LRI Children's Hospital

Paediatric Rheumatology Methotrexate therapy

Staff relevant to:	Medical and nursing staff providing methotrexate therapy within UHL Children's Hospital
Team approval date:	March 2022
Version:	1
Revision due:	March 2024
Written by:	Elizabeth Hall
Trust Ref:	C16/2022

Contents

1. Introduction and Who Guideline applies to 2
2. Methotrexate use in paediatric rheumatology 2
   2.1 Methotrexate- overview of Mechanism 2
   2.2 Indications for Methotrexate 2
   2.3 Dosage and route/methods of administration: 3
   2.4 Prescribing Information 3
   2.5 Folic Acid 4
   2.6 Methotrexate drug Interactions 4
   2.7 Contraindications 4
   2.8 Screening and recommendations before starting: 5
   2.9 Side Effects 6
   2.10 Cancer risk 6
   2.11 Blood monitoring 6
   2.12 Planned Surgery 7
   2.13 Chicken Pox contact 7
   2.14 Vaccinations 7
3. Education and Training 8
4. Monitoring Compliance 8
6. Key Words 8

1. Introduction and Who Guideline applies to

These guidelines provide prescribing and monitoring guidance for medical and nursing staff providing methotrexate therapy within UHL Children's Hospital. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on https://www.medicines.org.uk/emc/ and the BNFC

Methotrexate should only be initiated by and under the direction of a consultant paediatric rheumatologist, or a rheumatologist with an interest in paediatric rheumatology. This guideline is to be used by clinical staff involved in the care of children/ young people receiving Methotrexate treatment under the care of Paediatric Rheumatology.

2. Methotrexate use in paediatric rheumatology

Methotrexate has been clinically used for nearly 3 decades in Paediatric Rheumatology and is a useful DMARD for many paediatric and adolescent patients with Rheumatology conditions. It has transformed the outlook for children with Juvenile Idiopathic Arthritis (JIA). It is considered as the gold standard for patients that require a second line therapy (NICE, 2002; Ramanan et al., 2003; Foster and Brogan, 2012).

Methotrexate use is not isolated to JIA, it is also frequently used in other paediatric rheumatologically conditions such as juvenile dermatomyositis (JDM), scleroderma (particularly localised), juvenile systemic lupus erythematous (JSLE), localised scleroderma and vasculitis.

Methotrexate is also an effective and safe treatment used in children with chronic anterior and intermediate uveitis. These patients are jointly managed by paediatric Ophthalmology and Rheumatology where Rheumatology monitors and prescribes the Methotrexate treatment.

2.1 Methotrexate- overview of Mechanism (British Society of Rheumatology)

Methotrexate is a folic acid antagonist and is classified as an antimetabolite cytotoxic agent.

Cytotoxic Handling guidance must be followed. When handling Methotrexate, both oral tablets, liquid and subcutaneous injection devices, gloves must be worn, and Cytotoxic Sharps Bins (Purple Lidded) are essential for disposal of syringes, and injection PENS.

2.2 Indications for Methotrexate

Licensed use:

Methotrexate is available in a variety of forms (tablets, oral liquid, subcutaneous injection, and intravenous injection). Within UHL, only the oral and subcutaneous route is used. Although all forms are used to treat

rheumatology conditions in children of all ages, only the oral 2mg/ml methotrexate liquid (e.g. JylamvoTM or Rosemont brand) and the subcutaneous prefilled pens or syringes have a licence for use in children and only for children with polyarticular JIA aged three years and older.

Not licensed but widely used:

Methotrexate is not licensed but commonly used successfully in the treatment of conditions including juvenile idiopathic arthritis; juvenile dermatomyositis; vasculitis; uveitis; systemic lupus erythematosus; localised scleroderma; sarcoidosis as well as having a variety of non-rheumatology indications.

2.3 Dosage and route/methods of administration:

- Dose initially 10-15mg/m^2 once weekly oral or subcutaneous injection – there is no evidence of clinical benefit in higher doses, however the BNFC does give a maximum dose of 25mg/m^2 once weekly. Doses should be rounded to the nearest 2.5mg increment.

- Intramuscular administration should not be used as it is more painful than the subcutaneous route.

-Subcutaneous administration achieves a higher bioavailability than the oral route.

- Gastrointestinal upset is not necessarily reduced by the subcutaneous route.

2.4 Prescribing Information

The National Patient Safety Association (NPSA) highlighted errors with incorrect methotrexate dosing for patients and overdose of methotrexate for non-cancer indications is still on the NHS Improvements Never Events List.

Prescriptions must state the form, strength, dose and directions in full, including the day of the week the dose must be taken. “Take as directed” is not acceptable.
If methotrexate injection is prescribed, the brand name must be stated, to maintain a consistent device.

When Methotrexate tablets are required, prescribe oral methotrexate dose in multiples of 2.5mg tablets and the frequency as “ONCE a week on the same day each week”. The total dose in quantity of tablets and milligrams must be included. 10mg tablets MUST NOT be prescribed or dispensed.

Methotrexate is only given as a ONCE WEEKLY dose, whether oral, subcutaneous or in rare instances; intravenously. It is good practice to administer the same day each week for safety purposes and to promote concordance.

If it is being used in an unlicensed indication this must be explained to patient.

Oral Methotrexate should not be dispersed in water

All patients must receive a Childrens Rheumatology Methotrexate Monitoring book at treatment initiation and this must be updated each time a new script is issued as it

must be presented by the patient to the pharmacy with the prescription. The pharmacy will not issue the new medication until the updated booklet is received. This can be found on UHL- Your health pdf 'Use of Methotrexate to help your child's joint, skin or eye condition'.

2.5 Folic Acid

Folic acid should be prescribed when weekly Methotrexate treatment is initiated

- Folic acid should not be taken on the same day as methotrexate.

Folic acid supplementation during methotrexate therapy can reduce the risks of adverse effects including nausea, vomiting, abdominal pain, mouth ulcers, raised liver enzymes and bone marrow toxicity.

-By reducing the risk of adverse effects, folic acid supplementation helps to reduce the number of patients who discontinue methotrexate treatment.

-Folic acid should be taken for as long as the methotrexate therapy is continued.

-There is no standard dose- see side effects section for suggested doses.

2.6 Methotrexate drug Interactions

Prescribing of methotrexate with co-trimoxazole or trimethoprim is an ABSOLUTE CONTRAINDICATION in rheumatology practice and MUST NOT occur under any circumstances as methotrexate and trimethoprim have the same mode of action. Taking both together will affect blood cell reproduction. This contraindication applies to people that have taken methotrexate in the past 3 months

Reference should be made to the Children's British National Formulary and medicines.org to check the full list of drug interactions before prescribing Methotrexate.

Nonsteroidal anti-inflammatory and Methotrexate-

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to relieve pain and decrease inflammation. Because NSAIDS can affect kidney function and methotrexate is metabolized by the kidney, monitoring of the creatinine is recommended. As regular blood monitoring is carried out on children receiving Methotrexate, this is not considered a contraindication. This risk is increased with kidney disease or those receiving doses of methotrexate above 20mg/m^2.

2.7 Contraindications

- Active infection for example TB
- Ascites;
- Immunodeficiency syndromes for example SCID or HIV
- Significant pleural effusion
- Pregnancy and breast feeding.

2.8 Screening and recommendations before starting:

Action	**✓ or add comment when complete**
Clearly documented decision to start methotrexate with the dose, route, indication and consent.	
Paediatric rheumatology nurse specialist has delivered appropriate education regarding the medication with documentation of appropriate discussions and date of patient information sheets given.	
Ensure gloves and appropriate disposal bins are supplied if required. Cytotoxic Sharps bins are required for disposal of Methotrexate injection devices.	
Core data set should be recorded in clinical notes (active/restricted joint counts, physician and parent global, patient pain, CHAQ). If Uveitis patient, Name of Ophthalmology Consultant requesting the initiation of Methotrexate should be recorded.	
Baseline bloods including FBC, CRP and CRP, liver transaminase levels, serum creatinine/calculated GFR.	
Check Varicella immunity.	
Measles vaccination status.	
Ensure family know attending for regular blood tests is a requirement to receiving methotrexate.	
Confirm who will be prescribing the methotrexate	
Confirm who will be administering the methotrexate. If appropriate, members of the family may be trained to administer subcutaneous methotrexate.	
Females planning to get or who are pregnant should not handle Methotrexate.	
Consider pregnancy testing in Females of childbearing age.	
Consideration of lifestyle issues such as alcohol consumption and the importance of contraception for both males and females whilst taking methotrexate and for three months after methotrexate cessation.	

2.9 Side Effects

- Nausea and vomiting, including anticipatory nausea.

Strategies to help with this side effect include:

- Ondansetron orally for the day before and day after the dose
- Folic acid 5mg/dose given weekly. This can be split across the week especially in cases of resistant stomatitis, sore throat or ulcers (Refer to BNFC for all dosing regimens)
- Folic acid is not given on the day that methotrexate is given to prevent a theoretical reduction in methotrexate activity.

Symptoms may improve with subcutaneous rather than oral medication.

- Withholding NSAID on day of methotrexate.
- Eating a soft sweet during injection can help.
- Giving on Friday or Saturday night may reduce school absence.
- Psychological support may be beneficial.

Injection site erythema/pruritus is usually mild and transient.

2.10 Cancer risk

Cancer risk – in patients with autoimmune rheumatic disease, the incidence of malignancy is increased although the absolute risk remains low. There is considerable evidence that this risk may relate to the underlying disease although any additional role of immunosuppression and treatment remains unclear.

2.11 Blood monitoring

Bloods tests required -

- Full blood count
- Urea and electrolytes,
- Liver function tests (ALT/AST)
- Bone Profile.
- CRP and PV (to check response and disease activity).

Monitoring Regime:

- Check every four weeks for the first 2 months after starting methotrexate treatment or after changing the dose of methotrexate.
- If stable at 2 months check, check 6 weekly for three months.
- Thereafter check every two months, 3 monthly maximum for long term clinically stable children, but document in medical notes.

Abnormal Results:

When to consider suspending methotrexate:

• Platelet count less than 150x109/L.
• White cell count less than 3x109/L.
• Neutrophils less than 1.5x109/L.
• Lymphocytes less than 0.5x109/L
• Haemoglobin less than 90mg/dL (without another identifiable cause).
• AST or ALT three times the upper limit of the normal range.

Interpreting blood-monitoring results is challenging and evidence guiding intervention is limited.

Raised liver transaminases encountered during monitoring may be the result of factors other than methotrexate, often being caused by intercurrent infection.

Out of Hours

1. In the case of abnormal results the On Call Paediatric Team should contact the family and inform them to stop the Methotrexate. The Rheumatology team should then be contacted via email for further management.

2. Patients attending ED: Paediatric Rheumatology patients on MTX and/ or on Biological therapy with inter-current infections: Need to be reviewed by the Paediatric team and consider low threshold for antibiotics.

To ensure that blood monitoring intervals are complied with, Methotrexate prescriptions are issued at 8 or 12 weekly intervals.

2.12 Planned Surgery

Methotrexate treatment doses are not required to be withheld for planned surgery

2.13Chicken Pox contact

Children and young people on low dose methotrexate treatment are at greater risk of severe chicken pox.

Please refer to UHL Children's Hospital Guidelines **Chicken Pox Exposure UHL Childrens Hospital Guideline** for guidance, and consider IV or oral Aciclovir depending on clinical status.

2.14 Vaccinations

Children on low dose Methotrexate treatment are safe to receive all inactivated vaccinations.

Live vaccinations should not be given apart from the nasal influenza vaccine- this applies to children on Methotrexate alone and not those on biologics.

Please refer to the Immunisation against infectious disease: Green Book for a list of all live vaccinations available online.

3. Education and Training

Clinical staff should receive training in safe handling of cytotoxic drugs and also be trained how to use injection devices before administrating Methotrexate

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Monitoring of blood results are performed at the recommended intervals	Audit of ICE records	Cons/Specialist Nurse	Annually	Local audit group panel
Blood results are acted on appropriately	Audit of clinical records	Cons/Specialist Nurse	Annually	Local audit group panel

5. Supporting References

British Society for Rheumatology (2020). Methotrexate use in paediatric and adolescent rheumatology Information for health professionals. Available from: https://www.rheumatology.org.uk/Portals/0/Documents/Guidelines/Paediatric%20guidelines/Mexthotrexate_Paediatric_Adolescent_Rheumatology.pdf?ver=2020-03-19-150320-243 {Accessed 11/03/2022}

Foster, H. and Brogan, P. (editors) (2012) Paediatric 2012) Paediatric 2012) Paediatric rheumatology, Oxford: Oxford University Press.

Lucas, G..N..C, Leitão, A...C, Alencar, R..L, Xavier R.M.F, Daher E.F, Silva Junior G.B.D. Pathophysiological aspects of nephropathy caused by non-steroidal anti-inflammatory drugs. J Bras Nefrol. 2019 Jan-Mar;41(1):124-130. doi:10.1590/2175-8239-JBN-2018-0107

Ramanan, A, Whitworth, P & Baildam, E. (2003) Use of methotrexate in juvenile idiopathic arthritis, Archives of Disease in Childhood, 88 (3), pp197-200

6. Key Words

Cytotoxic, Folic acid, Juvenile Idiopathic Arthritis, Methotrexate, Vaccine

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Elizabeth Hall – Children's Specialist Nurse Sridhar Arani – Consultant Paediatrician Dave Harris – Principle Pharmacist	**Executive Lead** Chief Nurse
Details of Changes made during review: New guideline	