

Regional Guideline On Anti – TNF α Use in Children With Inflammatory Bowel Disease

A Clinical Guideline

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| For Use in: | Jenny Lind Children's Department |
| By: | Registered Paediatric Nurses and Medical Staff |
| For: | Children with Inflammatory Bowel Disease (IBD) |
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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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1. Objectives

- To promote understanding of anti- Tumour Necrosis Factor alpha (TNF) use and its risks in children with IBD.
- To ensure the safe administration of anti-TNF agents.
- To ensure minimum standards for anti-TNF use.
- To demonstrate a regional consensus on anti-TNF agent use in children with IBD.
- To provide a document to support the funding of anti-TNF agents within the region.

2. Introduction

What are anti-TNF α therapies?

Anti-TNF α therapies use antibodies to TNF α to block / reduce the production of TNF α [1]

- TNF α is a pro-inflammatory cytokine that plays a pivotal role in the inflammatory cascade that causes ulceration in the intestinal mucosa of patients with IBD [2].
- Infliximab (Remicade) is a chimeric (murine & human) monoclonal antibody which inhibits TNF α and is given by intravenous infusion. This is licensed for use by EMEA in children with Crohn's disease over 6 years of age.
- Adalimumab (Humira) is a more recently developed (fully humanised) monoclonal antibody that inhibits TNF α , but is given by subcutaneous injection [3].
- Children with Crohn's Disease have an increased number of cells in their gut mucosa producing TNF α [4].

Is there a beneficial clinical effect?

- **Extended guideline ECCO 2014 Ruemmele et al [37] and NICE report benefits to defined patient groups**
- A large prospective randomised study has shown Infliximab (5mg/kg) to be more effective in children than adults with moderate to severe Crohn's Disease at inducing a clinical remission (66% at 10 weeks) and maintaining this with repeated infusions (56% at 54 weeks) [5].
- Regular infusions of Infliximab reduces antibody formation and maintains better mucosal healing than episodic therapy [6].
- There have been several reports in children that have found Infliximab to be a safe and effective treatment in managing fistulizing Crohn's disease [7][8][9].
- Adults with fistulizing Crohn's Disease have been shown to have significant fistula closure with repeated infusions of Infliximab [10].
- Adalimumab has been shown to have a similar effect as Infliximab in adults with Crohn's disease [11][12].
- Adalimumab has also been shown to have some benefit in treating adults intolerant to / losing response to Infliximab [13][14].
- Infliximab has been shown to delay / prevent emergency surgery in children with acute severe Crohn's colitis [15].

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- Some adults with ulcerative colitis have also been shown to respond to Infliximab in prospective studies [16].
- In the case of treatment-resistant UC in adults, the use of Infliximab achieved a clinical response in about 65% at 8 weeks and 45% response at 54 weeks [16]. Given the significantly better results in children with Crohn's disease receiving Infliximab, it is likely that children with UC will also respond better than adults.
- There is some evidence that Infliximab may delay emergency surgery in adults and children with acute severe ulcerative colitis [17][18].
- There are currently no published randomised prospective studies using anti-TNF α in children with UC, although numerous case series have been published [19][20].
- The avoidance of an un-planned, emergency colectomy in a child or adolescent is paramount for both medical and psychological reasons. The benefit of delaying a colectomy, even if only for a few months, allows preparation of the child and family for the impact of life with a stoma. Although the option of Cyclosporin in acute Colitis still exists; this is not a maintenance therapy. The use of Infliximab in the acute setting therefore allows an assessment of response at 10-14 weeks, with the potential of continuing maintenance therapy if a clinical remission has been achieved.

What is the effect on growth?

- The cause of growth failure in children with IBD (particularly Crohn's disease) is multi-factorial. The inflammatory process itself plays a pivotal role in slowing linear growth [21].
- TNF α has been shown to suppress osteoblast formation and bone growth independent of malnutrition in animal models [22].
- Infliximab induction treatment is reported to reverse growth hormone resistance associated with IBD through suppression of systemic inflammation [23].
- Several studies have now documented increased linear growth velocity following Infliximab therapy [24][25][26].

Does Infliximab heal gut mucosa?

- Studies have shown sustained endoscopic healing after with regular infusions of Infliximab in adults [27] as well as in paediatric patients with Crohn's disease [26].
- Regular infusions of Infliximab maintain mucosal healing better than episodic therapy [6].
- There is some evidence that achieving mucosal healing improves long-term outcome in adults with Crohn's disease [6].

Are there any risks?

- See attached patient information sheet
- There is an increased risk of infectious complications (particularly if patients are on concomitant immunosuppression e.g. corticosteroids, cyclosporin) More of a risk of therapy inactive TB

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- There have been about 31 cases of hepatosplenic T-cell lymphoma in young, predominantly male patients with IBD receiving combination treatment with azathioprine and infliximab [28] [39]. The risks are currently quoted between 1/1000 and 1/10,000.
- Varicella – if patient not immune manage contact varicella as per “green book”. Advise patient of risk and importance of reporting contact to team or CAU.

3. Indications

The decision to start a child with IBD on anti-TNF α therapy should be made in discussion with a Consultant Paediatric Gastroenterologist. The patient should have disease distribution and severity reassessed before treatment. An ileo-colonoscopy (+/- radiographic imaging) should ideally be done within 4 weeks of the first infusion.

A. Crohn’s disease

NICE and ECCO guidelines 2014 are in place for Biologics induction of Infliximab and Adalimumab

I. A patient with either of the following is prescribed Infliximab

- a. The patient has severe Crohn’s Disease and;
- b. The patient’s condition is refractory to treatment with immunomodulating drugs and corticosteroids or the patient is intolerant of or experienced toxicity from these treatments and;
- c. Surgery is inappropriate for the patient.

or

- d. Serious Perianal Disease.

II. Infliximab treatment is repeated for patients who meet 1a-c above in the following circumstances

- a. The patient has responded to the initial or subsequent treatment course and then relapsed and;
- b. The decision is made by gastroenterologist experienced in the management of Crohn’s Disease.

Exception - Patient declines repeated treatment after being fully informed of the potential risks and benefits of repeated treatment

III. Infliximab is not provided to patients with fistulating Crohn’s Disease except when the patient meets the other criteria for eligibility

Other indications where the use of Infliximab has been shown to have some efficacy:

1. Once a patient is defined as having a clinical response / remission at 14-22 weeks, regular maintenance therapy typically with 8 weekly infusions of Infliximab at 5mg/kg/dose should be commenced. At present Infliximab responders have

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azathioprine discontinuing considered after about 6 months of Infliximab therapy. Patients are then reviewed at 6 monthly intervals to assess the ongoing clinical efficacy and need for ongoing therapy. This may include reinvestigation by endoscopy if clinical response is lost.

2. Growth failure in the presence of active Crohn's disease [25].
3. As bridging therapy (i.e. use of 3 infusion induction course) in severe Crohn's disease not responding to corticosteroids, where additional bridging therapy is required to reach full immunomodulator efficacy.
4. Pyoderma gangrenosum resistant to conventional therapy [31][32].

B. Ulcerative colitis

There are currently no national recommendations on anti-TNF α use in children with ulcerative colitis. However ESPGHAN guidelines Turner et al 2012 [38] state TNF as medical management in acute severe ulcerative colitis.

The following two indications for Infliximab use are increasingly accepted as appropriate for children with a confirmed diagnosis of ulcerative colitis:

1. Acute severe ulcerative colitis not responding to intravenous corticosteroid therapy, where emergency colectomy is to be avoided and additional bridging therapy (i.e. 3 infusion induction course) is required to await maximal immunomodulator efficacy.
2. Acute severe ulcerative colitis resistant to / dependent on corticosteroids where conventional immunomodulator maintenance therapy has become ineffective. Although this is less efficacious in adults with UC than indication 1, it is felt that surgery (i.e. subtotal colectomy and ileostomy) is now inappropriate for children and adolescents BEFORE a trial of anti-TNF α induction therapy, as there are a significant number of children in whom a colectomy may be delayed for many months [33].

Exclusions

- Patients with sepsis (i.e. fever > 38°C), or with clinically apparent infection or abscesses (discuss with consultant). Less serious infections (e.g. URTIs or simple UTIs) are not contra-indications but should be discussed with the responsible consultant.
- Patients who are hypersensitive to Infliximab (or other anti-TNF agents) or any other excipients.
- Female patients who may be / may become pregnant (should not become pregnant within 6 months of last dose).
- Patients with moderate or severe heart failure.
- Previous demyelinating disease (e.g. optic neuritis/MS).
- Evidence of prior history of TB or of current active TB. Recent close contact with an individual with active TB (see Appendix i).

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Definitions

A. Crohn's Disease

Moderate to severe Crohn's Disease:

Patient with very poor general health with weight loss & sometimes fever, severe abdominal pain and frequent diarrhoeal stools (> 3-4/day).

Patients may/may not be developing new fistulae or have extra-intestinal manifestations of disease.

This corresponds to a PCDAI (Appendix ii) > 30 [34].

Refractory / intolerant to treatment with immunomodulators:

Patient has received a full and adequately dosed course of Azathioprine (2.5mg/kg for minimum of 4 months) / methotrexate (25mg SC OW for minimum 12 weeks)

Clinician to agree locally as to what constitutes intolerance or toxicity of treatment.

Refractory to / dependent on corticosteroids:

Continuing disease activity unresponsive to corticosteroids (maximum dose of 2mg/kg or 40mg OD for > 2 weeks / equivalent IV dose) or dependence on corticosteroids (relapse during / soon after reducing course requiring other rescue therapy).

Surgery may be deemed 'inappropriate' when there is:

- Diffuse / panenteric disease and/or a risk of short bowel syndrome.
- Pancolitis that would require subtotal colectomy with fashioning of a long-term ileostomy.
- Severe perianal Crohn's disease.
- Child / family refusing surgical intervention.

Clinical response: Decrease from baseline PCDAI of ≥ 15 points and a total PCDAI score of ≤ 30 points.

Clinical remission: PCDAI score of ≤ 10 points.

Loss of response: An increase in the PCDAI score of ≥ 15 points from baseline at 2 consecutive visits at least 7 days apart **OR**

The subject's overall PCDAI score is > 30 points at any point

B. Ulcerative colitis

There is now a validated clinical disease activity index for children with ulcerative colitis (Appendix iii) [35] PUCAI

Activity scores:

< 10 = inactive disease

10 - 34 = mild disease

35 – 64 = moderate disease

> 65 = severe disease

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| Response | Small | ≥ 10 points |
| | Moderate response) | ≥ 20 points (moderate change represents clinically ‘significant’) |
| | Large | ≥ 35 points |

4. Admission schedule

Use in conjunction with checklist for 1st and Follow-up infusions – (Appendix iv)

- Administration of Infliximab is appropriate as a daycase.
- Patients should ideally be scheduled in small groups (3-4) to minimise drug wastage (Vial sharing should be approved in each unit administering Infliximab).
- It is not necessary for a patient to be seen by a doctor at every visit.
- All children are to be seen by an appropriate member of the gastroenterology team to record the first (week 0) or assessment (Week 14) PCDAI / PUCAI and complete the infusion checklist on each admission and data collected for biologic audit.
- Record base line observations (pulse, BP, temperature, weight and height).
- Medical review is required if there are signs of infection / history of recent contact with infection (mild viral illnesses / upper respiratory tract infections are not contra-indications to treatment).
- Apply EMLA / cold spray as appropriate.
- At each infusion, blood tests including FBC, LFT's, ESR, CRP, (consider Ca, P, Ferritin, B12 & folate) should be taken at cannula insertion.
- Ensure access to resuscitation trolley and appropriate medication (ie anaphylaxis medication).
- Ensure oxygen mask and tubing are connected.
- Ensure paediatric doctor is aware infusion will be in progress and is available within 5 minutes if called (senior nursing staff to give first-line anaphylaxis treatment as necessary).
- Administer infusion (see below).

5. Prescription

Infliximab 5 mg/kg as IV infusion over **2 hours** (see reconstituted information below) at 0, 2 & 6 weeks, then 8 weekly until infusion has been given for 6 months. After first 6 months give 5mg/kg as IV infusion over **1 hour**. If the child is less than **40kgs** then always give infusion over **2 hours**.

Only to be continued if clinical response achieved at 14 weeks.

Dose intensification 10mg/kg infusions may be used in an attempt to regain Infliximab efficacy. This is usually given as 3 10mg/kg doses over 2 hours before returning to 5mg/kg doses at 8 weekly intervals. Alternatively the dosing interval may be reduced following discussion with the lead clinician.

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If there is a delay of 10 weeks or more since the last infusion, consultant advice should be sought before the infusion as there is an increased risk of adverse reaction due to possible development of antibodies (see Appendix v). In this case prophylactic chlorphenamine (Piriton) and hydrocortisone should also be considered.

6. Preparation

- Infliximab must be stored at 2-8 degrees centigrade. Do not freeze.
- Calculate dose at 5mg/kg (each vial contains 100 mg Infliximab) and round up to the nearest 10mg.
- 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.
- Inject the water against the glass wall of the vial. Do not use the vial if the vacuum is not present.
- 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.
- 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 Infliximab is a protein. Do not use if there are opaque particles, discolouration or foreign particles present.
- Withdraw the same total volume as 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.
- Infliximab infusions should be administered via a sterile giving set and a 0.2 micron epidural filter. Connect the infusion with a y-connector and prime giving set with Infliximab solution. Infusions must be administered via a volumetric pump.
- If the last infusion was given > 10 weeks ago, a test dose of 10mls should be infused over 10 minutes (1ml/min) and the patient should be observed closely for any signs of anaphylaxis. If there are no adverse reaction or signs of hypersensitivity the infusion may continue at the normal rate.
- Administer infusion over a period of 1-2 hours
- Following reconstitution and dilution the infusion must be started as soon as possible and **AT THE LATEST** within 3 hours. Do not store any unused portion for later re-use.
- The Batch Number and Lot Number of vials must be recorded in the patient's notes.

7. Administration & Monitoring

- The patient should be monitored closely during the infusion period and should stay in ward area for the duration of the infusion and for at least 1 hour after the infusion has finished.
- Observations of BP, pulse and temperature must be recorded every 30 minutes for the first hour, then every 30 minutes until the infusion is completed and for 1 hour post infusion.
- Observe the cannula site for extravasation and the infusion for any changes in colour or consistency.

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- Report and record any adverse reactions to the child's named consultant.
- The cannula must remain in-situ until the patient is ready for discharge and should then be removed.
- All patients on Infliximab should have contact details of appropriate staff in case of a delayed reaction.
- Ensure patient is given Infliximab Alert card after first infusion.
- Ensure patient has forms for blood monitoring if appropriate.
- Make appointment for next infusion (schedule 6 monthly / annual clinic review as necessary).
- Ensure that appropriate discharge information is sent out.

8. Infusion-related reactions & Adverse Events

- Acute - within 24 hours of initial or subsequent infusions.
- Delayed - any reaction, which occurs from 24 hours-14 days post Infliximab treatment [36].

An acute infusion reaction may occur during an infusion, or within 1-2 hours post infusion. 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.
- About 3% were reported as mild, of these:
 - 1% were accompanied by urticaria, pruritus, fever and/or chills.
 - 1% were accompanied by chest pain, hypotension, hypertension and shortness of breath.
- 1% had severe reactions.
- Delayed reactions occurred in <1% of infusions. ie rash, fever, polyarthralgia, headaches and sore throat.

Treatment for infusion reactions

- Anaphylaxis (see Appendix v)
 - Discontinue the infusion and call for immediate medical attention according to APLS/EPLS guidelines.
 - Adrenaline IM 10 micrograms /kg.
 - Adrenaline nebuliser 5ml of 1/1000.
 - Salbutamol nebuliser 2.5mg.
 - Normal saline 20mls/kg IV bolus.
 - Steroids or Piriton.
- Moderate to severe reactions - discontinue infusion and seek a paediatric

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consultant decision about recommencement.

- Mild rash, nausea, headache or pruritus. Stop infusion, paediatric medical review. Administer Paracetamol and consider giving IV chlorphenamine. Consider restarting the infusion at 25% of the normal rate, increasing rate again if tolerated.
- Any infusion reaction should be reported to Consultant as a more severe reaction may occur at the next infusion.

9. Follow up

6 monthly assessment by:

Paediatric Gastroenterologist or Consultant with expertise in Paediatric Gastroenterology

Includes:

- Review of concomitant immunosuppressant use.
- Assessment of anti-TNF α efficacy.
- Discuss need for continuing therapy.
- Discuss risks of pregnancy.
- Assess growth and pubertal status.

Annual assessment by:

Paediatric Gastroenterologist

In addition to 6 month assessment:

- PCDAI / PUCAI score.
- Discuss benefit of annual endoscopic assessment.
- Review long-term treatment strategy.
- Transition planning, if appropriate.

11. Clinical Audit Standards

Patient entered onto regional IBD & Biologic database

Frequency and severity of adverse reactions documented on regional database

Assessment of efficacy (PCDAI/PUCAI) at treatment onset, 10-14 weeks and annually

12. Summary of development and consultation process

Current guidelines were developed following the generous provision of local protocols from paediatric gastroenterology teams at Royal Free, Alder Hey and Norfolk and Norwich University Hospitals. Initial draft guidelines prepared for EEPGN by MB and CS. Evidence of anti-TNF use in children reviewed by RBH and relevant references incorporated into second draft. Initial draft of patient information sheet kindly produced by Schering-Plough. This was modified for routine clinical use within the region and incorporated into guideline. Pharmacy aspects (IV monograph) prepared by SA/NG. Pre-final draft ratified at EEPGN meeting (8.12.2008) with final comments returned by 31.12.2008.

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15. Appendices

Appendix i

Guidelines for TB screening prior to the use of anti-TNF α therapies

These guidelines are based on the ‘BTS recommendations for assessing risk and for managing Mycobacterium Tuberculosis infection and disease in those patients due to start Anti-TNF α treatment. Thorax 2005;60:800-805.’

The use of anti-TNF α therapies is associated with a five fold increased risk of TB, mostly due to reactivation. Most cases of TB associated with Infliximab occurred within 3 cycles of treatment with a median time to onset of 12 weeks.

A risk assessment should be made to compare the risk of TB against an adverse event from Isoniazid prophylaxis. The absolute risk of TB varies with ethnicity and time since entry into the UK. The risk of an adverse event from Isoniazid prophylaxis is 278/100,000 in adults- there are no reliable data for children thus this figure should be used.

Risk Assessment

Before starting anti-TNF α therapies children should be assessed. This includes a clinical examination, history of any prior TB treatment or contact, a chest radiograph and, if appropriate, a tuberculin test. A tuberculin test is unreliable in children on immunosuppressants. These include oral steroids, azathioprine, 6-mercaptopurine, tacrolimus, methotrexate, cyclosporine, mycophenylate mofetil.

New assessment methods for identifying latent TB are being developed. These tests measure interferon production of the subjects T-lymphocytes in response to tuberculous antigens (T SPOT TB and QuantiFERON-TB Gold). There is currently no data on the performance characteristics of these tests in children or adults about to start anti-TNF α therapies. Thus these tests should not be routinely requested before starting anti- TNF α therapies.

Any child with:

- A history of previous TB or contact with TB.
- Inadequately treated TB.
- Evidence of TB on chest X-ray or examination.
- Positive tuberculin test (if had BCG >15 mm; if no BCG >5 mm).
- A risk calculation that indicates the need for prophylaxis should be discussed with an infectious diseases consultant.

If there is inactive, adequately treated TB it is reasonable to commence anti-TNF α therapies but regular 3 monthly clinical assessments need to be made. These should include chest X-ray and sputum analysis if there are respiratory symptoms.

The onset of new respiratory symptoms, especially within 3 months of starting anti- TNF α therapy should be promptly investigated.

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Recommended risk assessment:

If not on any immunosuppressant therapy for the previous 3 months:

History of prior TB/ TB contact
History of BCG
Clinical examination
Chest X-ray
Tuberculin test (2u)

If on immunosuppressant therapy

History of prior TB/ TB contact
History of BCG
Record ethnicity and place of birth (UK or other)
Clinical examination
Chest X-ray

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Appendix ii

PCDAI (Paediatric Crohn's Disease Activity Index)

Abdominal pain:

| | | |
|--|------|-------|
| None | = 0 | |
| Mild – brief, does not interfere with activities | = 5 | |
| Moderate/severe – daily, longer lasting, affects activities, nocturnal | = 10 | _____ |

Stools (per day):

| | | |
|--|------|-------|
| 0 – 1 liquid stools, no blood | = 0 | |
| Up to 2 semi-formed with small blood or 2 -5 liquid | = 5 | |
| Gross bleeding, or 6 or more liquid, nocturnal diarrhoea | = 10 | _____ |

Well-being

| | | |
|--|------|-------|
| No limitation of activities, well | = 0 | |
| Occasional difficulty in maintaining age appropriate activities, below par | = 5 | |
| Frequent limitation of activity, very poor | = 10 | _____ |

Abdomen

| | | |
|---|------|-------|
| No tenderness, no mass | = 0 | |
| Tenderness, or mass without tenderness | = 5 | |
| Tenderness, involuntary guarding, definite mass | = 10 | _____ |

Perirectal disease

| | | |
|--|------|-------|
| None, asymptomatic tags | = 0 | |
| 1-2 indolent fistulae, scant drainage, no tenderness | = 5 | |
| Active fistulae, drainage, tenderness, abscess | = 10 | _____ |

Extra-intestinal manifestations

[Fever 38.5 for 3 days over past week, definite arthritis, uveitis, Erythema nodosum, P. gangrenosum]

| | | |
|-------|------|-------|
| None | = 0 | |
| One | = 5 | |
| ≥ Two | = 10 | _____ |

Height

| | | | |
|-----------------------------------|-------------------------|------|-------|
| Diagnosis. (over last 4-6 months) | <1 centile decrease | = 0 | |
| | ≥ 1 <2 centile decrease | = 5 | |
| | >2 centile decrease | = 10 | _____ |

OR

Follow-up height velocity (over last 6-12 months):

| | | |
|-----------------|------|-------|
| ≥-1 SD | = 0 | |
| < -1 SD, >-2 SD | = 5 | |
| < -2 SD | = 10 | _____ |

Weight

| | | |
|---|------|-------|
| Weight gain or voluntary stable/loss | = 0 | |
| Involuntary weight stable, weight loss 1-9% | = 5 | |
| Weight loss ≥ 10% | = 10 | _____ |

Laboratory

HCT

| | | | | | |
|----------------|-------|-------|------------------|-------|-------|
| < 10 yrs | ≥33 | = 0 | Female 11-19 yrs | ≥34 | = 0 |
| | 28-32 | = 2.5 | | 29-33 | = 2.5 |
| | <28 | = 5 | | <29 | = 5 |
| Male 15-19 yrs | ≥37 | = 0 | Male 11-14 yrs | >35 | = 0 |
| | 32-36 | = 2.5 | | 30-34 | = 2.5 |
| | <32 | = 5 | | <30 | = 5 |

| | | | |
|---------------|-------|------|-------|
| Albumin (g/l) | ≥35 | = 0 | |
| | 31-34 | = 5 | |
| | ≥30 | = 10 | _____ |

| | | | |
|-------------|-------|-------|-------|
| ESR (mm/hr) | <20 | = 0 | |
| | 20-50 | = 2.5 | |
| | >50 | = 5 | _____ |

Sum PCDAI (/100) _____

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PUCAI (Paediatric UC Activity Index)

| | | |
|--|---|--------------|
| 1. Abdominal pain | | |
| | No pain | 0 |
| | Pain can be ignored | 5 |
| | Pain cannot be ignored | 10 |
| 2. Rectal bleeding | | |
| | None | 0 |
| | Small amount only, in less than 50% of stools | 10 |
| | Small amount with most stools | 20 |
| | Large amount (>50% of the stool content) | 30 |
| 3. Stool consistency of most stools | | |
| | Formed | 0 |
| | Partially formed | 5 |
| | Completely unformed | 10 |
| 4. Number of stools per 24 hours | | |
| | 0 - 2 | 0 |
| | 3 - 5 | 5 |
| | 6 - 8 | 10 |
| | > 8 | 15 |
| 5. Nocturnal stools (any episode causing waking) | | |
| | No | 0 |
| | Yes | 10 |
| 6. Activity level | | |
| | No limitation of activity | 0 |
| | Occasional limitation of activity | 5 |
| | Severe restricted activity | 10 |
| Sum of PUCAI | (/85) | _____ |

PUCAI User Guide

Most items contained in the PUCAI can be scored using the instructions provided within the instrument.

The following issues require additional clarification:

Time period for evaluation

- Answers should reflect a daily average of the last 2 days
- however, if clinical conditions are changing rapidly (eg during intense intravenous therapy), the most recent 24 hours should be considered and
- for patients undergoing colonoscopy, answers should reflect the 2 days before bowel prep was started.

Rectal bleeding

- “Large amount” should be selected if large amount of blood is present in most stools.

Number of stools per 24 hours

- Clustered several small stools over a very short period of time that could be related to tenesmus or incomplete evacuation should be considered as 1 stool.

Activity level

- Occasional limitation of activity = could attend school or equivalent but reduced activity (eg attends school but does not play at breaks) and
- severe restricted activity = could not attend school or equivalent activity.

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Appendix iii

Checklist/ clerking for children having 1st Infliximab infusion

| |
|--------------------------------------|
| <p><i>Large patient id label</i></p> |
|--------------------------------------|

Date:

| Action | Rationale | Tick each box below |
|---|---|-------------------------|
| Date and result of recent investigations documented in notes | Ensure up to date (ideally within 4 weeks) reassessment of disease extent / severity | Yes / No |
| Written patient information sheet provided and understood | | Yes / No |
| Consent form signed by family and senior medical staff | Appropriate informed consent / assent of family +/- child | Yes / No |
| Annual review date confirmed | Detailed annual review of treatment strategy +/- endoscopic assessment | Date for annual review: |
| TB screening complete: History sheet, Chest x-ray performed & result reviewed and documented in the notes | TB screening prior to infusion start | Yes / No |
| Varicella titres measured | Ensure immunity / contingency plan for non-immune | Yes / No |
| Exit strategy discussed and documented | Make family aware of options if lack of treatment response | Yes / No |
| Advise that treatment response to be assessed between week 10-14 (ie before the 4th infusion) | Ensure that only patients responding to therapy continue on to maintenance 8-weekly infusions | Yes / No |
| Has funding been agreed by the PCT: | Unable to prescribe treatment unless funding agreed | Yes / No |
| | | |
| Date for next infusion: | Name, signature and designation | |
| | | |

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Appendix iv Adverse reactions during infusion

| Type of reaction | Treatment Protocol (Dosages as below) | Prophylaxis for subsequent Infliximab Infusion | | | | | | | | | | | | |
|---|---|---|-----|------|--------------------------------------|-------------------|---------------|--------|-------------|---------------|--------|--------------|---------------|-------|
| <p>Mild</p> <p>Hyperaemia & Tachycardia</p> <p>Palpitations</p> <p>Diaphoresis (excessive sweating)</p> <p>Headache</p> <p>Dizziness</p> <p>Nausea</p> | <p>Slow infusion rate to 10ml/hr</p> <p>Chlorphenamine (IV)</p> <p>Paracetamol (oral)</p> <p>Monitor vital signs every 10 minutes until within normal limits.</p> <p>Wait 20 min then increase infusion rate as per regular protocol as tolerated.</p> <p>Monitor vital signs every 10 min until within normal limits</p> | <p>Pre-treat with oral paracetamol and chlorphenamine 1½ hours before infusion.</p> <p>Test dose Infliximab at 10ml/hr for 15 min</p> <p>If tolerated increase rate to infuse over 3 hours.</p> | | | | | | | | | | | | |
| <p>Moderate</p> <p>Hypo/hypertension (≥ 20 points systolic blood pressure)</p> <p>Hyperaemia</p> <p>Chest discomfort (e.g. tightening, pressure)</p> <p>Shortness of breath</p> <p>Palpitations</p> <p>Urticaria</p> | <p>Stop or slow infusion rate to administer Chlorphenamine (IV)</p> <p>Paracetamol (oral)</p> <p>Monitor vital signs every 5 min until within normal limits</p> <p>Wait 20 min, then restart infusion rate at 10ml/hr and increase infusion rate as per regular protocol as tolerated</p> <p>Monitor vital signs every 5 mins until within normal limits</p> | <p>Pre-treat with oral paracetamol and chlorphenamine 1½ hours before infusion</p> <p>Test dose Infliximab at 10ml/hr for 15 min</p> <p>If tolerated, increase infusion rate as per regular protocol as tolerated until 80ml/hour then increase to 150ml/hr until infusion finished</p> | | | | | | | | | | | | |
| <p>Severe</p> <p>Significant hypo/hypertension (≥ 40 points systolic blood pressure)</p> <p>Elevated temperature with rigors</p> <p>Hyperaemia</p> <p>Chest discomfort (e.g. tightening, pressure)</p> <p>Significant shortness of breath</p> <p>Stridor (if potential to lose airway call crash team on 2222)</p> | <p>Stop infusion</p> <p>Infuse normal saline (10mls/Kg)</p> <p>Maintain airway; give oxygen if available</p> <p>Epinephrine 1:1000 (IM) Dose may be repeated every 5mins for 3 doses</p> <p>Hydrocortisone 100mg (IV)</p> <p>Chlorphenamine (IV)</p> <p>Paracetamol (Oral)</p> <p>Monitor vital signs every 2 min until within normal limits</p> <p>If patient stabilises restart infusion increasing as per regular protocol until 80ml/hr as tolerated until infusion finished</p> <p>If patient requires a second dose of adrenaline call the crash team on 2222</p> | <p>Pre-treat with oral paracetamol and chlorphenamine 1½ hours before infusion.</p> <p>Hydrocortisone 100mg IV 20min before infusion</p> <p>Test dose Infliximab at 10ml/hr for 15 min</p> <p>If tolerated, increase infusion rate as per regular protocol as until 80ml/hour then increase to 100ml/hr until infusion finished</p> | | | | | | | | | | | | |
| <p>Chlorphenamine (ORAL)</p> <p>1month-2years 1mg twice daily</p> <p>2-6years 1mg every 4-6 hourly (max 6mg daily)</p> <p>6-12 years 2mg every 4-6 hours (max 12mg daily)</p> <p>12-18 years 4mg every 4-6 hours (max 24mg daily)</p> <p>Chlorphenamine (Subcutaneous, Intramuscular or Intravenous injection)</p> <p>1month-2years 250micrograms/kg (max2.5mg) repeated if required up to 4 times in 24 hours</p> <p>2-6years 2.5-5mg repeated if required up to 4 times in 24 hours</p> <p>6-12 years 5-10mg repeated if required up to 4 times in 24 hours</p> <p>12-18 years 4mg every 4-6 hours repeated if required up to 4 times in 24 hours (max 40mg daily)</p> <p>Epinephrine 1:1000(Intramuscular)</p> <table border="1"> <thead> <tr> <th>Age</th> <th>Dose</th> <th>Volume of adrenaline 1:1000 (1mg/ml)</th> </tr> </thead> <tbody> <tr> <td>6months - 6 years</td> <td>120micrograms</td> <td>0.12ml</td> </tr> <tr> <td>6 -12 years</td> <td>250micrograms</td> <td>0.25ml</td> </tr> <tr> <td>12 -18 years</td> <td>500micrograms</td> <td>0.5ml</td> </tr> </tbody> </table> | | | Age | Dose | Volume of adrenaline 1:1000 (1mg/ml) | 6months - 6 years | 120micrograms | 0.12ml | 6 -12 years | 250micrograms | 0.25ml | 12 -18 years | 500micrograms | 0.5ml |
| Age | Dose | Volume of adrenaline 1:1000 (1mg/ml) | | | | | | | | | | | | |
| 6months - 6 years | 120micrograms | 0.12ml | | | | | | | | | | | | |
| 6 -12 years | 250micrograms | 0.25ml | | | | | | | | | | | | |
| 12 -18 years | 500micrograms | 0.5ml | | | | | | | | | | | | |

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Appendix v

Information on Infliximab for the Treatment of

Paediatric Crohn's Disease

What is Infliximab?

Infliximab (Infliximab) belongs to a group of treatments known as BIOLOGICS. It is one of several biologics which are more specifically known as anti-TNF-alpha agents. Infliximab is an antibody which recognises and binds to TNF-alpha neutralising its effects to reduce inflammation and the symptoms associated with Crohn's Disease.

What is Infliximab used for?

Infliximab has been used to treat over 1 million patients worldwide, for a range of inflammatory conditions which affect the gut, skin, joints or spine. It was first licensed in the UK for adults with Crohn's disease in 1999, then for rheumatoid arthritis in 2000 and then for psoriasis in 2005. Infliximab received approval for the treatment of paediatric Crohn's disease (patients aged 6 – 17 years old) in June 2007.

Although all of these conditions are different, the common factor is inflammation, which can cause pain and damage to the body's tissues and structures. Infliximab has been shown to be beneficial in the management of paediatric Crohn's Disease.

Your child may be prescribed Infliximab if they have severe active disease which is not responding to standard treatments and where surgery is not appropriate.

The underlying cause of Crohn's Disease

There are a number of theories about what causes Crohn's disease, but none have been proven. The human system is made up of cells and proteins which protect people from infection. The most common theory is that the body's immune system reacts abnormally in people with Crohn's disease, mistaking bacteria, foods, and other substances for being foreign. The immune systems response is to attack these "invaders". During this process, white blood cells accumulate in the lining of the intestines, producing chronic inflammation, which leads to ulcerations (breaks in the lining of the gut) and bowel injury.

One of the key molecules responsible for this chronic inflammation is called tumour necrosis factor alpha or TNF- α . It is one of a range of chemicals naturally produced by the body to fight infections as part of the immune response. In conditions such as Crohn's Disease, there is an overproduction of TNF- α , which leads to the chronic inflammation seen in Crohn's disease.

Family influence

Crohn's disease tends to run in families, and about 20 to 30% of people with the condition have a family member or relative with some form of inflammatory bowel disease. There is no way of knowing which, if any, family members will develop Crohn's disease

Possible triggers

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Foreign substances in the environment (such as a virus or bacterium) may also be the direct cause of the inflammation, or they may stimulate the body's immune system to produce inflammation without control.

How Does Infliximab Work?

Tumour necrosis factor alpha or TNF- α is one of the key molecules responsible for this chronic inflammation. It is one of a range of chemicals naturally produced by the body to fight infections as part of the immune response. In conditions such as Crohn's Disease, there is an overproduction of TNF- α , which leads to the chronic inflammation seen in Crohn's disease.

Infliximab works by blocking the excess production of TNF- α which can reduce the inflammation in the gut. Patients may start to feel a difference within a few weeks after treatment has started.

How is Infliximab given?

Infliximab is a powder that is mixed with a water and salt solution to make up a clear liquid; this liquid is then given as an infusion. Infliximab is given into a vein, usually in the arm. The infusion will take about 2 hours. Your child will also be observed during the infusion and for 1 to 2 hours after the infusion has finished before being allowed to go home.

What is the dose of Infliximab?

The doctor will have decided the right dose; it is usually 5mg for every kilogram of weight. After the first infusion, the second infusion will be given 2 weeks later. The third infusion will be 4 weeks after the second infusion. Thereafter Infliximab may be given at 2 monthly intervals.

The appointment for the next infusion will be given to you before you leave the hospital. Please ensure that you attend the next appointment. If you miss the appointment, it may affect how the treatment works.

How long will Infliximab take to work?

The effects of Infliximab are often noticed within a few weeks of starting therapy. A check-up will be scheduled during the first 3 to 6 months of treatment to find out whether the treatment should be continued.

Will Infliximab work?

Infliximab has been prescribed because studies have shown that it improved Crohn's disease in the majority of patients who received it. However it is important to remember that no drug works for all patients.

Are extra health checks required with Infliximab?

There have been cases of tuberculosis (TB) reported in patients taking Infliximab; therefore all patients are screened for tuberculosis before starting Infliximab. Screening procedures may include a tuberculin skin test and a chest x-ray, depending on your

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hospitals TB screening policy. It is very important to let the doctor know if your child has had tuberculosis or if they have been in close contact with someone who has had tuberculosis.

Will there be any extra tests?

No, Infliximab does not require any extra tests but routine tests to monitor disease activity will still be required.

Can other medicines be taken with Infliximab?

It is a good idea to talk to your child's doctor or specialist nurse before taking any other medicines. Before starting Infliximab, the doctor or specialist nurse will perform a full review of your child's current medications. If your child should see another doctor, nurse or a dentist after they have started Infliximab, tell them that they are receiving Infliximab.

Other Considerations:

Vaccinations

Please discuss any vaccinations required with your child's doctor or specialist nurse before administration as the immune system is suppressed and on occasion can cause a severe reaction. It is advised that if possible, all vaccinations should be brought up to date in agreement with current vaccination guidelines, before your child starts their treatment with Infliximab.

It is recommended that the annual influenza vaccine (flu vaccine which is an injection) is given and this can be arranged through the family doctor. This should NOT be the nasal vaccination as it is a live vaccination.

Infections

If your child develops an infection the doctor or specialist nurse must be informed immediately. It is important that the next infusion of Infliximab is not given if your child has an infection or you suspect they may have an infection. If in doubt, speak with the doctor or specialist nurse.

Chicken Pox

Your child will be checked for their chicken pox status prior to starting infliximab. If they are not immune a vaccination will be offered if possible.

If your child comes into contact with an individual who has confirmed chicken pox ie a family member in the same house, immediate friendship group or on a sleep over whilst on Infliximab they will need checking again for antibody status even if previously immune.

If results are negative they will be offered either anti viral treatment or a vaccination as advised by NNUH virology.

Antibiotics

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Infliximab has not been shown to react with antibiotics and they can be taken if required. However, if an infection develops the doctor or specialist nurse must be informed immediately. It is important that the next infusion of Infliximab is not given if your child has an infection or you suspect they may have an infection. If in doubt, speak with the doctor or specialist nurse.

Contraception

It is recommended that a reliable form of contraception is used whilst receiving Infliximab and for 6 months after the last infusion. If planning to start a family or already pregnant, contact the doctor or specialist nurse in advance to discuss as treatment with Infliximab will need to be stopped.

Are there any side effects?

Like all medicines, Infliximab can have side effects. Some side effects may appear up to 6 months after the last infusion. Remember medicines affect people in different ways and it is very possible that none of the side effects mentioned here will be experienced. However, the possible side effect of any medication needs to be balanced against the risk of problems if the disease is not treated properly.

The doctor or specialist nurse must be informed immediately if any of the following occur during the infusion

- ❖ Pain or tenderness in chest, muscles, joints or jaw.
- ❖ Swelling of the hands, feet, ankles, face, lips, mouth or throat.
- ❖ Any difficulty swallowing or breathing (e.g. shortness of breath).
- ❖ Bumpy skin or other signs of an allergic reaction.
- ❖ Fever.
- ❖ Rash.
- ❖ Itching.

Please inform the doctor or nurse as soon as possible if you notice your child experiencing any of the following symptoms at all other times

- ❖ Difficulty breathing and dry cough.
- ❖ Problems passing urine such as stinging sensation.
- ❖ Changes in heartbeat, for example if it is beating faster than usual.
- ❖ Light-headedness.
- ❖ Tiredness.
- ❖ Hoarseness.
- ❖ Headache.
- ❖ Tingling.
- ❖ Numbness.
- ❖ Double vision or other problems with the eyes.

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- ❖ Weakness in arms or legs.
- ❖ Signs of liver problems for example: eyes or skin turning yellow. Dark brown urine, right-sided stomach pain.

The symptoms listed above can be signs of the more significant side effects. Below is a list of the full range of possible side effects with Infliximab

Common: headache, dizziness, nausea, abdominal symptoms, allergic reactions, rash, urinary, viral infections (for example herpes, influenza), respiratory infections (cold, sinus infections, bronchitis, pneumonia), infusion related reactions

Uncommon: depression, agitation, sleep disturbances, impaired wound healing, bacterial infections (for example tuberculosis, urinary tract infections, deep skin infections, sepsis), fungal infections, asthma, abnormal liver function, low blood cell counts including anemia, worsening of demyelinating nerve disease, autoimmune disease activation (SLE or systemic lupus erythematosus), worsening of heart failure, hair loss, bleedings, allergic anaphylactic reactions, injection site reactions.

Rare: gastrointestinal bleedings or perforation, circulatory failure, multiple sclerosis

Very Rare: Malignancies and lymphoproliferative disorders

In controlled studies of TNF-blocking agents, more cases of malignancies including lymphoma have been observed in patients receiving a TNF blocker compared to control patients.

One particular form of lymphoma has been observed in adolescent and young adult patients with Crohn's Disease. This form of lymphoma is called Hepatosplenic T-cell lymphoma (HSTCL). HSTCL is a very rare form of lymphoma in which the major sites of disease are the liver, spleen and bone marrow. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal, and is reported to occur most commonly in adolescent and young adult males.

The definition of a rare adverse event or reaction is one which has a likelihood of occurring in \geq (greater than) 1 in 10000 people to \leq (less than) 1 in 1000 people. HSTCL has been classified as being rare.

Additional liver tests (to see how well the liver is working) and blood tests may be done if any of the above symptoms occur.

If you notice any side effects that are not mentioned in this leaflet, please tell the doctor or specialist nurse.

Useful Contact Numbers:

| | |
|---|--------------|
| Children's Day Ward | 01603 287170 |
| Children's Assessment Unit | 01603 289774 |
| Children's Gastroenterology Specialist Nurses | 01603 286320 |
| Paediatric Consultants (via secretaries) | 01603 289936 |
| | 01603 287174 |