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Type: Guideline

Name: Safe administration of infliximab (including desensitisation)

Purpose

The purpose of this policy is to:

- To ensure the safe administration of intravenous infliximab to all patients receiving this medicine
- To detect early patient complications in relation to this medication.
- Outline the responsibilities of nursing staff in the administration, monitoring and post infusion care.

Using the appendices for **desensitisation of infliximab**, the purpose is also to:

- Allow patients with previously documented allergy to infliximab to receive doses safely
- Ensure that concentrations of infliximab are made correctly in the ward environment
- Ensure that pre-medications and 'when required' medications are appropriately prescribed for patients undergoing this process

Scope

This policy is for all nursing and medical staff involved with the care of patients receiving infliximab via intravenous infusion at CCDHB. This includes but is not limited to nursing staff, house officers, registrars, consultants and pharmacists.

Definitions

Infliximab belongs to a class of drugs known as biologics. It is provided as a white lyophilised powder, which when reconstituted, results in a clear, colourless to light yellow solution. This solution is then further diluted as per in the instructions in the protocol. Dilution is dependent on whether the patient is receiving standard treatment, or desensitising treatment.

Mechanism of action: Infliximab is a monoclonal antibody that binds to the human tumour necrosis factor alpha (TNF-alpha). TNF-alpha is a pro-inflammatory and immunoregulatory cytokine that, when overexpressed, mediates chronic inflammation. Infliximab neutralises the biological activity of TNF-alpha by binding with high affinity to the soluble and transmembrane forms of TNF-alpha.

Indications include but are not limited to:

- Crohn's Disease
- Ulcerative Colitis
- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Psoriatic Arthritis
- Psoriasis
- Sarcoidosis
- Behcet's Disease
- Ocular inflammation

Infusion Reactions

Reactions during infliximab infusion and hypersensitivity reactions after infusion are uncommon. Infusion reactions are most likely to occur during the first four infusions. Reactions are generally mild and managed by slowing the infusion rate and administering antihistamines and paracetamol (see adverse reaction plan below).

Pre-medications such as paracetamol, antihistamines and hydrocortisone are no longer routinely required as they have not been shown to reduce the incidence of infusion reactions. These medications should be available on the PRN section of the drug chart.

For patients undergoing **desensitisation**, pre-medication is mandatory (see Appendix 1).

Delayed hypersensitivity reaction can occur 3-12 days after re-treatment with infliximab following a break in treatment and consist of myalgia/arthralgia, fever and/or rash. Pruritus, facial/hand/lip oedema, dysphagia, urticaria, sore throat and/or headache can also occur. In the event of a delayed hypersensitivity reaction the patient should be advised to seek medical help.

Adverse effects include but are not limited to:

- headache, vertigo and dizziness
- viral infection
- serum-sickness like reaction
- throat irritation
- flushing
- rash/urticaria
- hypertension
- pyrexia
- nausea, abdominal pain, dyspepsia
- abnormal hepatic function

Adverse reaction plan

Reaction	Symptoms, signs	Management
Mild	Rash, urticaria	Slow/stop infusion for 10 minutes Administer paracetamol and antihistamine Restart infusion at 50% of baseline rate
Severe As per EWS: a score of 3-5 or one score of 3	Hypotension, bradycardia, respiratory compromise	Stop infusion Administer antihistamine, hydrocortisone and oxygen Request medical review

Pre-infusion assessment

This is ultimately the responsibility of the medical practitioner who has applied for infliximab but should be confirmed by the prescriber if that is not the same person.

Infliximab usually requires a special authority. Prescribers should consult the Pharmac website for details. (NB in some cases infliximab may be supplied via a NPPA or compassionate supply).

All patients prescribed infliximab need to have:

- negative pre-screening blood tests for chronic infection
    - There is regional variation but at a minimum this should include Quantiferon TB; Hepatitis B, Hepatitis C, and HIV serology
- chest x-ray completed and cleared (infliximab is contra-indicated in patients with TB)
- weight recorded and the dose calculated correctly based on this weight
- PRN medications charted for use in the event of an infusion reaction
    - Paracetamol 1g po, Loratadine 10mg po, Hydrocortisone 100mg IV
- patient consent form signed
- contraindications to infliximab have been excluded including:
    - active opportunistic infection, sepsis or abscess
    - moderate or severe heart failure (NYHA class III/IV)
    - previous hypersensitivity to infliximab
    - live vaccine within the last 6 weeks

Preparation of Infliximab for standard infusion

*NB. For patients undergoing **desensitisation of infliximab**, DO NOT use these instructions. Please refer to the appendices at the end of this guideline instead.*

All administration of infliximab should comply with the CCDHB Protocol Intravenous (IV) therapies administration and management available on Capital Docs

- Read through patient referral and check weight of patient
- Read guideline for the administration of infliximab
- Check prescription on drug chart includes patient's name, date, route, drug name, drug dose and has been signed
- The patient's weight has been recorded and the dose has been double checked against the patient's weight
- The number of vials has been correctly calculated against prescribed dose (each vial = 100mg)
    - **NB: the dose should be rounded to the nearest 50mg i.e. if the weight based dose calculation is 380mg, then 400mg should be administered.**
- Check vital signs and record prior to commencing infusion: blood pressure, heart rate, temperature and respiratory rate
- Obtain IV access and flush with 10ml 0.9% sodium chloride
- Check pre-medicines are charted and infliximab dose is correct. Ensure right patient, right drug, right dose, right time, and right route. Sign and date prescription with a second registered nurse.
- Remove caps from 10 mL water for injection ampoule and infliximab vial(s) and clean rubber stoppers with alcohol wipes
- Reconstitute each 100 mg infliximab vial by injecting 10 mL water for injection into each vial. Direct the stream of water for injection to the side of the vial, not directly on to the powder. Do not use the vial if a vacuum isn't present. Foaming on the solution is not unusual. The concentration of the reconstituted infliximab is 10 mg/mL.
- Remove and dispose of the needle and syringe in compliance with CCDHB protocol
- Swirl gently or slowly roll the infliximab vial (DO NOT SHAKE) in hands or on a smooth surface until the white powder is completely dissolved
- Allow the reconstituted powder to stand for 5 minutes before further manipulation, the liquid should be colourless/light yellow. A few fine particles are not unusual, but do not use if there are large particles, discolouration, or foreign particles
- Clean the port of a 0.9% sodium chloride 250 mL bag. Calculate the total dose volume of infliximab to be added to the bag, and remove the equal amount of 0.9% sodium chloride. Then, aseptically withdraw the infliximab dose from each vial and slowly add to the 250 mL bag.
- Gently rotate the bag to mix the solution (DO NOT SHAKE)
- Prime intravenous giving set. **Use ONLY an infusion set with an inline, sterile, non-pyrogenic, low protein binding filter (pore size 1.2 micron or less).**
- Place an additive label to the bag stating the dose of infliximab (in 250 mL 0.9% sodium chloride) and the time of reconstitution
- Check vital signs as per nursing care plan and inform medical staff if any reaction
- Refer to **'Infusion rate schedule for standard administration of Infliximab'** (below) for infusion rate
- On complete of the infusion, flush the IV cannula and tubing with 10 ml 0.9% sodium chloride
- Remove IV cannula and check and record phlebitis score

- Check vital signs post infusion. For doses 1-9, all patients are monitored/observed for at least one hour after the infusion is complete due to the risk of delayed onset allergic reactions

Infusion rate for standard administration of Infliximab

Initial infusion, week two infusion, week six infusion – to be infused over AT LEAST 2 HOURS

Prescribed dose of infliximab in 250 mL 0.9% sodium chloride, infused as follows:

Time	Infusion Rate (mL/hour)
T 0 minutes	10
T 15 minutes	20
T 30 minutes	40
T 45 minutes	80
T 60 minutes	150
T 90 minutes	250

For adult patients who have tolerated at least 3 initial 2 hour infusions, subsequent infusions may be given over a period **of at least 1 hour**. This needs to be prescribed as such by the Doctor based on the patient's previous dose history.
Prescribed dose of infliximab in 250 mL 0.9% sodium chloride, infused as follows:

Time	Infusion Rate (mL/hour)	Volume infused (mL)
T 0 minutes	100	25
T 15 minutes	300	225

Other considerations

Previous mild reaction, increase dose as tolerated **(note this is NOT desensitisation**)	12.5ml over 30mins 25ml over 30mins 50ml over 30mins Remainder to be infused over 90mins	
>10 weeks since last dose	Administer as per initial dose	
10mg/kg dose	Double administration time of previous infusion i.e. if previously over 1 hour then administer over 2 hours	

References

Notes on Injectable Drugs-Adults 7th Ed , New Zealand Hospital Pharmacists' Association, Wellington 2015

Janssen-Cilag (New Zealand) Ltd, Remicade®(Infliximab) Powder for Injection Datasheet (dated 20/01/16), accessed via http://www.medsafe.govt.nz/profs/Datasheet/r/Remicadeinj.pdf 07/17

Mourad AA, Boktor MN, Yilmaz-Demirdag Y, Bahna SL, Adverse reactions to infliximab and the outcome of desensitization, *Ann Allergy Asthma Immunol* 2015;115: 143-146

Appendix

Appendix 1: Infliximab Desensitisation Protocol

Associated forms

Infliximab - 2 Stage Infusion Administration Schedule CapitalDocs ID 1.103512

Infliximab - 3 Stage Infusion Administration Schedule CapitalDocs ID 1.103513

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Appendix 1 Infliximab Desensitisation Protocol

Pre-Infusion Instructions for Doctors:

1) Chart infliximab on the patient's medication chart on the once only section. The instruction should read '*As per Desensitisation Protocol'*

2) Patient should be specifically consented for desensitisation including the possible risks involved

3) Prescribe loratadine 20mg po for the night before (T -12 hours) and the morning of (T -2 hours) the infusion

4) Chart IV hydrocortisone 100 mg on the patient's medication chart on the once only section

5) Chart IM adrenaline 0.5mg (0.5mL of 1:1,000) on the patients medication chart on the once only section

6) Ensure that nurses are using correct infusion administration schedule: *3 Stage Infusion* or *2 Stage Infusion* (appendix 2a or 2b)

- 3 Stage Infusion is used for patients who are either:
- Receiving their first desensitisation of infliximab, OR
- Receiving subsequent desensitisation of infliximab following an infusion reaction on the previous dose

- **2 Stage Infusion is used for patients who are:**
- Receiving subsequent desensitisation of infliximab following an incident free previous dose

Sign and date appropriate infusion administration schedule (appendix 2a or 2b) in the top right corner for nurses to use during administration

Pre-Infusion Instructions for Nurses

1) This process can only begin once the Doctor has prescribed infliximab on the patient's medication chart and fulfills all of the criteria as listed above

2) Ensure that the correct protocol is used for the correct patient
- 3 STAGE INFUSION is used for patients who are either:
- Receiving their first desensitisation of infliximab, OR
- Receiving subsequent desensitisation of infliximab following an allergic reaction on the previous dose

- 2 STAGE INFUSION is used for patient who are:
- Receiving subsequent desensitisation of infliximab following an incident free previous dose

3) Reconstitute the infliximab as per the instructions in appendix 1

4) Give the patient's prescribed pre-medications as per the chart

5) Fill in the start time of the infusion on the infusion administration schedule

6) Any queries need to be answered before administration begins, by either the charge nurse manager, the prescribing doctor, or the pharmacist on the ward

Additional nursing Instructions for desensitisation:

1. There should be 1:1 nursing support (a special nurse)
2. Informed consent should be obtained by the prescribing doctor
3. Baseline observations should be made including heart rate, blood pressure, respiratory rate, oxygen saturation, and spirometry if appropriate.
4. A 20G or larger intravenous cannula should be inserted.
5. The following emergency drugs should be **at the bedside:**
    a. Loratadine 10mg
    b. Hydrocortisone 100mg
    c. Salbutamol 5mg nebule
    d. 1000mL normal saline
    e. High flow oxygen
    f. Adrenaline 0.5mg (=0.5mL of 1:1,000)
6. Doses given every 15 minutes
7. Observations to be made **every 30 minutes during procedure and if there is a clinical change.**
8. The patient should be observed for at least 2 hours following the last dose, with observations performed hourly.

Preparation of Infusion Solutions for Desensitisation

For patients undergoing their first infusion, it is a three step process – 3 Stage Infusion.

If patients have previously received infliximab via this three stage process and are having subsequent treatments, the first stage can be omitted – 2 Stage Infusion. See below for the infusion schedules.

Infusions made on the ward or outpatient clinic areas can only be used for 3 hours after compounding[1].

The 1 mg/mL and 0.1 mg/mL infusions can both be prepared immediately prior to the start of the infusion.

The 4 mg/mL solution will need to be prepared whilst the 1 mg/mL infusion is running to ensure stability.

For all infusions:

Step 1. To make 1 mg/mL solution:

- Remove 10 mL from a 100 mL bag 0.9% sodium chloride and discard.
- Reconstitute one 100 mg infliximab powder vial using 10 mL sterile water for injection. Do not shake the vial. Gently roll in the hands to disperse any clumps. Allow to sit for 5 minutes before further manipulation.
- Add the contents of the vial to the remaining 90 mL 0.9% sodium chloride bag.
- This is now a **1 mg/1 mL** solution.
- Further manipulation is required if patient is being infused for the first time (ie. 3 Stage Infusion). For second and subsequent infusions (ie. 2 Stage Infusion), no further manipulation of this is necessary and the bag should be labelled as 100 mg/100 mL infliximab in 0.9% sodium chloride.

For first infusions only (3 Stage Infusion only):

Step 2. To make 0.1 mg/mL solution:

- Remove 5 mL from a 50 mL bag 0.9% sodium chloride and discard.
- Remove 5 mL (5 mg) of the 1 mg/mL solution from the bag as made above and add to the 45 mL 0.9% sodium chloride bag.
- This will give a 5 mg in 50 mL, which is a **0.1 mg/mL** solution.
- Label as 5 mg/50 mL infliximab in 0.9% sodium chloride.
- Label the bag from step (1) as 95 mg/95 mL infliximab in 0.9% sodium chloride. Store in the fridge until required.

For all infusions:

STEP 3. To make 4 mg/mL solution:

- Remove 5mL 0.9% sodium chloride from a 50 mL bag and discard to leave 45mL inside the bag.
- Reconstitute three 100 mg infliximab vials, each with 10 mL sterile water for injections. As above, do not shake the vials. Gently roll in the hands to disperse any clumps. Allow to sit for 5 minutes before further manipulation.
- Add the contents of the vials to the 45 mL 0.9% sodium chloride to give a total of 300 mg in 75 mL 0.9% sodium chloride. This is a **4 mg/mL** solution.

Use ONLY an infusion set with an inline, sterile, non-pyrogenic, low protein binding filter (pore size 1.2 micron or less).