Cambridge University Hospitals NHS
NHS Foundation Trust

NHS
Cambridgeshire and Peterborough
Clinical Commissioning Group

Shared Care Guideline
Methotrexate- in paediatric Crohn's disease

Executive Summary

- Methotrexate is a disease modifying agent that can be used to manage inflammatory bowel disease; it is second line treatment for inducing and maintaining remission in refractory Crohn's disease and is used where other treatments have not been tolerated.
- Methotrexate should be taken ONCE weekly on the same day each week
- Patients should be prescribed concomitant folic acid, starting at once a week but may be increased to a maximum of six times per week (excluding day of methotrexate) if required for side effects. Low dose methotrexate should not exceed 25mg per week
- Response can usually be seen in 4-12 weeks.
- Due to teratogenicity in male and female patients, patients must use adequate contraception for the duration of methotrexate therapy, and for 3 months after discontinuation of therapy for female patients and until discussion with hospital specialist for male patients
- Regular monitoring is required of: FBC, LFTs, U+E, ESR and CRP and the hospital specialist should be referred to if toxicity suspected.

- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document here

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1. Scope
For use in areas within the Trust, general practice and district general hospitals where patients are managed by general paediatricians.

2. Aim
To provide advice on the safe prescribing, monitoring and administration low dose methotrexate for use in the management of paediatric Crohn's disease

3. Introduction
Methotrexate is a disease modifying agent that can be used to manage inflammatory bowel disease, second line treatment for inducing and maintaining remission in refractory Crohn's disease or where other treatments have not been tolerated.
Methotrexate is a folic acid antagonist which belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis. Mode of action in Crohn's disease thought to be due to inhibition of cytokine and eicosanoid synthesis.
Methotrexate should be considered for maintaining remission only in people who:

- Needed methotrexate before to induce remission
- Have tried but did not tolerate azathioprine or mercaptopurine for maintenance

- Have contraindication to azathioprine or mercaptopurine (for example, deficient TPMT activity or previous episodes of pancreatitis)

4. Abbreviations

- BCG-bacillus Calmette-Guérin
- BNFc-children's British National Formulary
- CRP C-Reactive protein
- CNS-central nervous system
- ESR-erythrocyte sedimentation rate
- FBC-full blood count
- GP-general practitioner
- LFT's-liver function tests
- MMR-measles, mumps and rubella vaccine
- NSAIDs-non-steroidal anti-inflammatory drugs
- U & E-urea and electrolytes
- TPMT-thiopurine methyltransferase

5. Dose and Administration

Methotrexate is taken once a week, on the same day each week. This day should be specified and recorded in the patient's notes within EPIC and the information passed to the general practitioner (GP) when the request is made for shared care. A patient may be initiated on oral methotrexate therapy and then transferred to parenteral treatment to increase tolerability, or they may commence treatment with parenteral therapy. Both indications are unlicensed.

5.1 Dose in paediatrics

Severe acute Crohn's disease and maintenance of remission of severe Crohn's disease: 15mg/m2 (maximum 25mg), once weekly. In adolescent patients the consultant in charge of the patient may choose to use the adult dose as below:

5.2 Dose in adults

Severe Crohn's disease, induction of remission: 25mg once weekly by intramuscular or subcutaneous injection. Maintenance of remission: 10-25mg once weekly by mouth. Initial dose of 25mg once weekly given to achieve remission over 12-16 weeks, then reduced to a maintenance dose of 15mg once weekly.

Response may take 6-12 weeks, although patients often observe a response between 4-8 weeks

Maximum dose is 25mg once a week.

During maintenance dose can be reduced according to response to lowest effective dose.

There are two strengths of methotrexate tablets available (10mg and 2.5mg). To avoid confusion and reduce the risk to patients, **methotrexate must be prescribed and dispensed as 2.5 mg tablets only**.

The injection is available as Metoject® prefilled pen 50mg in 1ml of methotrexate in differing volumes to allow self-administration of the correct dose. In paediatrics in certain circumstances – patient specific - other injectable options may be available these include Nordimet prefilled pen containing

25mg in 1ml of methotrexate and Zlatal prefilled syringe containing 25mg in 1ml of methotrexate. The dose is given once weekly and should not usually exceed 25mg once a week.

All communication (letters, patient held record books etc.), discharge prescriptions and FP10s should normally carry the following details:

- Weekly dose (methotrexate usually taken/injected once a week on a specified day)
- Day of the week dose taken/injected (always same day each week).
- Usual strength of tablets the patient takes (e.g. if patient takes 10mg per week on Mondays as four x 2.5mg tabs, this should be clearly indicated on the prescription, i.e. four x 2.5mg tablets weekly total 10mg weekly, taken on Monday) or usual strength of injection the patient administers.

Patients and parents/carers should be given a 'methotrexate patient held record book' detailing the dose, start date, method of administration and blood results at the initiation of treatment by the hospital team. Monitoring blood results should be entered into this record. Patients should be advised to bring their methotrexate book to all appointments or consultations with a health professional including the community pharmacy where their prescription is dispensed. It is the responsibility of all health care professionals to keep the booklet up to date.

Further information can be found in the Summary of Product Characteristics:
http://www.medicines.org.uk/emc/

5.3 Folic acid

Methotrexate is a folic acid antagonist causing reduced folic acid uptake at cell level. Folate deficiency plays an important role in the development of methotrexate related side effects. Folic acid supplementation is therefore routinely given to reduce toxicity particularly the most common side effects such as nausea, vomiting and stomatitis.

All patients on methotrexate should normally be started on folic acid at a dose of at least 5mg per week (do not give on methotrexate day). For paediatric patients unable to swallow tablets, a dose of 1mg daily except on day of methotrexate is given by syrup formulation (usual strength of folic acid syrup is 1mg in 2mL). The folic acid dose may be increased or the administration time changed if the patient develops significant gastrointestinal side effects following methotrexate administration.

6. Adverse Effects

Common (≥ 1 in 100 and < 1 in 10)

- Gastrointestinal disturbances:
  - Anorexia
  - Nausea
  - Vomiting
  - Diarrhoea
  - Ulcerative stomatitis (oral ulceration)
  - Rarely gastrointestinal ulceration
- Alopecia (usually minor)

Uncommon (≥ 1 in 1000 and < 1 in 100)

- Hypersensitivity reaction
  - Fever
  - Rigors

  - Rash
- Bone marrow suppression
  - Leucopenia
  - **Thrombocytopenia**
  - Anaemia
- Central Nervous System (CNS) disturbances
  - Headache
  - Drowsiness
  - Blurred vision

Rare (but significant) (≥ 1 in 10000 and < 1 in 1000)

- **Hepatoxicity** (liver cirrhosis reported) – see section 7 Cautions for advice on alcohol consumption. Avoid methotrexate if pre-existing liver disease.
- **Pulmonary toxicity** (interstitial pneumonitis often associated with eosinophilia, rarely pulmonary fibrosis). This is not dose related and presents with dry cough, dyspnoea and often fever**. In paediatric patients please seek advice from the specialist team before stopping treatment.**

The patient should be advised to report:

- Any signs and symptoms suggestive of infection as this may be a marker of bone marrow suppression i.e.
  - Sore throat
  - Fever
  - Chills
  - Unexplained bruising or bleeding
- Any signs of liver toxicity
  - Severe nausea and vomiting
  - Abdominal discomfort and dark urine
- Respiratory effects (shortness of breath)

The patient should report such symptoms to the GP, who should contact the hospital specialist clinician or specialist nurse as appropriate (see actions to take in the event of abnormal test results/symptoms below)..

Further information can be found in the Summary of Product Characteristics:
http://www.medicines.org.uk/emc/

7. Cautions

Whilst on methotrexate, patients should avoid live vaccines such as:

- Oral polio
- Oral typhoid
- Measles, mumps and rubella (MMR)
- Bacillus Calmette-Guérin (BCG)
- Yellow fever

Contact hospital specialist for advice on any vaccinations if required. Nb: Seasonal flu and pneumococcal vaccines (‘Pneumovax II’) are safe to give during methotrexate treatment.

- Patients who have never had chickenpox or shingles may be at risk of severe infection whilst being treated with methotrexate. Patients should be advised to avoid close contact with people

who have active chickenpox or shingles (especially if they do not have a known history of chickenpox or they know they do not have VZV IgG antibody). Patients should report any such contact (or if they develop chickenpox or shingles) to their GP or specialist for further advice. Administration of Herpes Zoster (shingles) vaccine to appropriate individuals is considered safe. The hospital specialist will advise in each individual case.

- Where time allows, children and young people who are known to be non-immune to VZV will be immunized prior to commencing methotrexate. If this is not clinically appropriate, parents/carers are given information on actions in the event of VZV exposure – namely to keep the child off school if VZV is in the class, and contact the specialist team. They may need treatment with VZIG or a prophylactic course of acyclovir.
- Excretion of methotrexate may be reduced by non-steroidal anti-inflammatory drugs (NSAIDs), with possible increased toxicity. Patients should be advised to avoid self-medicating with over the counter NSAIDs.
- Concomitant administration of a folate antagonist eg Septrin (co-trimoxazole) and trimethoprim, have been reported to cause acute megaloblastic pancytopenia. Hence concomitant use with methotrexate should be avoided. Prophylatic Septrin may be used on specialist advice only.
- Other antibacterials such as tetracyclines, penicillins or ciprofloxacin may increase methotrexate toxicity. In the case of ciprofloxacin treatment; close monitoring of FBC and LFT's should take place during concomitant treatment (rare reports of methotrexate toxicity during concomitant use with ciprofloxacin).
- Due to teratogenicity in male and female patients, patients must use adequate contraception for the duration of methotrexate therapy, and for 3 months after discontinuation of therapy for female patients and until discussion with hospital specialist for male patients
- Alcohol consumption in moderation, e.g. the occasional glass of wine, is not contraindicated. Young people must be advised not to 'binge drink'. Patients should stick to well within normal limits i.e. maximum of 14 units per week for men and women http://www.nhs.uk/Livewell/alcohol/Pages/Effectsofalcohol.aspx

Further information can be found in the Summary of Product Characteristics: http://www.medicines.org.uk/emc/

8. Contraindications

- Significant liver impairment (any persistent 2-forl rise in liver transaminases before or during therapy if LFTs do not normalise after two weeks of withholding methotrexate).
- Moderate to severe renal impairment
- If on methotrexate, avoid during pregnancy (and for 3 months after stopping methotrexate) and breastfeeding.
- Active infection and immunodeficiency syndromes.
- Severe haematological impairment or profound deterioration
- If pneumonitis suspected.
- Hypersensitivity to the active substance or to any of the excipients
- Concurrent vaccination with live vaccines
- If stomatitis develops

Further information can be found in the Summary of Product Characteristics: http://www.medicines.org.uk/emc/

9. Interactions

- **Concomitant administration of a folate antagonist e.g. Septrin® (Co-trimoxazole) or trimethoprim, have been reported to cause acute megaloblastic pancytopenia. Hence concomitant use with methotrexate MUST be avoided. Prophylactic Septrin may be initiated on specialist advice ONLY.**
- Other antibacterials such as tetracyclines, penicillins or ciprofloxacin may increase methotrexate toxicity. For paediatric patients, the specialist team are happy for their patients to receive short courses (up to 7 days) of antibiotics without stopping the methotrexate. If in any doubt please check with the paediatric specialist team. If a patient requires an antibiotic course over 2 weeks, then advice from the specialist team, or pharmacy, should be sought. If methotrexate is held it should be restarted on the usual day of administration.
- Excretion of methotrexate may be reduced by non-steroidal anti-inflammatory drugs (NSAIDs), with possible increased toxicity. Patient should be advised against self-medicating with over the counter NSAIDs.
- **Sulfasalazine**
- **Mercaptopurine-** Methotrexate increases the plasma levels of mercaptopurine. The combination of methotrexate and mercaptopurine may therefore require dose adjustment.
- **Proton-pump inhibitors**- Concomitant administration of methotrexate and omeprazole or pantoprazole may lead to delayed renal elimination of methotrexate
- **Patients should avoid 'live' vaccines such as Oral Polio, Oral Typhoid, measles, mumps and rubella (vaccine) (MMR), bacillus Calmette-Guérin (BCG) and yellow fever, whilst on immunosuppressive therapy.**
- See BNF Appendix 1 for a full list of interactions with methotrexate.
- See the Trust's methotrexate drug interactions of clinical significance guideline for further detailed advice on the management of methotrexate interactions.
- If in doubt, contact the hospital specialist.

Contact hospital specialist for advice on any vaccinations if required.

- **Note**: yearly influenza vaccine is recommended in patients on methotrexate therapy.

Further information can be found in the Summary of Product Characteristics:
http://www.medicines.org.uk/emc/

10. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

Record all blood results in the methotrexate patient held record book.
FBC, LFT's, U+E's, ESR and CRP should be monitored weekly for the first two months of treatment. If the results remain stable the frequency of monitoring can then reduce to monthly.

The following tables include advice on what action to take if blood test results fall below certain limits or if the patient reports one of the adverse events below:

Blood Test Results	Action
White cell count (WCC)< 3.5 $x10^9$ /L	Contact hospital specialist
Neutrophils <2.0 $x10^9$ /L	Contact hospital specialist

Neutrophils < 1.5 x10^9/L	**Stop treatment** and contact hospital specialist
Lymphocytes < 0.5 x10^9/L	Contact hospital specialist
Platelets <150 x10^9/L	**Stop treatment** and contact hospital specialist
>2-fold rise in AST,ALT or falling albumin	**Stop treatment** and contact hospital specialist
Renal function- significant deterioration from baseline	**Stop treatment** and contact hospital specialist

Symptoms	**Action**
Oral ulceration/stomatitis (severe mouth ulcers)	**Stop treatment** and contact hospital specialist
New or increasing dyspnoea or persistent dry cough or fever (with no other obvious cause- suspected pneumonitis)	**Stop treatment** and contact hospital specialist
Abnormal/unexplained bruising or bleeding	Take FBC and **stop methotrexate** if abnormal; contact hospital specialist immediately
Persistent or severe sore throat	Take FBC and **stop methotrexate** if abnormal; contact hospital specialist immediately
Severe or persistent infection	**Stop methotrexate** and take FBC; contact hospital specialist immediately
Nausea, abdominal discomfort, diarrhoea, anorexia	Increase folic acid dose (max 5mg daily not on methotrexate days). If not effective or if severe symptoms stop treatment and contact hospital specialist immediately.
Whites of the eyes become yellow or patient develops severe skin itching	**Stop treatment** and contact hospital specialist
Varicella Shingles	If the patient does not have immunity, check VZV IgM – ASAP and administer IVIG with 72 hours of exposure Contact the paediatric gastroenterology team with ANY concerns Oral acyclovir and supportive treatment

11. Shared Care Responsibilities

a. Hospital specialist:

- Send a letter to the GP requesting shared care for the patient. Agreement to shared care will be assumed unless GP advises otherwise.
- Initiate treatment and prescribe the first month of treatment.
- When serology shows non-immunity to chicken pox this should be reported to the GP with a request to provide varicella-zoster vaccination for the patient (if clinical urgency allows)
- Routine clinic follow-up on a regular basis.
- Send a letter to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments
- Evaluation of any reported adverse effects by GP/general paediatrician/ community nursing team or patient
- Update patient held record book after clinic appointment with blood test results and current dose

- To provide any advice to the patient/carer when requested.
- Ensure that backup advice is available at all times.

b. General Practitioner:

- Agreement to shared care guideline by the GP.
- Monitor patient's overall health and well being
- If the hospital is supplying methotrexate via Homecare (see section 12 below), the GP does not need to prescribe the drug or any other ancillaries.
- If the hospital is **not** supplying methotrexate via Homecare, the GP should prescribe the drug treatment and any ancillaries on FP10, e.g. purple cytotoxic bin.
- Monitor blood results (FBC, creatinine and electrolytes and LFTs) in line with recommendations from paediatric gastroenterology team
- Communicate blood results to the gastroenterology team
- Report any adverse events to the paediatric gastroenterology team, where appropriate.
- Help in monitoring the progression of disease
- Request advice from the hospital specialist when necessary.
- Provision of pneumococcal type and annual influenza vaccination (not live version). Prevenar is given for patients < 2 years of age, Pneumovax for patients > 2 years of age.
- Where a patient has not been vaccinated against or remains non-immune to chicken pox or shingles, consult the local virologist (or microbiologist) who will advise on the need for varicella zoster immunoglobulin (VZIG) or acyclovir.
- Complete blood monitoring details in the methotrexate book or provide information to be included within it and ensure that patient understands they should carry the book at all times.

c. Patient or parent/carer:

- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
- Patients must not exceed the recommended dose.
- Patients must attend their scheduled clinic and blood test appointments (where relevant) and bring hand-held record book to all appointments.
- Must inform other clinical staff that they are receiving treatment.
- Report any adverse effects to the hospital specialist or GP.
- Discuss potential benefits and side effects of treatment with the specialist and GP, to identify whether they have a clear picture of these from the specialist and to raise any outstanding queries.
- Check that where possible the specialists have provided a patient-held record or information sheet for monitoring and/ or to alert other clinical staff to the treatment they are receiving.
- Share any concerns they have in relation to treatment with methotrexate.

1. Subcutaneous Methotrexate

Patients are assessed by the hospital team for suitability and the specialist team may decide to set up the Homecare service or request prescriptions to be continued by the GP. If through homecare, Medication is delivered directly to the patient's home address at a pre-arranged time and also included are all the disposables, sharps bins, spill kits and training. Cytotoxic waste is also removed.

Prescribing and monitoring of subcutaneous methotrexate is the same as oral, however the drug must be prescribed by brand (e.g. Metoject, Zlatal or Nordimet).

2. Contact numbers for advice and support

Specialist	Post	Telephone
Mary Brennan	Paediatric Gastroenterology Clinical Nurse Specialist	01223 274757
Kate Wakefield	Paediatric Gastroenterology pharmacist	01223 254417
Dr Robert Heuschkel	Consultant Paediatric Gastroenterologist	Secretary - 01223 274827
Dr Franco Torrente	Consultant Paediatric Gastroenterologist	Secretary - 01223 349483
Paediatric IBD helpline/email		01223 274757 paediatricibd@addenbrookes.nhs.uk
Out of Hours	Paediatric registrar on call via switchboard	01223 245151 – request paediatric on call registrar is bleeped
Fax number		01223 596367

3. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service service Equality and Diversity statement.

4. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

5. Document Management

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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics http://www.medicines.org.uk/emc/