LRI Children's Hospital

Paediatric Rheumatology Methotrexate therapy

Staff relevant to:	Medical and nursing staff providing methotrexate therapy within children's rheumatology within UHL Children's Hospital
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1. Introduction and Who Guideline applies to

These guidelines provide prescribing and monitoring guidance for all staff providing Childrens Rheumatology methotrexate therapy within UHL Children's Hospital. It should be read in conjunction with the relevant 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 paediatrician with an interest in paediatric rheumatology. G.P's do not generally prescribe Methotrexate for children so supplies are provided by the hospital.

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 numerous rheumatological conditions, most commonly Juvenile Idiopathic Arthritis (JIA). It is considered as the gold standard for patients that require a second line therapy to intra-articular steroids (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 the Ophthalmology team assess the eyes and rheumatology team monitors and prescribes the Methotrexate treatment

Patient information - Methotrexate | Side-effects, uses, time to work (versusarthritis.org)

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 Childrens Rheumatology, only the oral and subcutaneous routes are used. Although all forms are used to treat rheumatology conditions in children of all ages, only the oral 2mg/ml methotrexate liquid (e.g. Jylamvo™ 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, uveitis as well as having a variety of non-rheumatology indications.

2.3 Pre treatment Screening and Information

All patients must be assessed for suitability and give informed verbal consent (which must be documented in a clinic letter when the nursing team conduct their medical education/training) before the first dose of methotrexate treatment is given. Prior to commencing methotrexate therapy, all patients should receive patient education from rheumatology CNS. Families must be made aware that attending regular blood test is a requirement to receiving methotrexate.

Pre Treatment

Vaccination – Varicella and Measles – If negative or inadequate antibodies then vaccinate prior to starting methotrexate if possible. Both VZV and MMR are live vaccines and there should be a two to four week gap before starting Methotrexate therapy. If the patient requires both VZV and MMR vaccine, they can be given on the same day. If they are not given on the same day, there must be a 4 week gap between both vaccines. Vaccines can be given by either the patients GP or they may be prescribed on the children's drug chart and processed by the children's satellite pharmacy.

Pregnancy test – Children of post-menarchal age, exclude pregnancy prior to commencing treatment through a urine-pregnancy test during their medical education session.

Administration training assessment (subcutaneous only) - Appendix 1

2.4 Dosage and route/methods of administration:

- Dose initially 15-20mg/m^2 once weekly oral or subcutaneous injection – there is no evidence of clinical benefit in higher than 20mg/ m^2 doses, however the BNFC does give a maximum dose of 25mg/m^2 once weekly. Doses must be rounded to the nearest 2.5mg increments usually to a maximum of 25mg.

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

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

- Intramuscular administration should not be used as it is more painful than the subcutaneous route, less effective for treatment and causes increased side effects.

2.5 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 formulation, strength, dose and directions in full, ONCE a week on the same day each week". "Take as directed" is not acceptable. Methotrexate is only given as a ONCE WEEKLY dose, whether oral or subcutaneous. It is good practice to administer the same day each week for safety purposes and to promote concordance. If being used in an unlicensed indication this must be explained to patient.

- If methotrexate injection is prescribed, the brand name must be stated, to maintain a consistent device on which the child/carer will have been trained.

If Methotrexate tablets are required, prescribe dose in multiples of 2.5mg tablets. 10mg tablets MUST NOT be prescribed or dispensed.

Oral Methotrexate must not be dispersed in water, instead the patient must be prescribed the liquid formulation. The family must inform the team if their child vomits, or spits it out - the dose should never be repeated.

All patients must receive a children's methotrexate information card summarising their dosing and administration schedule.

2.6 Contraindications to Methotrexate

• Active infection for example TB including active TB.

• Ascites

Severe liver or renal impairment

• Immunodeficiency syndromes for example SCID or HIV

• Significant pleural effusion

Pre existent blood dyscrasia

• Pregnancy and breast feeding.

2.7 Side Effects

- Nausea and vomiting, including anticipatory nausea
    - Risk factors for symptoms include – adolescence, treatment for longer than 1 year
    - No link between nausea and size of dose
    - The effect of gender is not known
    - The effect of route of administration is unclear – both routes are reported as both better and worse for causing symptoms of nausea and vomiting

Proactive strategies to help with this side effect include:

- Folic acid 5mg/dose (tablet or liquid) initially given weekly as per BNFC on a different day to the methotrexate from initiation until it is stopped.
    - 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.
    - The frequency of the dose can be increased especially in cases of resistant stomatitis, sore throat or ulcers e.g. twice and three times a week except on the day of methotrexate doses
- Ondansetron orally for the day of (1 hour before the dose) and thereafter 12 hourly following the dose. (not in BNFC)
    - Age 4-11 years 150micrograms/kg (Max 4mg) - 12 hourly as required
        - 12 years and older 150 micrograms/kg (Max 8mg) - 12 hourly as required
- Referral to children's rheumatology psychology methotrexate workshop especially for anticipatory symptoms

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.

Injection site erythema/pruritus is usually mild and transient.

Other side effects include: mouth ulcers, hair loss, skin rash, anaemia (can be treated with iron supplements) neutropenia, leucopoenia, thrombocytopenia, interstitial pneumonitis and fibrosis, liver impairment, skin reactions

2.8 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.

2.9 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. Parents/carers should be reminded to inform the Childrens Rheumatology team if the child has an active infection/rash/unexplained bruising. Parents should also be reminded to inform the rheumatology team following any infective episodes diagnosed by the GP.

Nonsteroidal anti-inflammatory and Methotrexate-

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

2.10 Blood monitoring

The following bloods tests are required for all patients on Methotrexate therapy to assess for any developing adverse effects that may require treatment changes.-

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

2.10.1 Blood Monitoring Regime:

- Initiation and dose increase:
    - Week 0 (baseline), Week 2, Week 6, Week 10, Week 14. From week 14 consider testing every 3 months if appropriate.

Restarting after break for an abnormal result/infection

- Retest a few days prior to restarting treatment and only restart methotrexate if results are satisfactory
- If results satisfactory retest after dose 2 to decide if to proceed further. Review again after dose 6 and then return to previous regime (monthly or 3 monthly as above)

The responsibility of monitoring the bloods would fall under the prescriber.

2.10.2 Abnormal Results:

Interpreting blood-monitoring results is challenging and evidence guiding intervention is limited. Discuss any queries with the children rheumatology team. The following information is based on BSPAR recommendations.

Consider suspending methotrexate if:

Liver Function Tests

ALT - Over 100 (three times the upper limit of the normal range) pause the dose for two weeks and discuss with consultant to consider dose reduction (or consider discontinuation if persistent/recurrent rise in ALT)

Recheck LFT in 2 weeks time, if below ALT below 100, can restart methotrexate.

Full Blood Count

- White cell count less than 3.5 $x10^9$/L.
- Haemoglobin less than 80mg/dL (without another identifiable cause – note mild anaemia is part of many rheumatological conditions and patients can have concurrent iron deficiency).
- Platelet count less than $150x10^9$/L.
- Neutrophils less than $1.5x10^9$/L.
- Lymphocytes less than $0.5x10^9$/L

Please note raised liver transaminases and deranged blood counts encountered during monitoring may be the result of factors other than methotrexate, often being caused by intercurrent infection and occasionally due to active disease such as JDM, JSLE. Please discuss these cases with paediatric rheumatology consultant.

2.10.3 Out of Hours

1. In the case of abnormal results the On Call Paediatric Medical Team should contact the family and inform them to stop the Methotrexate. The Paediatric Rheumatology team should then be informed via email on paedrheumadvice@uhl-tr.nhs.uk to provide further management.

2. Patients attending CED: Paediatric Rheumatology patients on MTX and/or on Biological therapy with inter-current infections need to be reviewed by the Paediatric Medical team and have a low threshold for starting antibiotics. Methotrexate should be stopped during active infection and paediatric rheumatology team informed as stated previously.

To ensure that blood monitoring intervals are complied with, Methotrexate prescriptions are issued at 12 weekly intervals according to their testing regimen.

2.11 Planned Surgery

Methotrexate treatment does not need to be withheld for planned elective surgery however individualised decisions should be made for procedures considered to have a high risk of infection and should be balanced against the risk of disease flare. (Handbook of pre-operative medicine)

2.12 Chicken Pox contact

Children and young people on low dose methotrexate treatment are at greater risk of developing 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. Methotrexate doses should be withheld until recovery as advised by the Paediatric Rheumatology team.

2.13 Vaccinations

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

Live vaccinations should not be given except for the nasal influenza vaccine- that can be given to children on Methotrexate alone or on doses lower than 20mg a week. Please refer to the "Immunisation against infectious diseases" Chapter 19 for the most up-to-date guidance on the annual influenza vaccine.

2.14 Pregnancy/Contraception

It is important for children of post-menarchal age to be on contraception if they are sexually active as methotrexate is teratogenic. Methotrexate does not affect any type of contraception however, if Methotrexate can lead to diarrhoea and vomiting and if this is the case the contraceptive pill may not be effective. If this occurs, patients should be advised to refer to the product information leaflet or seek further advice from the paediatric rheumatology team.

Methotrexate used in early pregnancy can cause miscarriage and birth defects. Once methotrexate therapy has stopped, it can remain in the body for some time and therefore is recommended that women avoid getting pregnancy for six months after finishing treatment.

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. Staff should also receive a yearly update on this training.

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}

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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	
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Details of Changes made during review: V2 – detail on screening, side effect management, testing regimes, actions on abnormal results, added all appendices V3 – change to blood monitoring, vaccination, appendix's 2 and 3 removed as no longer being used, added information on pregnancy and breastfeeding, ondansertron dosing changed as per BNFc	

NAME S

METHOTREXATE ADMINISTRATION ASSESSMENT TOOL

Parent's assessment for the safe administration of sub cut Methotrexate at home.

Leaflet provided- Using your child's Metoject® Date Given_____

Procedure	Y/N Comments	Y/N Comments
	DATE	DATE
Before opening the box Check the drug is Metoject® PEN. Check expiry date, the dosage and that the box has the correct name on it.		
Collect tray, gauze, gloves, cytotoxic sharps bin and plaster (Gloves are not required for self-administration).		
Wash or gel hands and put on non-sterile gloves.		
Remove the PEN from packaging.		
Do not remove the protective cap until you are ready to administer the injection		
Check the name, dose and expiry		

Check PEN for damage. Check the medicine through the inspection window, it should be clear and yellow		
Ensure child is sitting in a comfortable position.		
Select appropriate site to administer injection (usually alternate thighs).		
Gently grip the skin at the injection site using thumb and index finger and maintain throughout the injection process.		
Remove protective cap -Only remove the protective cap when you are ready to administer the injection -Do not bend or twist the cap while pulling off -Do not try to put the cap back on once it's removed		
Immediately place cap in Purple topped Sharps Bin		
Hold the pen firmly and position the blue needle cover at a 90-degree angle against the skin, with the inspection window facing towards you so you can see it		
Start the injection To start the injection, push the pen down all the way This will slide the blue needle		

cover up into the pen and the injection will start automatically		
Hold PEN in place for 5 seconds until the medicine is injected A first acoustic signal, or click, indicates the start of the injection The blue plunger will move down in the inspection window Keep holding the pen until all the medicine is injected **DO NOT REMOVE THE PEN DURING INJECTION**		
The injection is complete when either: – you hear a 2nd acoustic signal, or click shortly after the first, – OR the blue plunger has stopped moving and fills the inspection window – OR five seconds have passed		
Remove the pen by pulling it straight up from the injection site		
Place used PEN in Sharps Bin immediately		
Dab the injection site with gauge/cotton wool if any droplets of drug visible Apply Plaster.		
Safely dispose of PEN in special sharps bin.		

Wash and Dry Hands		
Ensure the importance of safe storage of Methotrexate and sharps bins is understood. **METHOTREXATE IS NOT TO BE STORED IN A FRIDGE**		
Able to discuss when not to administer Methotrexate.		
Awareness of how to access help during normal and out of hours.		
Awareness of what to do if the medication is spilt		
Date and signature		

Declaration

I, _____ feel that I have the necessary knowledge, and feel confident and willing to undertake home administration of METHOTREXATE to my son/daughter (delete as necessary).

Signature _____ Name _____ Date _____

I have assessed that _____ has the necessary knowledge and that they are competent in the safe administration of Methotrexate using the Metoject® PEN.

Signature _____ Name _____ Date_____

Designation_____

Appointment Dates for teaching-
Home visit Require Y/N If Yes Date-
Equipment (Tick Box)

Sharps Bin		**MTX PENs**		**Gloves**		**Gauze**		**Plasters**	