**Scottish Paediatric & Adolescent Rheumatology Network**

**Guideline for Infliximab Use**

Infliximab is an anti-inflammatory monoclonal antibody, derived from human and mouse cells. Infliximab inhibits the pro-inflammatory cytokine tumour necrosis factor alpha (TNF-alpha). It has been shown to be effective in the management of many paediatric rheumatological conditions including:

* Juvenile idiopathic arthritis (JIA): active arthritis (all JIA subtypes except systemic onset juvenile idiopathic arthritis), failure of methotrexate monotherapy, failure of other anti tumour necrosis factor alpha (antiTNF) therapy, requirement to administer antiTNF therapy via intravenous (IV) route for patient concordance/tolerability Juvenile Systemic Lupus Erythematosus
* JIA with active uveitis which has failed to respond to methotrexate monotherapy, where adalimumab has failed or adalimumab is not recommended due to route of administration
* Idiopathic uveitis which has failed to respond to methotrexate monotherapy, where adalimumab has failed or adalimumab is not recommended due to route of administration.
* Juvenile dermatomyositis (JDM) after inadequate response to methotrexate and prednisolone
* Chronic nonbacterial osteomyelitis (CNO) after inadequate response to pamidronate

**Contra-indications:**

* History of hypersensitivity to infliximab, other murine proteins or to any of the excipients
* Tuberculosis – in certain situations a decision may be made to give infliximab alongside anti-TB treatment if no other options available but this is at the clinician’s discretion
* Severe infections e.g. sepsis, abscesses and opportunistic infections
* Moderate or severe heart failure
* Pregnancy
* MS or recent onset of demyelinating disorders

**Cautions:**

* Family history of MS or demyelinating disorders
* History of malignancy
* Chronic hepatitis B infection
* Heart failure
* Predisposition to infection
* Risk of delayed hypersensitivity reactions if drug free interval exceeds 12 weeks.
* Severe needle phobia and potential vascular access problems

**Pre-assessment considerations:**

* Full clinical history
* Height, weight, pubertal status
* Immunisation history – Consider delaying infusion for 4 weeks administration of live vaccinations as per green book guidance - [Greenbook\_chapter\_6.pdf (publishing.service.gov.uk)](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/655225/Greenbook_chapter_6.pdf)
* Bloods including FBC, ESR, U&E, LFT, creatinine, CRP, ANA, dsDNA, varicella zoster serology.
* Varicella Zoster serology, hepatitis B and C status, HIV status, EBV and CMV IgG should be checked if not done previously and only repeated if thought to be clinically relevant.
* Chest X-ray: To be performed and resulted prior to commencing infliximab if not performed in the last 3 months and if no relevant symptoms have developed in the interim.
* Quantiferon gold/Elispot (can use Mantoux as an alternative if quick result needed)
* Pregnancy test for all females over 12 years of age who have reached menarche.
* Patient information to be given and discussed with the patient and carers

**Dosage**

* **Induction**

Infliximab will be administered at a dose of 6mg/kg, rounded to the nearest 10mg, as an intravenous infusion over a 2 hour period using the following regimen:

1st Dose – Week 0

2nd Dose – Week 2

3rd Dose – Week 6

* **Maintenance**

Standard dosing is 6mg/kg as an intravenous infusion every 4-8 weeks, adjusted depending on response and trough drug levels. Dose and frequency will be adjusted in response to clinical response plus therapeutic drug monitoring. Doses of 10mg/kg may be used in severe disease, or if disease control has been lost. This strategy would be initiated only following the advice of the consultant paediatric ophthalmologist or rheumatologist and usually following measurement of infliximab level and antibodies

**Monitoring Prior to Infusion**

Ensure the following is complete before commencing the infusion:

* Pregnancy test for all females over 12 years of age who have reached menarche.
* Ensure there is no underlying infection.
* Site an intravenous cannula in an appropriate vein.
* Take bloods to check FBC, U&E’s, LFTs, CRP, and ESR – do not wait for blood results before starting.
* Infliximab levels and antibodies if requested.
* Baseline temperature, pulse, respiratory rate, blood pressure. Record these immediately prior to commencing the infusion.

**Hydrocortisone Pre-medication**

In those patients who have experienced previous mild/moderate infusion reactions the following premedication should be administered 30 minutes prior to infusion commencing. This could also be considered if a patient has admitted non-compliance with co-medication in which case their risk of infusion reaction is theoretically higher.

Hydrocortisone (sodium succinate) intravenous bolus injection dosing:

* Children aged 1 - 5 years - 50mg
* Children aged 6 - 18 years - 100mg

**Preparation(6)**

To prepare the infusion:

* Reconstitute each 100mg vial of infliximab with 10mL of water for injection directing the stream of water to the glass wall of the vial. Final concentration 10mg/ml.
* Gently swirl the solution by rotating the vial to dissolve the powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE.
* Allow the reconstituted solution to stand for 5 minutes.
* Check that the reconstituted solution is colourless or light yellow. Do not use if opaque particles, discolouration or other foreign particles are visible.
* Calculate the required volume of reconstituted infliximab for the prescribed dose.
* Withdraw the required infliximab volume from the 250ml 0.9% sodium chloride infusion bag, ensuring that the final dose of infliximab does not exceed 1000mg. For doses above 1000mg contact pharmacy for advice.
* Slowly add the total volume of reconstituted infliximab to the infusion bag and mix gently.
* The infusion is now ready to be administered.

**Administration:**

* Prior to starting the infusion ensure emergency drugs are available in the ward area in case of any adverse reaction.
* All medications should be given in accordance with [the hospitals Safe Use of Medicines Policy](http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/ClinicalGuidance/General/Medicines%20Policy%20and%20procedures%20-%20December%202009.pdf).
* Check all prescribed doses of infliximab are correct for the patient.
* Administer any prescribed premedication if required.
* Administer infliximab infusion using an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 micron or less).
* Visually inspect the infusion for particulate matter, discolouration or foreign particles.
* Infuse at 125ml/hr for doses over 2 hours, or 250ml/hr for doses over 1 hour for doses less than 1000mg. For doses above 1000mg contact pharmacy for advice. (Decision regarding how long to give infusion over may vary according to local protocol and clinician discretion. Generally aim to give slower if higher risk of infusion reaction or first time having this medicine. E.g. may wish to give over longer period e.g. 2-3 hours, for the first 3 infusions and then an hour thereafter. )
* Flush with 30ml of Sodium Chloride 0.9% at the same rate as the infliximab infusion.
* We would encourage patients to stay for an hour after their first 3 infusions

**Monitoring**

**During the infusion**

* Monitor pulse, temperature, respiratory rate and blood pressure every 30 minutes during the infusion.
* Acute infusion reactions may develop anytime during or after the infusion.
* If a patient develops a reaction follow the infusion related reaction treatment guidance in appendix A.

**Post infusion**

* Monitor pulse, temperature, respiratory rate and blood pressure every 30 minutes for 1 hour post a 2 hour infusion
* Monitor pulse, temperature, respiratory rate and blood pressure every 30 minutes for 30 minutes post a 1 hour infusion.
* If a patient develops a reaction follow the infusion related reaction treatment guidance in appendix A.
* Advise patients and carers to report any signs of infection or possible side effects. Delayed hypersensitivity-like reactions may appear 1-14 days after the infusion.
* Advise patients and carers to seek immediate medical advice if hypersensitivity symptoms occur. Delayed reactions are more likely to occur if a patient has had a previous course of infliximab.

**Possible side effects**

See BNFc or Summary of Product Characteristics for full list of side effects.(2,5)

**Common or very common**

* Anaemia
* Constipation
* Dizziness
* Fatigue
* Gastrointestinal discomfort
* Hypertension/hypotension
* Increased risk of infection
* Infusion related reaction
* Skin reactions

**Uncommon**

* Anxiety
* Heart failure
* Seizure
* Thrombocytopenia

**Rare or very rare**

* Cyanosis
* Demyelinating disorders
* Pancytopenia

**Frequency not known**

* Bone fracture

References:

1. 1. Joint Formulary Committee. British National Formulary (Online) London: BMJ Group and Pharmaceutical Press. Available at [http://www.medicinescomplete.com]. Accessed 10/12/19.
2. Medusa IV Monographs (2019). Infliximab. Available at [<https://medusa.wales.nhs.uk/>]. Accessed 10/12/19.
3. Angeles‐Han, Lo, M. S., Henderson, L. A., Lerman, M. A., Abramson, L., Cooper, A., Parsa, M. F., Zemel, L. S., Ronis, T., Beukelman, T., Cox, E., Sen, H. Nid., Holland, G. N., Brunner, H. I., Lasky, A., & Rabinovich, C. E. (2019). Childhood Arthritis and Rheumatology Research Alliance Consensus Treatment Plans for Juvenile Idiopathic Arthritis–Associated and Idiopathic Chronic Anterior Uveitis. Arthritis Care & Research, 71(4), 482–491. <https://doi.org/10.1002/acr.23610>

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*NOTE*

*This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient’s case notes at the time the relevant decision is taken.*