

# Therapeutics Bulletin

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## Low-dose Methotrexate Toxicity and Monitoring

Methotrexate (MTX), a dihydrofolate reductase inhibitor, is associated with a variety of adverse effects over a wide range of severity. These adverse effects are dose and treatment regimen related.

MTX is used in high dose regimens ( $\geq 1\text{g}$  given in cyclic fashion) for its cytotoxic effects on malignant cells. MTX is also widely used for its immunosuppressant effect on systemic inflammatory diseases. It is licenced for use in rheumatoid arthritis and psoriasis at low doses (5 to 25 mg weekly). Off-label MTX uses include Crohn's disease, SLE, myositis, and vasculitis treatment.

Common low-dose MTX adverse effects are rarely life-threatening, but often result in premature discontinuation of the best therapeutic alternative for a given individual.

This bulletin provides guidance to routine safety monitoring of patients on low-dose MTX.

## Methotrexate Toxicity

### Bone marrow failure

Although rare, low-dose MTX toxicity may be life threatening, mainly due to myelosuppression. A significant fall in blood cell count should actuate withdrawal of MTX therapy and specialist consultation.

Factors associated with MTX related pancytopenia are patient age  $> 75$ , renal failure, MTX-drug interactions (particularly co-administration of other anti-folate drugs), dose errors, hypoalbuminaemia and pre-existing folate deficiency.

### Immune suppression

In contrast to many immunosuppressant therapies, methotrexate is relatively safe and has a low risk of infection with its use. If infections do occur MTX should be stopped immediately to prevent systemic dissemination.

A randomised controlled trial showed that perioperative continuation of MTX treatment does not increase the risk of infection or surgical complications in patients with rheumatoid arthritis.

### Hepatotoxicity

Clinically serious liver disease is rarely seen in patients receiving low-dose MTX. High cumulative dose, heavy alcohol intake and pre-existing liver disease, increases the risk of hepatotoxicity. Routine liver function tests are not a reliable indicator of early MTX-induced liver fibrosis. Therefore, patients with a cumulative dose  $> 5\text{g}$  MTX should be referred to liver clinic to consider liver biopsy and / or fibroscan.

### Pulmonary toxicity

Methotrexate pneumonitis is a rare potentially fatal hypersensitivity reaction. It is most frequently observed within the first year of treatment and the incidence is higher in patients with pre-existing interstitial lung disease.

Folic acid reduces MTX haematological toxic effects and improves continuation of therapy and compliance. Folinic acid rescue therapy following high or toxic doses of MTX helps prevent myelosuppression, renal failure, pneumonitis and mucositis.

## Routine Safety Monitoring

Table 1 summarizes the safe use of MTX. It is a guide only, which may be overridden at the discretion of the consultant dermatologist, gastroenterologist or rheumatologist.

**Table 1: Methotrexate (MTX) dosing and monitoring**

### Section A: Dosing and treatment instructions

MTX treatment:	<b>Standard dose:</b>	5mg - 25mg once a week
	<b>Starting dose:</b>	10-15mg per week
	<b>Dose increase:</b>	2.5mg per week (to a maximum of 25 mg/week) or as determined by the consultant
	<b>Patient information:</b>	Explain <b>once weekly</b> administration on a <b>fixed day</b> Alcohol consumption should be avoided or minimised Consult clinician before taking other medications
	<b>Elderly patients:</b>	Consider dose reduction (↓ hepatic/renal function and folate reserves)
	<b>Renal impairment:</b>	Withhold MTX and consider rescue therapy in acute renal failure. Adjust dose to renal function in worsening chronic renal failure.

eGFR (ml/min)	MTX dose adjustment
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> 50	None
20 – 50	50% of standard dose
<20	Stop and use alternative drug

Adjunctive therapy:	<b>Folic acid:</b>	Consider adding, 5mg oral once a week at least 24 hours after MTX. Increase frequency if patients have gastrointestinal side effects.
	<b>Contraception:</b>	Male and female child bearing age patients and their partners must use effective contraception during MTX treatment and for at least 3 months thereafter.
	<b>Concomitant medications:</b>	Avoid drugs with nephrotoxic or hepatotoxic potential and refer to the drug interactions table below.
	<b>Folinic acid:</b>	In case of overdose and/or toxicity, folinic acid should be administered within the 1 <sup>st</sup> hour, as treatment is less effective if > 4 hours has elapsed. Folinic acid 10mg/m <sup>2</sup> IV/IM/orally every 6 hours should be administered until serum MTX is <10 <sup>-8</sup> M. If 24 hour serum creatinine is 50% above baseline, or 24 hour MTX level > 5x10 <sup>-6</sup> M , or 48 hour MTX level >9x10 <sup>-7</sup> M , increase dose to 100 mg/m <sup>2</sup> IV every 3 hours until serum MTX is <10 <sup>-8</sup> M.  Patients should be well hydrated with normal saline.

### Section B: Clinical and laboratory monitoring

#### Clinical Monitoring

1. **Rule out contra-indications to MTX prior to initiation (via history, examination and baseline special investigations outlined below)**

- Pregnancy and lactation
- Severe renal impairment
- Severe liver insufficiency
- Pre-existing blood dyscrasias
- Serious local or systemic infections or immunodeficiency
- Interstitial lung disease
- Known MTX hypersensitivity
- Ulcers of the oral cavity and known active gastrointestinal ulcer disease
- Alcohol abuse

Note: All patients should be screened for TB symptoms and investigated for active TB if indicated. Pleural effusions and ascites should be drained prior to initiation of methotrexate therapy since systemic toxicity of MTX may be enhanced due to prolongation of the elimination half-life.

2. **Monitor patient's response to MTX treatment**

<b>Time to clinical response:</b>	3 weeks to 6 months	Lack of MTX efficacy at 25mg per week for three months is considered treatment failure
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<b>Specific adverse effects:</b>	Rash or oral ulceration	Withhold MTX and discuss with consultant
	New or increasing dyspnoea	Withhold MTX and discuss urgently with consultant
	Severe sore throat or abnormal bruising	Immediate FBC and withhold MTX until result available

### 3. Monitor concomitant medication and alcohol use

#### Notable drug interactions:

<b>Probenecid, penicillin, NSAIDs</b>	MTX renal clearance is reduced (clinically significant interaction with NSAIDs and MTX is rare)
<b>Co-trimoxazole</b>	MTX anti-folate effect is increased and greatly increases the risk of marrow aplasia.
<b>Phenytoin</b>	MTX anti-folate effect is increased
<b>Alcohol</b>	MTX hepatotoxicity risk increased

### 4. Monitor cumulative MTX dose

Patients without pre-existing liver disease with a cumulative dose >5g MTX should be referred to liver clinic to consider liver biopsy and / or fibroscan.

#### Laboratory safety monitoring schedule

Special Investigation	Baseline	Continuous*	Withhold MTX and discuss with consultant:
FBC & diff	✓	✓	Total WCC < 3.5 x10 <sup>9</sup> /L, Neutrophils <2 x10 <sup>9</sup> /L, Platelets < 150 x10 <sup>9</sup> /L (consider folinic acid rescue therapy) MCV > 105 fl (check serum B12, folate and TSH)
AST, ALT, ALP, bilirubin and albumin	✓	✓	AST or ALT > 2xULN Unexplained fall in serum albumin (in absence of active disease) Bili > 85.5 μmol/L - MTX contraindicated/stop
Urea, creatinine and eGFR	✓	✓	Acute renal failure – withhold MTX Chronic renal failure – dose adjust (refer to dosing instructions above)
βHCG	✓	Repeat when indicated	If elevated - MTX contraindicated (abortifacient and teratogenic). In case of Inadvertent pregnancies - refer to obstetrician
CXR	✓ (within the last 6 months)	Repeat when indicated	Interstitial lung disease (consider lung function test) Serious active infection
HBV/HCV serology	✓	If clinically indicated	
HIV serology	✓	If clinically indicated	
MTX levels	MTX therapeutic drug monitoring (TDM) is of value in MTX toxicity, renal failure and overdose only. There is no established role for routine TDM in low-dose MTX use.		

Note:

#### \* Recommended continuous monitoring frequency

**Rheumatology:** FBC and ALT after 1 month, then 3-6 monthly.  
**Dermatology:** FBC and diff after one week. Then all tests indicated above once 2 weekly for 2 months. Thereafter, once 2-3 monthly.  
**Gastroenterology:** All tests indicated above within 4 months of starting therapy then monthly.

Notes:

- When a dose increase has occurred close monitoring should be reinstated for at least 6 weeks
- More frequent monitoring should be considered in patients with pre-existing organ dysfunction and those taking concomitant drugs that may lead to increased MTX plasma exposure and toxicity (eg NSAIDs).

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