Clinical Guideline

INFLIXIMAB AND ADALIMUMAB – TREATMENT OF CHILDREN WITH INFLAMMATORY BOWEL DISEASE WITH ANTI-TNF BIOLOGICS

SETTING	Bristol Royal Hospital for Children
FOR STAFF	Medical, Nursing and Pharmacy Staff
PATIENTS	Children with Inflammatory Bowel Disease (IBD)

Inflammatory Bowel Disease

Children with inflammatory bowel disease may develop severe gastro-intestinal symptoms of diarrhoea, abdominal pain and bleeding, as well as weight loss and poor growth. Currently there is no cure. Treatment options includes aminosalicylates, corticosteroids, immunosuppressants, antibiotics, nutritional supplementation, dietary measures and biologics. A significant number of children remain treatment resistant.

This guideline focuses on the use of the TNFα inhibitors, Infliximab and Adalimumab for Inflammatory Bowel Disease. Both of these medicines are biological medicines which are medicines derived from living cells or organisms. See the Biosimilar Medicines Policy for more information.

Infliximab

Infliximab is a tumour necrosis factor alpha (TNF-α) inhibitor

Funded indications for infliximab

- Infliximab should only be prescribed by a paediatric gastroenterologist experienced in the management of Inflammatory Bowel disease.
- It must be discussed at a multidisciplinary team meeting which must include at least 2 consultants and ideally other professional groups appropriate to the disease area.
- It is included on the NHSE high cost drugs list and therefore patients must meet the following comissioning criteria in order for funding to be approved. Where applicable a blueteq form must be completed prior to prescribing.

Infliximab for Crohn's disease[1]:

Infliximab is recommended by NICE (see TA187) and funded by NHSE for paediatric patients who meet the following criteria:

a. The patient is 6 – 17 years old
b. The patient has severe active Crohn's disease
c. The patient's condition is refractory to treatment with immunomodulating drugs (E.g. azathioprine, methotrexate) and corticosteroids or the patient is intolerant of or has experienced toxicity from these treatments and;
d. Surgery is inappropriate for the patient
e. Blueteq form required.

OR

a. The patient is 6 – 17 years
b. The patient has fistulising and /or perianal Crohn's disease which has not responded to primary therapy with antibiotics (metronidazole +/- ciprofloxacin)
c. NB. this is an unlicensed indication but is commissioned via the NHSE commissioning medicines for children in specialised services policy.
d. No blueteq form is available – pharmacy team to inform pharmacy funding of patient details and indication.

Infliximab for Ulcerative Colitis [2,3]:

Infliximab is recommended by NICE (see TA329 and TA163) for patients who meet the following criteria

a. The patient is 6 – 17 years old
b. Infliximab should be considered for treatment of children with Ulcerative Colitis whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.
c. Blueteq form required.

OR

a. The patient is 6 – 17 years old
b. Infliximab may also be considered for the treatment of acute exacerbations of severely active Ulcerative Colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient.
c. NB. this is an unlicensed indication but is commissioned via the NHSE commissioning medicines for children in specialised services policy.
d. Blueteq form not required – pharmacy team to inform pharmacy finance.

Children under 6 years old

Infliximab may be given for children with IBD younger than 6 years of age. However, due to the limited available evidence this is not approved by NICE. A blueteq form is not required for patients aged 2-6 years, please inform pharmacy team who will liaise with pharmacy finance. If considering for a child of <2yrs please discuss this with the gastroenterology pharmacist as other forms of approval may be required.

Prior assessments

Prior to initiating infliximab treatment [4,5]:

- Assess risk of infection:
  - Assess for risk of tuberculosis (TB) [6]
    - History of contact.
    - History of travel to endemic areas.
    - Perform chest x-ray/Mantoux and Quantiferon test (In Bristol – high risk of dormant TB compared with other areas of the southwest). For patients outside of Bristol to follow local TB screening advice.
  - Varicella Zoster
    - Varicella IgG titre: if no clear history of infection and titre not already done
  - Pelvic infection
    - If pelvic and/or perianal sepsis is suspected then ultrasound scan and MRI scan are essential prior to starting treatment with infliximab.
  - Risk of chronic hepatitis B and C where there is a family history of being from an endemic country
  - Record patient vaccination status
- Document discussion of pregnancy.
  - Pregnancy should be avoided during the treatment course and for at least 6 months following cessation.
- Document in notes or clinic letter discussion of indication, complications and parental agreement. Include risk of anaphylaxis, serious infections and tumours (including hepatosplenic lymphoma).
- Complete biologics initiation form on Infoflex

On the day of infusion (see checklist)

- Check parents/patient have read information leaflet on infliximab.
- Confirm documented discussion and record that verbal consent has been obtained.
- Take history to assess the risk of possible intercurrent illness or the presence of perianal abscess(bacterial , viral or fungal infection). Check baseline observations including heart rate, blood pressure and temperature. Discuss with consultant gastroenterologist if concern patient is unwell and/or has temperature because of infection. (Temperature can be because of active disease)
- Take a blood sample for FBC, LFTs, Ca, Phosphate, U+Es, ESR, CRP (results not required prior to infusion unless any clinical concerns).
- Before the 4th infusion and at least 6 monthly thereafter take a blood sample for infliximab drug level and antibodies
- Prescribe emergency drugs in case of anaphylaxis +/- prophylactic medications (see appendix 1)
- Record disease activity score (wPCDAI or PUCAI) using appendix 3 or 4 of this document

Prescribing Infliximab

Prescribe by brand. Keep patients on the same brand (unless on consultant advice to switch). If this is inappropriate please discuss with consultant and refer to the biosimilar medicines policy for alternatives.

Pre-medication: This may not be necessary; however this will be assessed on a patient by patient basis. Possible indications include history of atopy/asthma, previous infusion reason or if restarting infliximab following a treatment free period. Discuss with consultant if in any doubt.
If required, children should receive IV hydrocortisone (4mg/kg; max 200mg) at least 30 minutes prior to infusion of Infliximab and IV chlorphenamine and oral paracetamol (doses as per BNFc).

Anaphylaxis – due to the risk of infusion reactions all patients should be prescribed anaphylaxis medicines on the PRN section of the chart. See appendix 1

If signs of anaphylaxis (e.g. bronchospasm, hypotension, etc) appear, the infusion should be stopped immediately and appropriate treatment given.

Infliximab standard dose:
5mg/kg over at least 2 hours – starting with test dose (see rates).
Where appropriate round the dose to the nearest 100mg to reduce wastage.
The dose should be diluted to a total volume of 250ml sodium chloride 0.9%

Induction regime:
Administered at:
Week 0
Week 2
Week 6

Maintenance regime:
There should be a plan at the outset for using infliximab, with the length of course clearly defined e.g. 3 doses and then reassessment.

- If remission is induced then a maintenance dose of 5mg/kg/dose 8 weekly may be sufficient.

Alteration to standard dosing [7]

- Patients with severe colitis may require higher and more frequent dosages in the induction period for example 10mg/kg 0, 1, 4 weeks in acute severe colitis[8]
- Patients who develop loss of response from infliximab may benefit from a repeat drug induction regime
- Patients who develop low drug levels/raised antibodies may benefit from a dose increase and/or more frequent infusions in order to prevent loss of response.
- Younger/lower weight patients are likely to require more frequent administration/higher dose than standard dosing to maintain drug levels and clinical response.

Administration

Rates:

	Test dose	Remainder of infusion	Total infusion time
First three induction doses	20ml/hr for 15 mins	120ml/hr to complete infusion	2 hours
5mg/kg maintenance doses*	20ml/hr for 15 mins	240ml/hr to complete infusion	1 hour
Maintenance doses greater than 5mg/kg*	20ml/hr for 15 mins	240ml/hr to complete infusion	1 hour

* maintenance doses up to 10 mg/kg may be given over 1 hour provided induction doses were tolerated[9] - discuss with gastro team first.
Note - The infusion rate may be slowed in those patients who have had a significant previous infusion reaction.

Reconstitution:

- Reconstitute each 100mg vial with 10 ml of water for injections.
- After reconstitution each ml contains 10mg of infliximab.
- Gently swirl the solution by rotating the vial to dissolve the powder. DO NOT SHAKE.
- Allow to stand for 5 minutes.

The reconstituted solution is colourless to light yellow and opalescent. The solution may develop a few fine translucent particles as infliximab is a protein.

Dilution:

- Dilute the total volume of the reconstituted infliximab solution dose to 250 ml with sodium chloride 0.9%. Gently mix.

Administration equipment:

- Use low protein-binding filter (pore size 1.2 micrometer or less e.g. Codan I.V.STAR® 4.5 Set). Order via EROs.

Comments:

- Stored in the fridge prior to use
- All vials, ampoules and solution bags are for single use only.
- Administer reconstituted solutions immediately
- Ensure that all anaphylaxis medications are prescribed. The infusion should be stopped immediately if signs of infusion reaction occur.
- Do not infuse infliximab concomitantly in the same intravenous line with other agents.
- Patients should be given the special alert card provided with infliximab

Ordering:
An inpatient prescription chart with added infusion chart should be completed with a recent patient weight and the appropriate dose. The prescription should be sent to the inpatient paediatric pharmacy, level 3, BRHC (Mon-Fri) **at least one working day in advance** of the admission. Infliximab should be available / have been dispensed **by the morning of the infusion.**

Monitoring during and after infusion:

If signs of anaphylaxis (e.g. bronchospasm, hypotension, etc) appear, the infusion should be stopped immediately and appropriate treatment given.

- Baseline observations (including blood pressure and temperature) should be checked prior to every infusion and every 15 minutes during the infusion.
- A doctor does not need to be routinely present during the administration of infliximab unless there was a reaction to the previous infusion (see below)
- All patients receive a test dose at the beginning of each infusion (see rate). If no reaction occurs, the rate can be increased (see rates).
- If minor reactions are observed during the test dose, and the patient has not been pre-treated, antihistamines and/or paracetamol should be administered in addition to hydrocortisone prior to increasing the rate.
- A doctor must be present, at least during the initiation of the infusion, in subjects with a prior recent infusion reaction.
- If an infusion is stopped because of a reaction and the reaction is not severe, the infusion may be restarted with caution.
- If the patient has had a previous infusion reaction but no longer has ongoing infusion reactions with IV steroid cover, a doctor does not need to be present
- The patient should be monitored (with baseline observations every 30 mins) for at least 1 hour after the first 3 infusions. Once on a maintenance regime, if the patient has not had any adverse reactions they can be discharged 30 minutes post infusion.
- If a further infusion is planned, this should be booked in the admissions diary before the patient leaves Puzzlewood /ward and the next dose of infliximab prescribed.

Treatment duration (Crohn's Disease and Ulcerative Colitis):

The effectiveness of treatment should be assessed around the time of the 4th infusion. At this point a review of the clinical and biochemical response to treatment and of the drug levels and antibodies should be performed to plan the frequency/dose of further infusions and the need for any additional treatment.

Infliximab should be given as a planned course of treatment until treatment failure. Patients should then be reassessed at least annualy to determine whether ongoing treatment is still clinically appropriate. In those patients whose disease relapses after Infliximab treatment is stopped; they should have the option to restart provided they had responded to the initial treatment course.

Treatment with infliximab is preferably started in conjunction with another long-term immunosuppressive maintenance agent to minimise the formation of antibodies to infliximab. Stopping co-existing immunosuppression after six months should be considered (there is emerging data of lymphoma risk with infliximab which may or may not be related to concomitant administration of azathioprine/6 mercaptapurine and infliximab). Children are continually reassessed to monitor whether other therapies / surgery are useful in reducing the long-term exposure to infliximab.

Drug levels

Infliximab drug levels and antibodies should be measured prior to the fourth infusion (usually 14 weeks on standard regime) and at least 6 monthly. Some hospitals will get levels before every infusion as part of biosimilar funding arrangements. Pre-dose trough levels of ≥5 ug/ml should be targeted for mucosal healing in Crohn's disease[10]. The presence of antibodies does not contra-indicate further doses of Infliximab however, dose and frequency may be altered to prevent loss of response. Results should be fed back to/collated by the specialist nurses so that patients can be discussed by the Bristol team.

Adalimumab[1,3,5]:

Adalimumab is a recombinant human monoclonal antibody that binds specifically to TNF-α, blocking interaction with its cell surface receptors and thereby limiting the promotion of inflammatory pathways.

Funded indications for Adalimumab:

- Adalimumab should only be prescribed by a paediatric gastroenterologist experienced in the management of Inflammatory Bowel disease.
- It must be discussed at a multidisciplinary team meeting which must include at least 2 consultants and ideally other professional groups appropriate to the disease area.
- It is included on the NHSE high cost drugs list and therefore patients must meet the following comissioning criteria in order for funding to be approved. Where applicable a blueteq form must be completed prior to prescribing.

Adalimumab for Crohn's disease:

Adalimumab is recommended by NICE (see TA187) and funded by NHSE for paediatric patients who meet the following criteria:

- The patient is 2 – 17yrs old (nb. unlicensed 2-5 yrs)
- The patient has severe active Crohn's disease which has not responded despite full and adequate treatment with primary nutrition therapy, an immunosuppressant and corticosteroids, or who are intolerant to or have contraindications to such therapies.
- Blueteq form required.

Adalimumab can be given as monotherapy i.e without concomitant immunomodulator.

Adalimumab for Ulcerative colitis:

The use of adalimumab for UC in paediatrics is unlicensed but recommended by NICE (see TA329) and funded by NHSE for paediatric patients who meet the following criteria:

- The patient is 2-17 yrs old
- The patient has severely active Ulcerative Colitis which has failed to respond to standard therapies including corticosteroids AND 6-mercaptopurine or azathioprine or who are intolerant to or have contraindications to such therapies.
- If the patient is over 6 years old they should have tried and failed infliximab first (unless contraindicated)
- Blueteq form required

Prescreening and documentation: The same for adalimumab as for infliximab as detailed above.

Prescribing Adalimumab

Premedications / anaphylaxis medicines: Not required

Preparations available at UHBW:

- 1st line: **Amgevita** - 20mg pre-filled syringe, 40mg pre-filled syringe, 40mg pre-filled pen
- Other preparations:
  - **Humira** – 40mg autoinjector pen, 40mg pre-filled syringe, 40mg paediatric vial. (NB. MDT discussion and switch back form required – see appendix of Biosimilar policy)

- **Imraldi** – 40mg prefilled syringe or 40mg prefilled pen (this is the 1st line adult preparation – consider initiating this instead of Amgevita if the patient is close to transition age)

Prescriptions / Administration: Patients are usually initiated on treatment at home via the pharmacy homecare service. They provide training which enables the patients (or carer) to self administer the treatment. Prescriptions are done on the pharmacy homecare prescription form which are clinically screened by the inpatient paediatric pharmacy team and dispensed by the external pharmacy homecare company. A registration form is required with the first prescription. If treatment needs to be started more urgently, the clinical nurse specialist will supervise the first doses in hospital. The same prescriptions/registrations are required but an additional inpatient prescription is required for the doses given in hospital.

Dosing :

By subcutaneous injection

Standard regimen:
Child 6–17 years (body-weight up to 40 kg) Initially 40 mg, then 20 mg after 2 weeks; maintenance 20 mg every 2 weeks, increased if necessary to 20 mg once weekly, review treatment if no response within 12 weeks of initial dose.

Child 6–17 years (body-weight 40 kg and above) Initially 80 mg, then 40 mg after 2 weeks; maintenance 40 mg every 2 weeks, increased if necessary to 40 mg once weekly (alternatively 80mg every 2 weeks), maximum 40 mg administered at a single site, review treatment if no response within 12 weeks of initial dose.

Accelerated regimen – (most commonly used):
Child 6–17 years (body-weight up to 40 kg) Initially 80 mg, then 40 mg after 2 weeks; maintenance 20 mg every 2 weeks, increased if necessary to 20 mg once weekly, maximum 40 mg administered at a single site, review treatment if no response within 12 weeks of initial dose.

Child 6–17 years (body-weight 40 kg and above) Initially 160 mg, dose can alternatively be given as divided injections over 2 days, then 80 mg after 2 weeks; maintenance 40 mg every 2 weeks, then increased if necessary to 40 mg once weekly, maximum 40 mg administered at a single site, review treatment if no response within 12 weeks of initial dose.

Treatment duration:

The effectiveness of treatment should be assessed around the time of the 5th dose (8 weeks). At this point a review of the clinical and biochemical response to treatment should be performed as well as drug levels to plan the frequency/dose of further injections and the need for any additional treatment.

Adalimuimab should be given as a planned course of treatment until treatment failure. Patients should be reassessed at least annualy to determine whether ongoing treatment is still clinically appropriate. In those patients whose disease relapses after Adalimumab treatment is stopped; they should have the option to restart provided they had responded to the initial treatment course.

Drug levels

Adalimumab drug levels and antibodies should be measured around the fifth injection (usually 8 weeks on standard regime) and at least 6 monthly. Pre-dose trough levels are not necessary. A level of ≥7.5 ug/ml should be targeted for mucosal healing in Crohn's disease[10]. The presence of antibodies does not contra-indicate further doses of Adalimumab however, dose and frequency may be altered to prevent loss of response. Results should be fed back to/collated by the specialist nurses so that patients can be discussed by the Bristol team.

Table A

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RELATED DOCUMENTS AND PAGES	Biosimilar Medicines Policy, July 2020. University Hospitals Bristol and Weston NHS Foundation Trust. Available at: http://nww.avon.nhs.uk/dms/download.aspx?did=21598 [Accessed 5th Nov 2020]
AUTHORISING BODY	Paediatric Gastroenterology Governance Group
SAFETY	Very low risk of infusion reaction with infliximab Please ensure checklist pre-infusion (appendix 2) is completed
QUERIES AND CONTACT	Paediatric Gastroenterology Department secretaries 01173429451

Appendix 1

Anaphylaxis medication to be prescribed for all patients receiving an infliximab infusion.

Adrenaline 1:1000 (1mg/ml) for IM injection
Child less than 6 years 150 micrograms (0.15ml)
Child 6-12 years 300 micrograms (0.3ml)
Child > 12 years if small / pre-pubertal 300micrograms (0.3ml)
Child > 12 years 500 micrograms (0.5ml)

Hydrocortisone (as sodium succinate) IM or slow IV injection
Infant < 6 months 25mg
Child 6 months -6 years 50mg
Child 6-12 years 100mg
Child >12 years 200mg

Chlorphenamine IM or slow IV injection
Infant < 6 months 250 micrograms/kg
Child 6 months - 6 years 2.5mg
Child 6 – 12 years 5mg
Child >12 years 10mg

Appendix 2

Check-List for patients receiving Infliximab infusion at induction:

Infusion	Week 0	Week 2	Week 6
Information leaflet given to and read by parents / child			
Documented discussion by Consultant for whole treatment course - check clinic letters (only once)			
Assessment to exclude possible intercurrent illness			
History of contact with TB ascertained. Local screening tests for TB completed			
Activity indices documented (PCDAI, PUCAI)			
IBD bloods taken			
Risk of pregnancy discussed/checked (if required)			
Anaphylaxis treatment medications prescribed			
Premedication's prescribed (if required)			

Appendix 3

Weighted Paediatric Crohn's Disease Activity Index (wPCDAI score)[11]

History (Recall, 1 week)			
Abdominal Pain			Score
0 = None	10 = Mild: Brief, dose not interfere With activities	20 = Moderate/Severe: Daily longer lasting, affects Activities, nocturnal	_____
Patient Functioning, General Well-Being			Score
0 = No limitations of activities, Well	10 = Occasional difficulty in maintaining age appropriate Activities, below par	20 = Frequent limitation of activity, very poor	_____
Stools (per day)			Score
0 = 0-1 liquid stools, no blood	7.5 = Up to 2 semi-formed with small Blood, or 2-5 liquid	20 = Gross bleeding, or ≥ 6 liquid, or nocturnal Diarrhoea	_____
Laboratory			
Erythrocyte Sedimentation Rate			Score
0 = < 20mm/hr	7.5 = 20 – 50 mm/hr	15 = > 50mm/hr	_____
Albumin			Score
0 = ≥ 3.5g/dL	10 = 3.1-3.4g/dL	20 = ≤ 3.0g/dL	_____
Examination			
Weight			Score
0 = Weight gain or voluntary Weight stable/loss	5 = Involuntary weight stable, weight loss 1-9%	10 = Weight loss ≥ 10%	_____
Perirectal Disease			Score
0 = None, asymptomatic tags	7.5 = 1-2 indolent fistula, scant Drainage, no tenderness	15 = Active fistula, drainage tenderness, or abscess	____
Extra-intestinal Manifestations			Score
(fever ≥ 38.5°C for 3 days over past week, definite arthritis, uveitis, E. nodosum, P gangrenosum)			
0 = None		10 = One or more	____
			Total score (0-125):

Disease remission	<12.5
Mild activity	>15
Moderate activity	>40
Severe activity	>57.5

Appendix 4

Paediatric ulcerative colitis activity index (PUCAI score)[12]

	Item	Points
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 wakening)	
	No	0
	Yes	10
6	Activity level	
	No limitation of activity	0
	Occasional limitation of activity	5
	Severe restricted activity	10
	Sum of PUCAI (0 – 85)	

Disease remission	<10
Mild activity	10-35
Moderate activity	40-60
Severe activity	≥65