patient's PBS authority script (if patient receiving PBS funded Infliximab ONLY)

  AND/OR

  B) The patients weight i.e. 5 mg/kg (10 mg/kg if on dose escalation at discretion of treating Gastroenterologist)
- If dose interval is less than 8 weeks formal drug committee approval is required (CHW only)
- **Observations** should be undertaken to establish a baseline reading to detect any reactions to the Infliximab: temperature, pulse, respirations, blood pressure and oxygen saturation should be performed. These should be attended immediately prior to the administration of the Infliximab.
- The patient must have a new cannula inserted or the cannula must be < 3 days old.
- Prior to commencement of infusion blood sampling should occur at the time of cannulation and laboratory investigations sent for: FBC, EUC, CMP, Albumin, LFT, ESR and CRP. Infliximab pre-infusion trough levels may be requested depending on the patient's clinical condition. These will be ordered by the Gastroenterology Team or Clinical Nurse Consultant where appropriate.

At CHW

- A pre-medication of intravenous corticosteroid (methylprednisolone 2 mg/kg to a maximum of 40 mg) is to be administered 30 minutes prior to the commencement of the infusion. Antihistamines may also be administered if a previous reaction has been documented in this patient or at the discretion of the Gastroenterologist. (CHW)

At SCH

- 30 minutes prior to commencing each Infliximab infusion, a pre-medication of:
  - IV Hydrocortisone 4 mg/kg/dose, max.120 mg
  - Oral antihistamine (e.g. Fexofenadine 30 mg < 12 years; 60 mg >12 years)
  - Oral Paracetamol 15 mg/kg/dose, max.1000 mg.(SCH)

Equipment

All Equashield equipment is available from Clancy Ward or Turner Ward (CHW) and Kids GPS Medical Day Unit (SCH)

- Infliximab 100 mg vial, appropriately labelled

- Water for injection (WFI)100 mL bottle
- Equashield 10 ml Syringe, Equashield Vial adaptor (VA-20/2 red top) Equashield Spike adaptor
- 250 mL bag of 0.9% sodium chloride
- Intravenous administration set and burette
- 0.2 micron low protein binding filter
- Intravenous double spiker
- 50 mL bag 0.9% sodium chloride
- PPE

Administration (Standard infusion rate over 2 hours)

1. **Dosage:** 5 mg/kg as an intravenous infusion over 2 hours using an IV giving set and low protein binding filter.
2. **Maximum Dose:** 10 mg/kg (doses above 5 mg/kg are made by the Gastroenterologist).
3. Standard infusion rate for the first 4 doses. Patients who do not tolerate rapid infusion protocol may revert to the standard infusion protocol.
4. Don protective personal equipment. SCHN Hazardous Drugs Administration Guideline currently under development.
5. Reconstitute each 100 mg vial of Infliximab with 10mL of sterile water for injection using a closed system (i.e. Equashield). **Gently swirl** the solution to dissolve the powder: **DO NOT SHAKE.** Allow the vial to stand for 5 minutes.
6. Dilute the prescribed dose of the reconstituted solution to 250 mL with 0.9% sodium chloride. Use a 250 mL bag of 0.9% Sodium Chloride solution for infusion. Remove amount of Sodium Chloride equal to total volume of reconstituted Infliximab to be injected. Final concentration should be between 0.4-4 mg/mL.
7. Do **not** infuse alongside other products in the same intravenous line.
8. 8. Administer the infusion as per prescribed. Rates are as table below:

TIME (minutes)	Infliximab INFUSION RATE
0-15	Commence at 10 mL/hr for 15 min
15-30	Increase to 20 mL/hr for 15 min
30-45	Increase to 40 mL/hr for 15 min
45-60	Increase to 80 mL/hr for 15 min
60-90	Increase to 160 mL/hr for 30 min
90-120	Increase to 250 mL/hr for 30 min

9. After completion of infusion, flush the line with 0.9% Sodium Chloride 20 mL at the same rate.

Precautions & Observations

- Ensure resuscitation equipment and medication available (adrenaline, antihistamine and IV hydrocortisone) prior to administering the drug.
- Close monitoring of the patient should occur during the infusion and for 1- 2 hours post infusion – this includes checking and documenting:
  - Pulse, BP, Respiratory Rate and Temperature – every 15 minutes for 1 hour
  - Pulse, BP, Respiratory rate and Temperature every 30 minutes 1 hour
  - Hourly until observation period of 1-2 hours is completed
  - Continuous pulse oximetry.
- The resident medical officer is NOT required to stay in the clinical area during the infusion.
- The patient must stay in the clinical ward area during the 1-2 hours post-infusion observation period to monitor for signs of adverse reactions.
- **2 hour post infusion observation period is required for all doses of Infliximab during induction period (first 3 initial infusions given over 6 weeks.**
- IV cannula should remain in-situ during the period of observation.

Administration - Rapid infusion rate over 1 hour – Requires approval of treating Gastroenterologist

1. After a minimum of 4 infusions of Infliximab have been completed without complication or adverse reaction, at the discretion of the treating gastroenterologist, subsequent infliximab infusion may run as a rapid infusion over 1 hour [3,17].
2. **Only** available for patients on 5 mg/kg dose
3. **Caution** is required if considering rapid infusion in any child **under 25kg**.
4. Administer the infusion as prescribed. Follow the infusion rates below:

TIME (minutes)	Infliximab INFUSION RATE
0	Commence at 60 mL/hr for 10 min
10	Increase to 120 mL/hr for 10 min
20	Increase to 250 mL/hr until infusion complete

5. After completion of infusion, flush the line with 0.9% Sodium Chloride 20 mL at the same rate.
6. Pulse, BP, Respiratory Rate and Temperature – every 15 minutes throughout the infusion.
7. Pulse, BP, Respiratory rate and Temperature every 30 minutes post completion of the infusion.

8. Patient should stay for a **minimum of 1 hour** following infusion to monitor for adverse reaction.
9. IV cannula should remain in-situ during the period of observation.

Adverse Reactions

Emergency resuscitation equipment must be available at all times.

Patients should be monitored closely for the signs of infusion reaction to Infliximab such as:

- Fever
- Chills
- Pruritus
- Rash/Urticaria
- Dyspnoea
- Hypertension
- Hypotension
- Chest pain

In the event of infusion reaction escalate care as per BTF

Mild reaction (fever, chills, headache, dizziness, palpitations, nausea)

- STOP INFUSION, do not discard the Infliximab.
- Escalate as per BTF
- Discuss with the Consultant/Fellow regarding the appropriateness of restarting IFX at a slower rate ie.10 ml/hr
- Progressively increase infusion by 20 ml/hr every 15 minutes as tolerated.
- Document any reaction. If remainder of infusion tolerated, consider additional premedication with Paracetamol and Antihistamine for subsequent infusions.

Moderate reaction (mild symptoms plus chest discomfort; dypnoea, hypo/hypertension (>20mmHg SBP) ; urticaria, increased temperature

- STOP INFUSION, do not discard Infliximab
- Escalate as per BTF
- Administer Antihistamine IV
- Discuss with the Consultant/Fellow regarding the appropriateness of restarting Infliximab at a slower rate ie.10 ml/hr
- If infusion restarted progressively increase the rate by 20 ml/hr every 15 minutes as tolerated.
- Document any reaction

- If remainder of infusion tolerated, premedicate with paracetamol and antihistamine for all subsequent infusions

Severe reaction (Dyspnoea, tachycardia, chest pain, hypotension, Anaphylaxis)

- STOP INFUSION
- Call rapid response, and escalate care as BTF
- Consider Adrenaline **1:1000** 0.1 ml/kg IM

Review and Documentation

Patients should be reviewed in the day stay unit on the day of infusion as per site specific requirements. Patients should be seen in the Inflammatory Bowel Disease clinic at least every 3-4 months. Documentation will be as per site specific requirements. Paediatric Crohn's Disease Activity Index (PCDAI) and Paediatric Ulcerative Colitis Index (PUCAI) forms are available through ADHOC charting in powerchart.

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