Diagnosis and Treatment of Methotrexate (MTX) Neurotoxicity in Oncology Patients

Inclusion Criteria: Oncology patients receiving methotrexate (intrathecal or intravenous) who present with new neurologic symptoms concerning for methotrexate neurotoxicity.
Exclusion Criteria: Patients not receiving methotrexate; diagnosis of ischemic stroke, PRES, CNS infection, metabolic derangement, or leukemic CNS involvement.

Has the patient received intrathecal or intravenous methotrexate (*particularly high dose*) within the previous 2-21 days?

No →
- Off guideline and continue evaluation as clinically indicated.

Yes ↓

Assessment

Clinical Presentation – symptoms may include; but not limited to the following:

- Altered mental status
- Aphasia
- Ataxia
- Dysarthria/slurred speech
- Facial asymmetry
- Headache
- Hemiparesis
- Hemisensory deficits
- Seizures
- Visual disturbance

Note: *Symptoms may fluctuate / wax and wane*

Neuroimaging (for pre-existing)

- Magnetic Resonance Imaging (MRI) brain with diffusion-weighted imaging (DWI) may demonstrate restricted diffusion in a non-vascular distribution.

Exclusion of alternative diagnoses – Evaluate for:

- Acute ischemic stroke
- Posterior reversible encephalopathy syndrome (PRES)
- Central nervous system (CNS) infection
- Metabolic derangements
- Leukemic CNS involvement

Interventions

Diagnostic Evaluation

- Complete Blood Count (CBC)
- Comprehensive Metabolic Panel (CMP)
- Vitamin B12 level
- Methotrexate level
- Additional studies as clinically indicated to evaluate for infection or metabolic abnormalities

Neuroimaging

- Obtain non-contrast Computed Tomography (CT) head to rule out acute hemorrhage or other intracranial pathology, STAT.
- If symptoms persist or methotrexate neurotoxicity remains suspected, obtain:
  - MRI brain with and without contrast with DWI
  - Consider Magnetic Resonance Angiography/Magnetic Resonance Venography (MRA/MRV) when clinically indicated to exclude alternative diagnoses.

➔ **Proceed to Page 2**

Recommendations/ Considerations

- Methotrexate neurotoxicity is a syndrome-based clinical diagnosis supported by timing, clinical presentation, neuroimaging, and exclusion of alternative etiologies.
- Oncology team must be notified and involved in the work up and care.
- MRI findings may be normal; diagnosis should not rely solely on imaging findings.

If acute stroke is suspected, follow the ***Acute Stroke – Oncology Code Stroke Protocol*** immediately.

Approved Evidence Based Medicine Committee
Original: 7/15/2026

Diagnosis and Treatment of Methotrexate (MTX) Neurotoxicity in Oncology Patients

Continued from Page 1

If clinical presentation and workup are consistent with MTX neurotoxicity and alternative diagnosis is excluded, proceed with treatment:

Pharmacologic Management

Dextromethorphan

- 2 mg/kg/day orally divided twice daily (max 120 mg/day)
- Continue for up to 7 days
- Discontinue sooner if symptoms resolve

and/or

Aminophylline

- 2.5 mg/kg IV (max 100 mg; *use ideal body weight*)
- Infuse over 1 hour every 24 hours until symptom resolution
- Obtain aminophylline level before the third dose
- Goal serum concentration: < 15 mcg/Ml

and/or

Vitamin B12

- Begin Vitamin B12 100 mcg daily
- Continue pending Vitamin B12 level
  - If Vitamin B12 < 200 pg/mL, continue supplementation
  - If Vitamin B12 level is normal, discontinue supplementation

Medication Considerations

- Aminophylline is a major substrate of CYP1A2.
- The following drugs are in Category D or above and should be avoided as they increase theophylline level and have the potential to cause theophylline toxicity:
  - Belumosudil
  - Carbamazepine
  - Systemic erythromycin
  - Moderate or strong CYP1A2 inhibitors

Additional Recommendations / Considerations

- Leucovorin is *not recommended* for treatment of methotrexate neurotoxicity unless otherwise clinically indicated.
- Vitamin B6 and folic acid are *not routinely recommended* because evidence supporting their use is limited.
- Consult Neurology and the primary Oncology service for ongoing management.
- Consider repeat MRI if neurologic symptoms persist despite an initially unrevealing study and clinical suspicion remains high.

Discharge Criteria

- Neurological symptoms have resolved or significantly improved.
- No alternative neurologic emergency requiring inpatient management is identified.
- Patient is clinically stable.
- Appropriate Oncology follow-up has been arranged.
- Caregivers understand return precautions.

Patient / Family Education

- Methotrexate neurotoxicity is an uncommon but recognized complication of methotrexate therapy.
- Symptoms are often temporary and generally improve with supportive care, with complete resolution in most cases.
- Return immediately for:
  - New weakness
  - Difficulty speaking
  - Vision changes
  - Seizure
  - Altered mental status
  - Worsening neurologic symptoms
- It is important to have close follow-up with the Oncology team.

References

Afshar, M., Birnbaum, D., & Golden, C. (2014). Review of dextromethorphan administration in 18 patients with subacute methotrexate central nervous system toxicity. *Pediatric Neurology*, *50*(6), 625–629. https://doi.org/10.1016/j.pediatrneurol.2014.01.048 (Level III)

Apiraksattayakul, N., Jitprapaikulsan, J., Sanpakit, K., & Kumutpongpanich, T. (2024). Potential neurotoxicity associated with methotrexate. *Scientific Reports*, *14*(1), 18548.https://doi.org/10.1038/s41598-024-69263-0 (Level III)

Ayalon, I., Friedman, S., Binenbaum, Y., Oppenheimer, N., Shiran, S., Grisaru-Soen, G., Uliel-Sibony, S., Glatstein, M., Kaplan, J.M., & Sadot, E. (2019). A case of methotrexate neurotoxicity presented as status epilepticus, encephalopathy, and high fever. *Journal of Investigative Medicine High Impact Case Reports*, *7*. https://doi.org/10.1177/2324709619862311 (Level V)

Bernini, J. C., Fort, D. W., Griener, J. C., Kane, B. J., Chappell, W. B., & Kamen, B. A. (1995). Aminophylline for methotrexate-induced neurotoxicity. *Lancet (London, England)*, *345*(8949), 544–547. https://doi.org/10.1016/s0140-6736(95)90464-6 (Level III)

Bhojwani, D., Bansal, R., & Wayne, A. S. (2021). Managing therapy-associated neurotoxicity in children with ALL. *Hematology. American Society of Hematology. Education Program*, *2021*(1), 376–383. https://doi.org/10.1182/hematology.2021000269 (Level V)

Bhojwani, D., Sabin, N. D., Pei, D., Yang, J. J., Khan, R. B., Panetta, J. C., Krull, K. R., Inaba, H., Rubnitz, J. E., Metzger, M. L., Howard, S. C., Ribeiro, R. C., Cheng, C., Reddick, W. E., Jeha, S., Sandlund, J. T., Evans, W. E., Pui, C.-H., & Relling, M. V. (2014). Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *32*(9), 949–959. https://doi.org/10.1200/JCO.2013.53.0808 (Level III)

Donaghy, R., Singer, L., & Dixit, K. (2024). Intrathecal methotrexate, central nervous system toxicity, and response to N-methyl-D-aspartate antagonism: An adult case series. *Neuro-Oncology Practice*, *11*(5), 665–669. https://doi.org/10.1093/nop/npae051 (Level V)

Drachtman, R. A., Cole, P. D., Golden, C. B., James, S. J., Melnyk, S., Aisner, J., & Kamen, B. A. (2002). Dextromethorphan is effective in the treatment of subacute methotrexate neurotoxicity. *Pediatric Hematology and Oncology*, *19*(5), 319–327. https://doi.org/10.1080/08880010290057336 (Level III)

Forster, V. J., van Delft, F. W., Baird, S. F., Mair, S., Skinner, R., & Halsey, C. (2016). Drug interactions may be important risk factors for methotrexate neurotoxicity, particularly in pediatric leukemia patients. *Cancer Chemotherapy and Pharmacology*, *78*(5), 1093–1096. https://doi.org/10.1007/s00280-016-3153-0 (Level V)

Fustino, N. J., Juhl, K., & Leister, J. (2021). Dextromethorphan administration on day 0 and day 7 for secondary prevention of methotrexate-induced neurotoxicity in childhood acute lymphoblastic leukemia: A retrospective case series. *Journal of Pediatric Hematology/Oncology*, *43*(2), e284–e287. https://doi.org/10.1097/MPH.0000000000001714 (Level V)

Inaba, H., Khan, R. B., Laningham, F. H., Crews, K. R., Pui, C.-H., & Daw, N. C. (2008). Clinical and radiological characteristics of methotrexate-induced acute encephalopathy in pediatric patients with cancer. *Annals of Oncology*, *19*(1), 178–184. https://doi.org/10.1093/annonc/mdm466 (Level III)

Jaksic, W., Veljkovic, D., Pozza, C., & Lewis, I. (2004). Methotrexate-induced leukoencephalopathy reversed by aminophylline and high-dose folinic acid. *Acta Haematologica*, *111*(4), 230–232. https://doi.org/10.1159/000077573 (Level V)

Peled, Y., Levin, D., Shiran, S., Manisterski, M., Shukrun, R., & Elhasid, R. (2022). Prevalence and management of methotrexate-induced neurotoxicity in pediatric patients with osteosarcoma: a single-center experience. *International Journal of Clinical Oncology*, *27*(8), 1372–1378. https://doi.org/10.1007/s10147-022-02184-y (Level IV)

Peyriere, H., Poiree, M., Cociglio, M., Margueritte, G., Hansel, S., & Hillaire-Buys, D. (2001). Reversal of neurologic disturbances related to high-dose methotrexate by aminophylline. *Medical and Pediatric Oncology*, *36*(6), 662–664. https://doi.org/10.1002/mpo.1149 (Level V)

Razi, W., Haque, A. U., Sadiq, H., Ullah, R., Jabbar, N., & Mirza, S. (2021). Safety and efficacy of aminophylline in intrathecal methotrexate-related neurological toxicity in large pediatric oncology centre. *Journal of the College of Physicians and Surgeons--Pakistan: JCPSP*, *31*(4), 481–484. https://doi.org/10.29271/jcpsp.2021.04.481 (Level IV)

Rubin, M. F., & Kuhn, A. K. (2020). Management of methotrexate-induced neurotoxicity with aminophylline plus dextromethorphan in a pediatric patient with pineoblastoma. *Pediatric Blood & Cancer*, *67*(12), e28515. https://doi.org/10.1002/pbc.28515 (Level V)

Santangelo, A., Bartolini, E., Nuzzi, G., Foiadelli, T., Michev, A., Mina, T., Trambusti, I., Fichera, V., Bonuccelli, A., Massimetti, G., Peroni, D. G., De Marco, E., Coccoli, L., Luti, L., Bernasconi, S., Nardi, M., Menconi, M. C., Casazza, G., Pruna, D., … Orsini, A. (2022). The clinical impact of methotrexate-induced stroke-like neurotoxicity in paediatric departments: An Italian multi-centre case-series. *Frontiers in Neurology, 13*, Article 920214. https://doi.org/10.3389/fneur.2022.920214 (Level V)

Śliwa-Tytko, P., Kaczmarska, A., Lejman, M., & Zawitkowska, J. (2022). Neurotoxicity associated with treatment of acute lymphoblastic leukemia chemotherapy and immunotherapy. *International Journal of Molecular Sciences*, *23*(10), 5515. https://doi.org/10.3390/ijms23105515 (Level I)