Trust Protocol for the Management of Infliximab Infusions in Adult Patients with Rheumatological Conditions

A Clinical Guideline recommended for use

For use in:	Rheumatology Day Unit
By:	Registered Nurses competent in the administration of intravenous therapy and Medical Staff
For:	The treatment of patients with rheumatological inflammatory disease
Division responsible For document:	Division 1
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If Yes - does the guidelines deviate from the recommendations of NICE? If so why?	No

This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.
The Trust's guidelines are made publicly available as part of the collective endeavour to continuously improve the quality of healthcare through sharing medical experience and knowledge. The Trust accepts no responsibility for any misunderstanding or misapplication of this document.

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Infliximab is used in Rheumatology for the following conditions:

Ankylosing spoindylitis

Behcets vasculitis

Psoriatic arthritis

Rheumatoid arthritis

Use is line with local commissioned decisions and NICE as documented in TAG recommendations document

NICE:

NICE ID 694: TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (including a review of TA143 and TA233) Final appraisal determination

NICE TA 199: Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis

NICE TA Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (TA195)

NHSE commissioning statement for Behcets vasculitis

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PATIENTS SUITABLE FOR INFLIXIMAB INFUSION

Nurse:
Gives - full explanation of procedure to patient
Examines - patient for best venous access
Records - base line vital signs and asks about recent infections
Doctor ensures - blood tests are within agreed range (FBC, U&E, LFTs, CRP, ESR) for this patient

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Nurse:
Weighs - patient and calculates - Infliximab dose at appropriate dose at 3 - 5mg/kg and ensures prescribed by doctor
Prepares - Infusion according to package insert
Establishes - Venous access using cannula

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Nurse:
- Ensures Medical cover is available
- Ensures resuscitation equipment is to hand
- Ensures Adrenaline, Hydrocortisone and Chlorphenamine is available and in date
- Ensures oxygen and tubing is connected
- Records Pulse and Blood Pressure (30 mins for after infusion commences and prior to discharge if indicated)

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Infusion: Before infusion - consider giving patient Hydrocortisone/Chlorphenamine if previous reaction
First Infusion - administer test of 10 mls over 15 minutes and observe for signs of hypersensitivity or anaphylaxis

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Reactions:
If they occur, they may respond to
- Stop the infusion rate and restart at a lower rate
- Administering antihistamine as prescribed
- Discontinuing the infusion

Infusion should be discontinued if:
- Anaphylaxis occurs and inform doctor

Report and record ANY adverse reaction

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End of infusion
-Disconnect cannula, and leave in situ for one hour post infusion for first three infusions and then half an hour for subsequent infusions.
- Complete documentation in medical notes
- When safe to do so, remove line

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PATIENT
- Give follow-up appointment
- Give blood request forms
- Alert to potential side effects
- Give contact numbers in case of problems

Trust *Policy / Guideline* for the Management of: *Condition or Procedure* in Adults and / or Children (title needed on every page)

Trust Protocol for the Management of Infliximab Infusions in Adult Patients with Rheumatological Conditions

Objective

To ensure the correct administration of Infliximab by Registered Nursing staff who are trained to work to this protocol.

Rationale

Infliximab is one of a potent group of biologic agents which needs to be administered by suitably trained nurses.

Indications for using Infliximab anti TNF a therapy according to NICE Guidelines (TA 104, 143, 195, 199).

Infliximab is indicated for:

Ankylosing spondylitis and non-radiographic axial spondyloarthritis

Infliximab is not currently commissioned for this indication but there is a cohort of patients who received this prior to TA 143 and there is a positive Final Appraisal Determination from NICE that states:

Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs.

Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop.

The response to adalimumab, certolizumab pegol, etanercept,golimumab or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued ifthere is clear evidence of response, defined as:

- A reduction In The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) Score To 50% Of The Pre-Treatment Value Or By2 Or More Units And
- A reduction in the spinal pain visual analogue scale (VAS) by2 cm or more.

Behcets Vasculitis

NHSE has commissioned this on a prior approval basis for individual patients. Infiximab must only be prescribed when permission is granted from a specialist centre.

Psoriatic arthritis

Infliximab is recommended for the treatment of adults with active and progressive psoriatic arthritis when the following criteria are met.

- The person has peripheral arthritis with three or more tender joints and three or more swollen joints, and

- The psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination. (TA 199)

Treatment should normally be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules.

Infliximab treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks. An adequate response is defined as an improvement in at least two of the four PsARC criteria, (one of which has to be joint tenderness or swelling score) with no worsening in any of the four criteria.

People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response (see 'Etanercept and efalizumab for the treatment of adults with psoriasis' [NICE technology appraisal guidance 103], 'Infliximab for the treatment of adults with psoriasis' [NICE technology appraisal guidance 134] and 'Adalimumab for the treatment of adults with psoriasis' [NICE technology appraisal guidance 146] for guidance on the use of tumour necrosis factor [TNF] inhibitors in psoriasis).

Rheumatoid arthritis

Infliximab in combination with methotrexate, is recommended as a treatment option only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs (TA195).

Treatment with infliximab should be continued only if there is an adequate response 6 months after initiation of therapy. Treatment should be monitored, with assessment of DAS28, at least every 6 months and continued only if an adequate response is maintained (TA 195)

When using DAS28, healthcare professionals should take into account any physical, sensory or learning disabilities, communication difficulties, or disease characteristics that could adversely affect patient assessment and make any adjustments they consider appropriate.

Broad recommendations

- Patients referred for Infliximab therapy can be treated as a day case, unless otherwise indicated by their Consultant.
- Only qualified staff whom are trained and competent in the administration of Infliximab therapy should administer treatment.
- A member of the medical team must be available for the first hour of the first infusion in case of any adverse advent.
- All Medicines must be prescribed.

- Exclude infection prior to each administration
    1. Monitor temperature
    2. Urinalysis –if positive to blood, protein or nitrites send for MSU

Patient Inclusion criteria

- Patients who have been referred to the Rheumatology Specialist Nurse

Patient exclusion criteria

A check must be made to ensure that the above patients are excluded.

Patients with Tuberculosis.

- **Patients with sepsis, infection, abscesses, and opportunistic infections.**
- **Patients who are hypersensitive to Infliximab.**
- **Female patients who are pregnant unless agreed by referring Consultant**
- **Patients with moderate or severe heart failure.**
- **Patients with a history of cancer unless agreed by referring Consultant**
- **Patients with known demyelination.**

When to withhold treatment:

- Signs and symptoms of intercurrent infection.
- Worsening coexisting illness.
- Forthcoming surgeries omit at 4 weeks before.
- Suspected malignancy.
- Withhold treatment after the 36th week of pregnancy, unless directed by patients Consultant and Obstetrician but can be restarted after delivery.

Precautions

1. Pregnancy or lactating mothers:

Treatment with Infliximab during pregnancy must be a Consultants decision. Infliximab should not be given in pregnancy after the 36th week, but can be restarted after delivery.

Adequate contraceptive precautions should be taken by women of childbearing age. Similarly, nursing mothers should be advised not to breastfeed for a minimum of six months after administration.

Check if female patients could be pregnant or breastfeeding. If in doubt do not give Infliximab and refer to referring clinician.

2. Heart Failure:

Infliximab should not be used with new or worsening symptoms of heart failure. If a decision to continue treatment is made, the patient's cardiac status should be closely monitored and recorded, by the patients Consultant or Cardiologist

3. Reactivation of Pulmonary Tuberculosis (Pulmonary TB)

A chest x-ray is mandatory due to the increased risk of reactivation of Pulmonary TB following Infliximab administration. Ensure chest x-ray result has been checked by a

clinician before treatment commences. Where there is a possibility of previous exposure to Pulmonary TB the patient should be discussed with the Respiratory Physicians. **NB:** Latent TB needs to be treated with standard anti-tuberculosis treatment before receiving Infliximab if clinically indicated, and risks and benefits have been fully considered.

All patients should be screened for hepatitis B/C (antibodies).

Varicella Zoster antibodies (if negative discuss with patients Consultant)
Infliximab should be withheld if results unavailable or unless authorized by the patients Consultant.

Dosage and administration

Infliximab is for intravenous use in adults.
Infliximab must be prescribed by brand name for example 'Remicade' or by the biosimilar 'Remsima'.

Infliximab 3- 5 mg/kg is given as an IV infusion at 0, 2 and 6 weeks and then every 8 weeks as directed by the patients Consultant. Dose escalation must be discussed with the prescribing clinician and the Drugs and Therapeutics Committee.

If an infusion has not been given to a patient for more than 15 weeks there is a high risk of subsequent infusion reactions. In this instance special precautions may be required and a Consultant opinion should be sought prior to infusion. Consider administration of Hydrocortisone and Chlorphenamine.

Patients who are established on a maintenance programme who have received 4 infusions without complications or infusion reactions can receive accelerated infusions over 1 hour. Results from data indicate a similar safety profile to 2-hour infusions. (Fairclough et al 2006, Buch et al 2006) - (Summary of Product Characteristics, 2011).

Adverse events

Any adverse events must be documented in the patient's case notes, a yellow reporting card completed (legal requirement). In addition a full record of any adverse event must be made in the patient's medical notes to ensure that future care takes account of possible allergies.

Infusion related reactions

Infliximab has been associated with acute infusion-related reactions including anaphylactic reactions and delayed hypersensitivity reactions

Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

Infusion reactions are either described as:

1. Acute - within 24 hours of initial or subsequent infusions.
2. Delayed - any reaction, which occurs from 24 hours-14 days post Infliximab treatment (Cheifetz *et al* 2003).

An acute infusion reaction may occur during an infusion within seconds, or within 1-2 hours post infusion. If acute infusion reactions occur, the infusion must be interrupted and stopped immediately and managed accordingly. Any reaction must be reported to patients referring clinician. **Patients must remain within the clinical environment for 1 hour for post infusion monitoring.**

Signs and symptoms of infusion related reactions:

Approximately 5% of Infliximab infusions are accompanied by acute reactions. 3.1% were reported as mild, of these:

< 1% was accompanied by urticaria, purities, fever and/or chills.

1% was accompanied by chest pain, hypotension, hypertension and shortness of breath.1% had severe reactions.

Delayed reactions occurred in <1% of infusions, i.e. rash, fever, polyarthalgia, headaches and sore throat (Cheifetz *et al* 2003).

If an acute reaction occurs either reduce the rate of the infusion, or administer prophylaxis medication, or discontinue the infusion if necessary. Report reaction to referring clinician

Management of reactions: Please refer to- Appendix 1

Registered Nurse procedures and guidelines

A decision to prescribe Infliximab must be made by the patients Consultant

Before commencing the infusion the following equipment must be within easy access: Dynamap machine and cardiac arrest trolley.

Ensure the following drugs are available for administration in the event of an acute infusion reaction:

Paracetamol PO 1g prn

Chlorphenamine IV 10-20 mg prn

Chlorphenamine PO 4mg prn

Hydrocortisone IV 100-200mg prn

Adrenaline 1:1000 IM (0.5mL)

Salbutamol nebuliser 2.5mg

'Insert cannula' and flush according to Trust Guidelines-Medicines Management (2014)

Pre infusion checklist

1. Ensure chest x-ray within last 12 months has been reported on by doctors and is normal.
2. Ensure patient does not have any known sensitivity to Infliximab or other murine proteins.

3. Patient has been informed of the risks, benefits and possible infusion reactions of treatment and has been supplied with verbal and written information to support this.

4. Ensure patient has documented consent for treatment
5. Ensure results from routine bloods have been reported on, (FBC, LFT's, U+E's & CRP).
6. Ensure patient's weight as recorded is correct.
7. Ensure the patient has no signs of infection? If yes, contact a Doctor from the Rheumatology team to assess the patient before commencing infusion.
8. Undertake a urine dip stick test, if necessary send MSU and treat accordingly
9. Check for any possible contact with TB, and record status in patients' medical records
10. Inform patients of signs of TB and to report: persistent cough, wasting/weight loss, fever
11. Ensure patients who are at risk of HBV infection are evaluated prior to commencing treatment with Infliximab
12. Has the patient developed any heart failure? If yes contact prescribing Consultant before commencing infusion
13. Pregnancy and Infliximab should be discussed fully in females of child bearing age and avoided if breastfeeding whilst on treatment and for 6 months after last dose.
14. Monitor base line observations: pulse, BP, temperature and oxygen saturation levels and record on nursing documentation.
15. Ensure anaphylaxis medication and resuscitation equipment is readily accessible.
16. Ensure oxygen mask and tubing are connected.

Preparation

1. Infliximab must be stored at 2-8 degrees Centigrade. Do not refreeze.
2. Calculate the dose required (each vial contains 100 mg Remicade). 3-5mg/kg Infusions must be prepared in a clean treatment area with segregation between clean and contaminated products, using strict aseptic technique throughout the process, following the Trust Hand Hygiene policy.
3. Due to the high costs of treatment, sharing of vials for immediate use is permitted following the risk assessment by the Medicines Management Group. Sharing of vials only applies in Rheumatology.
4. Personal protective clothing must be worn, i.e. gloves, aprons and face mask**.**
5. Reconstitute each vial with 10mLs of Water for Injection using a 21-gauge needle or less. Swab vial top with a 70% alcohol swab and allow to dry.
6. Inject the water against the glass wall of the vial. Do not use the vial if the vacuum is not present.
7. Swirl the solution gently by rotating the vial to dissolve the powder. DO NOT SHAKE THE VIAL. It is not unusual to see some foaming of the solution.

8. Allow to stand for 5 minutes. Solution should be colourless to light yellow and opalescent. It is normal to see a few fine translucent particles, as Remicade is a protein. Do not use if there are opaque particles, discolouration or foreign particles are present.
9. Withdraw the same total volume of the reconstituted drug from 250ml Sodium Chloride 0.9%. Slowly add the total volume of reconstituted Infliximab to the 250ml infusion bag. Gently mix. Fix additive drug label according to Trust policy.
10. Infliximab infusions should be administered via a sterile giving set and a 0.2 micron epidural filter. Connect the infusion with a y-connector. Infusions must be administered via a volumetric pump.
11. At every infusion a test dose of 20mls should be infused over 15minutes and the patient should be observed closely for any signs of reactions or hypersensitivity.
12. If there are no adverse reaction or signs of hypersensitivity the infusion may continue.
13. Administer infusion over a period of not less than 2 hours (2ml/min) for the first 3 infusions. Accelerated infusions over 1 hour (4ml/min) may be administered if the patient has not had any reaction following their first 3 infusions, (Summary of Product Characteristics, 4.2, 2011)
14. Following reconstitution and dilution the infusion must be started as soon as possible and completed within 3 hours. DO NOT STORE ANY UNUSED PORTION FOR FURTHER RE-USE.
15. The Batch Number of vials must be recorded in the patient's notes or drug chart.

Monitoring

1. The patient should be monitored closely during the infusion period.
2. Observations must be recorded every 15 minutes for the first hour, and then every 30 minutes until the infusion is completed and for 1 hour post infusion until the patient is discharged. Measurements must be documented.
3. Observe the cannula site for extravasation and the infusion for any changes in colour or consistency.
4. Report and record any adverse reactions.
5. The cannula must remain in-situ until the patient is ready for discharge and then removed.
6. On discharge ensure that the patient has contact numbers in case of adverse reactions following discharge. Ensure patient is given Infliximab alert card- Anaphylaxis to Anti TNFα is contra-indicated for further treatment.

Post Treatment and Follow up monitoring

- Bloods should be repeated no less than 1 week before each infusion including FBC, U&Es LFTs, CRP, and then monthly whilst on treatment, or unless otherwise directed by patient's clinician.
- Record any suspected side effects

- Inform patient of possible delayed hypersensitivity reaction post infusion and to seek immediate medical advice, ensure contact numbers are given for out of hours advice

The appropriate NICE approved efficacy scores should be re-calculated every three to six months depending on duration of therapy whilst patients continue with Infliximab to assess the efficacy of treatment.

Clinical Audit Standards

To ensure that this policy is compliant with the above standards, the following monitoring processes will be undertaken:

The decision to treat and to repeat treatment should only be made by a Consultant Rheumatologist.

Data will be entered onto a database and this will be used to provide numbers for costing purposes to the CCGs

The number, type and severity of adverse incidents to treatment will be monitored to ensure that they remain within acceptable limits and that the correct management was adhered to.

The audit results will be reviewed regularly.

Staff selection and training

Only Registered Nurses' who have successfully completed the Trust's IV Drug Therapy Clinical Skills Study Day or equivalent, and undertaken the relevant Infliximab training sessions (as below), will be eligible to perform administration of Infliximab infusions.

Training

Nurses are training in the Rheumatology Day Unit to observe the preparation, administration and monitoring of patients receiving infliximab.

It is the responsibility of the nurse to remain updated with research and developments in this area of treatment.

Summary of development and consultation process undertaken before registration and dissemination

This guideline has been drafted by the author Caroline Ferrari in conjunction with Pharmacy Services, on behalf of the Rheumatology Department. During its development it has been circulated for comment within the Pharmacy Department, Rheumatology.
Where appropriate comments have been incorporated into the final version, which has been endorsed by the Professional Protocols, Policies and Guidelines Committee.

Distribution list/ dissemination method

Pharmacy Services
Rheumatology Department
Rheumatology Directorate
Trust Intranet

References

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NICE ID 694: TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (including a review of TA143 and TA233) Final appraisal determination

NICE TA 199: Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis

NICE TA Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (TA195)

Appendix 1

Management of Reactions

Mild Hypersensitivity Reactions:

Clinical Signs: Mild rash, pruritus, headaches, pyrexia

Action:

- Reduce infusion rate by half
- Administer oral chlorphenamine 4mg for rash or itch, and/or 1 gram paracetamol for headache or pyrexia
- If symptoms persist, STOP infusion and administer 100-200mg IV hydrocortisone and a further 10-20mg IV chlorphenamine and treat as a moderate reaction.
- If improvement; continue with infusion at the reduced rate and monitor closely for any further signs on hypersensitivity.
- Patients can be discharged after 2 hours post infusion as long as no further signs of hypersensitivity.
- Instruct patient to report any further reaction on discharge immediately by contacting the Rheumatology on call team via the hospital switchboard. DECT phone 4336

Moderate Hypersensitivity Reaction;

Clinical Signs: Urticaria/rash, mild hypertension, tachycardia, mild wheeze, nausea

Action:

- STOP infusion
- Lay patient flat and maintain airway
- Administer 100-200mg IV hydrocortisone & 10-20mg chlorphenamine by slow injection
- Check vital signs and oxygen saturation
- Medical decision to restart infusion
- Seek medical advice if reaction continuing/ worsening treat as SEVERE REACTION
- Will require admission for overnight assessment
- Discharge following medical review if well.

Severe Infusion Reaction

Clinical signs: Hypotension, respiratory distress, swollen lips and/or airways, reduced or lost consciousness, reduced oxygen saturations, flushed or pale appearance.

Action:

- STOP Infliximab
- Call crash team 2222
- Lay patient flat and maintain patent airway
- Administer 0.5ml 1:1000 adrenaline IM, as per Medicine Management 2007
- Administer oxygen @10 -15litres/minute and monitor oxygen saturation levels, pulse and BP
- If improvement in condition continue to monitor closely and arrange overnight admission for observation.
- No improvement, as per Medicines Management 2007 repeat adrenaline; administer chlorphenamine 20mg IV and hydrocortisone 200mg IV. Administer dextrose saline 1litre rapidly if hypotension persists.

Begin basic life support

Appendix 2

Departmental Record of Signatories

This is the departmental list of all those who have read and agreed to act within the parameters of this protocol. Each individual has kept a signed copy of the protocol for his / herself.

Print Name	Sign	Date