B-QuiCK: Prescribing methotrexate safely

This summary focuses on prescribing oral low-dose methotrexate in the community for people with autoimmune conditions, e.g. rheumatoid arthritis, psoriasis.

Overview

- Always co-prescribe folic acid (5 mg/once weekly)
- Adverse effects (see NZF for a complete list):
  - Most common: gastrointestinal symptoms, e.g. nausea, vomiting, diarrhoea, mucositis and mucosal ulceration
  - More serious: myelosuppression, hepatotoxicity and pulmonary toxicity
- Single high oral doses rarely cause toxicity (limited absorption), but repeated lower doses increase risk
  - Toxicity usually results from accumulation, e.g. renal impairment, interactions, dosing errors such as daily dosing, tablet strength confusion
- Clinical factors that increase risk of toxicity:
  - CKD ≥ G3
  - Increasing age
  - Significant co-morbidities
  - Pre-existing liver disease
  - Obesity
  - Alcohol consumption
  - Concomitant use of medicines that decrease renal clearance of methotrexate
  - History of toxicity with other conventional synthetic DMARDs (e.g. leflunomide, sulfasalazine)
  - Combination treatment with another DMARD
  - Cytopenia or elevated liver transaminases within preceding six months

Methotrexate is often initiated in a specialist care setting; however, specialist involvement is not a requirement for funded treatment and clinicians who are confident about prescribing methotrexate can initiate it in primary care

Pre-treatment screening

- ☐ Assess for contraindications and cautions: click here for details
- ☐ Request baseline laboratory tests: FBC, LFTs, serum creatinine, pregnancy test (where appropriate)
  Additional tests may be required depending on indication for methotrexate
- ☐ Treat active infections and consider prophylactic treatment if latent tuberculosis or history of hepatitis B
- ☐ Check patient is up to date with National Immunisation Schedule vaccinations, as well as influenza, COVID-19 and pneumococcus
  - Consider varicella zoster (shingles) vaccination (Shingrix) and varicella (chickenpox) vaccination (Varilrix) if no history of varicella infection or immunisation
  - Avoid live vaccines during treatment, unless dose is ≤ 0.4 mg/kg/week
- ☐ Assess respiratory history and conduct a respiratory examination
  - Arrange further investigations, e.g. respiratory function testing, chest X-ray, if: respiratory symptoms, pre-existing respiratory condition or significant risk factors (e.g. smoking and aged ≥ 40 years); seek respiratory advice as needed
- ☐ Assess for other methotrexate toxicity risk factors, e.g. alcohol intake
- ☐ Check for potential medicine interactions, including prescription, OTC and complementary medicines, e.g. trimethoprim +/- sulfamethoxazole, penicillins, tetracyclines, ciprofloxacin, NSAIDs; use the NZF interactions checker

Initiating low-dose oral methotrexate

Avoid ambiguity when prescribing methotrexate and include all relevant information about how to take it correctly. Click here for tips to reduce the risk of dosing errors when prescribing.

- Initiate methotrexate at a low dose and up-titrate according to response and tolerability
- Doses usually range from 7.5 mg to 25 mg, **once weekly**, depending on the indication; see NZF for details
- Once optimal treatment response is achieved, gradually reduce to the lowest effective dose
- Co-prescribe folic acid to reduce risk of adverse effects (unapproved indication): 5 mg, once weekly, to be taken on a different day to methotrexate
  - "*Methotrexate Monday, folic acid Friday*"
- Provide comprehensive patient information about how to take methotrexate, risks associated with treatment and strategies for reducing risk (ideally both verbally and in writing)
  - Educate about symptoms and signs that indicate urgent need for medical attention, e.g. dyspnoea, non-productive dry cough, fever, severe sore throat, unexplained bruising
  - Click here for a patient information sheet

Monitoring for adverse effects and toxicity

- Monitor for adverse effects and toxicity, e.g. mouth ulcers, nausea, vomiting, infection, sore throat, bruising, dyspnoea; evaluate/manage as indicated (see Table 1 for guidance)
- Perform skin examinations periodically, especially if increased risk of skin cancer
- Monitor laboratory parameters regularly (FBC, LFTs, serum creatinine). Initially, every two to four weeks, and then less frequently; see Table 2 for recommendations.
  - Interpret trends alongside absolute values, and consider alternative causes. Investigate further if significant changes compared to previous results, persistent abnormal results or deterioration.
- Assess other risk factors for toxicity at least annually, e.g. alcohol intake; adjust monitoring frequency accordingly

Recognise methotrexate overdose

Symptoms include mucositis, mouth ulcers, fever, diarrhoea, erythema and cutaneous necrolysis (skin necrosis with blistering and peeling; rare). Assess adherence; ask about the number of tablets they take and frequency.

Chronic low-dose oral methotrexate overdose can be fatal. Urgently refer to secondary care if suspected overdose; treatment for methotrexate toxicity may be required.

Table 1. Managing adverse effects associated with methotrexate. N.B. This list is not exhaustive.

Adverse effect	Recommended action
Mouth ulcers	Reduce the dose or withhold methotrexate if ulcers are severe. Request full blood count; seek specialist advice as needed. Folinic acid (calcium folinate) mouth wash may be recommended (formulated from tablets; funded on prescription or recommendation from a Specialist). Depending on the clinical situation, consider increasing the frequency of folic acid supplementation to twice per week or more (can be up to six times per week).
Nausea and vomiting	Advise the patient to take methotrexate with food or before bed. Consider prescribing ondansetron for severe nausea (unapproved indication); prescribe 8 mg, to be taken two hours before methotrexate dose (repeated 12 and 24 hours later, if required). Subcutaneous administration (weekly) of methotrexate may be considered if nausea limits tolerability.
Infection	Manage as indicated; ideally avoid anti-folate antibiotics, e.g. trimethoprim, sulfamethoxazole. If infection is severe (e.g. requiring IV antibiotics), withhold methotrexate and seek advice from a specialist.
Severe sore throat, abnormal bruising	Withold methotrexate and request an urgent full blood count; seek haematology advice regarding any abnormalities
New or increasing dyspnoea or dry, non-productive cough	Withold methotrexate or decrease dose and seek specialist advice; referral for a chest X-ray and/or pulmonary function testing may be indicated

Table 2. Laboratory monitoring recommendations for patients taking methotrexate. N.B. Additional laboratory tests may also be required depending on the condition methotrexate is prescribed for, and management considerations for individual patients may differ; use clinical judgement and seek specialist advice, as required.

Laboratory test	Frequency	Intervention threshold	Recommended action
Full blood count*	▪ At baseline[3, 6] ▪ Every two to four weeks, initially, then monthly for three months.[3, 6] If the dose is stable and laboratory test results are normal, frequency can be reduced to every three to six months.[3, 6] ▪ Two weeks following a dose increase.[6] If laboratory test results are normal, return to usual monitoring schedule. N.B. More frequent monitoring is recommended for patients with risk factors for toxicity[6]. Click here for details.	Platelets < 150 × 10^9/L[6,18] Neutrophils < 1.6 × 10^9/L[6] Lymphocytes < 1.0 × 10^9/L[6,18] Eosinophils > 0.5 × 10^9/L[6, 18]	May indicate toxicity; seek specialist advice and consider withholding methotrexate.[3, 6]
Liver function tests		ALT/AST over twice the upper limit of normal[6] Progressive reduction in serum albumin or a result below the lower limit of normal in the absence of an alternative cause, e.g. active inflammation[6]	
Serum creatinine		Significant deterioration in renal function or renal impairment[3, 6]	Investigate the cause of renal function decline and reduce methotrexate dose or consider withholding treatment until renal function improves.[3, 6] Methotrexate is contraindicated in patients with severe renal impairment.[3]

* Elevated mean corpuscular volume (MCV) is no longer considered a reliable predictor of methotrexate toxicity or an indication to discontinue treatment[6]