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Aggressive Lymphoma Workshop

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Glucarpidase and High-dose methotrexate

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DEFINITION

Table 1. Common high-dose MTX regimens

Indication	ALL	Osteosarcoma	Lymphoma
HDMTX dose	1–5 g/m^2	8–12 g/m^2	1–8 g/m^2
Infusion duration	24–36 h	4 h	2–6 h
Leucovorin start time	42 h	24 h	18–24 h
MTX monitoring times[a]	24 h, (36 h), 42 h, 48 h	24 h, 48 h, 72 h	24 h, 48 h, 72 h

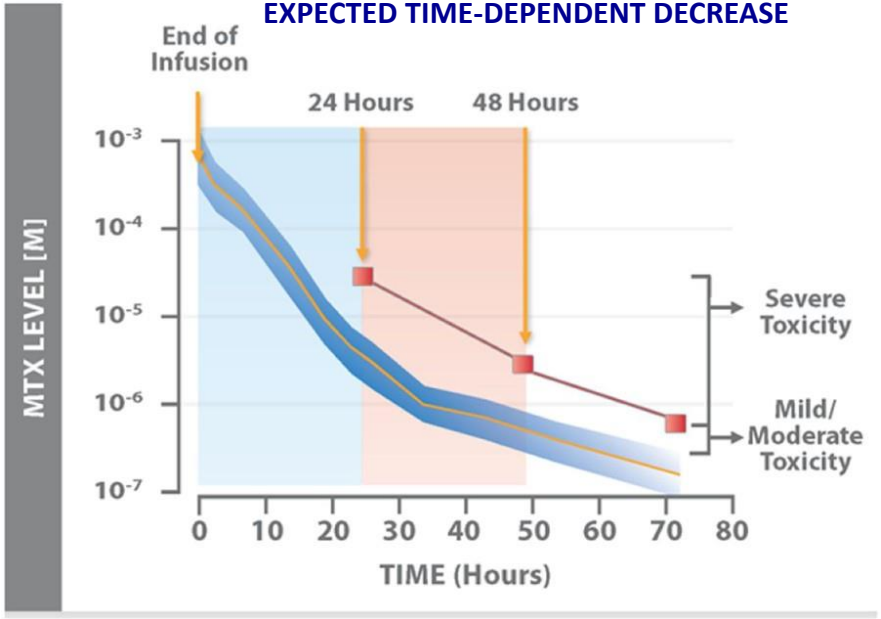
[a]Most hospitals monitor plasma MTX concentrations until MTX ≤0.1–0.2 µM. In ALL patients, 36 h concentrations are occasionally monitored.
Abbreviations: ALL, acute lymphoblastic leukemia; HDMTX, high-dose methotrexate; MTX, methotrexate.

≥ 500 mg/m^2 per cycle regardless of administration schedule → Leads to high initial plasma concentration (10-1000 µmol/L) → Leads to sustained plasma levels (>1 µmol/L for 12-30 h) → Treatment needed to diminish toxicity

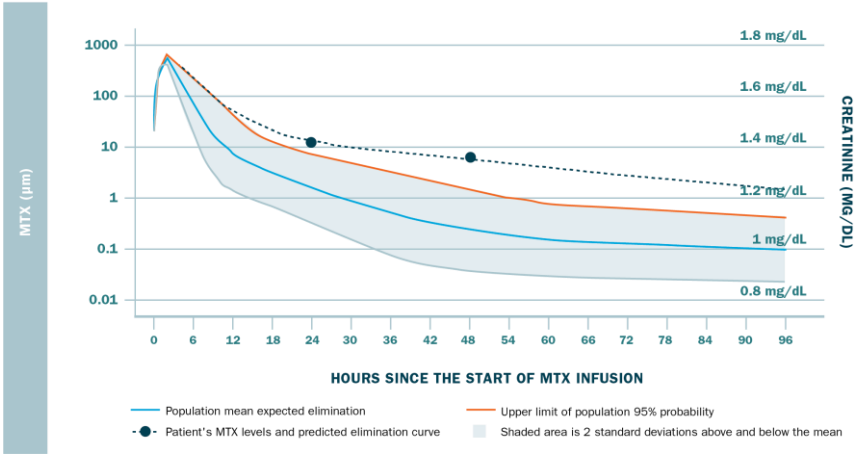
1.LaCasce AS. Therapeutic use and toxicity of high-dose methotrexate. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2016
2. Ramsey LB, Balis FM, O'Brien MM, et al. Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance. Oncologist. 2018 Jan;23(1):52-61.

NORMOGRAM

EXPECTED TIME-DEPENDENT DECREASE



UNEXPECTED TIME-DEPENDENT DECREASE - TOXICITY



- **80% to 90% of MTX* is eliminated unchanged in the urine** within the first 12 to 24 hours of administration.

Oncologist, Volume 21, Issue 12, December 2016, Pages 1471–1482, https://doi.org/10.1634/theoncologist.2015-0164

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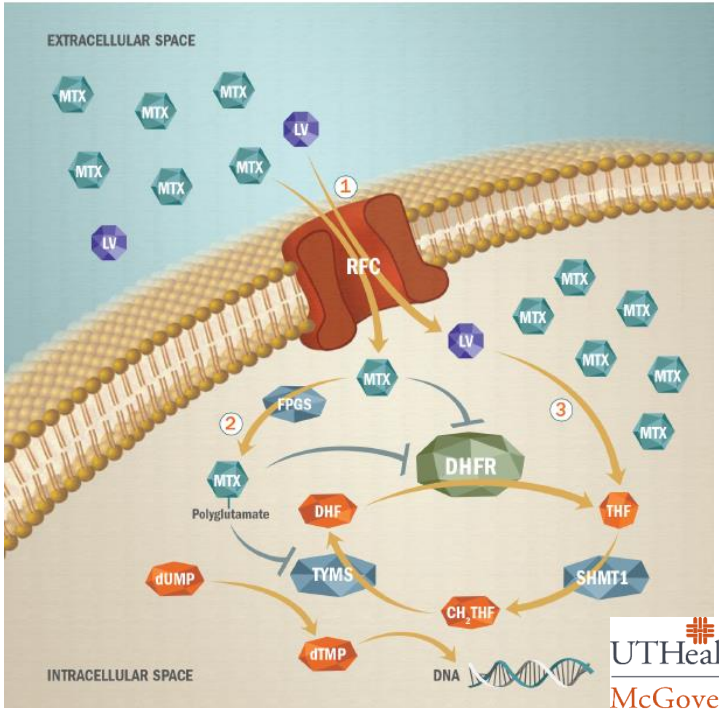
MECHANISM OF TOXICITY – NONRENAL AND RENAL

- MTX enters the cell competes with folates and LV
- MTX is polyglutamated and binds to and irreversibly inhibits dihydrofolate reductase (DHFR)
- Rapidly dividing cells most affected by MTX :

  Cancer cells / Lining of GI tract/ Blood-forming cells

- Leucovorin provides intracellular rescue, restoring tetrahydrofolate stores, allowing resumption of DNA and RNA synthesis
- **RENAL TOXICITY : EXTRACELLULAR METHOTREXATE**



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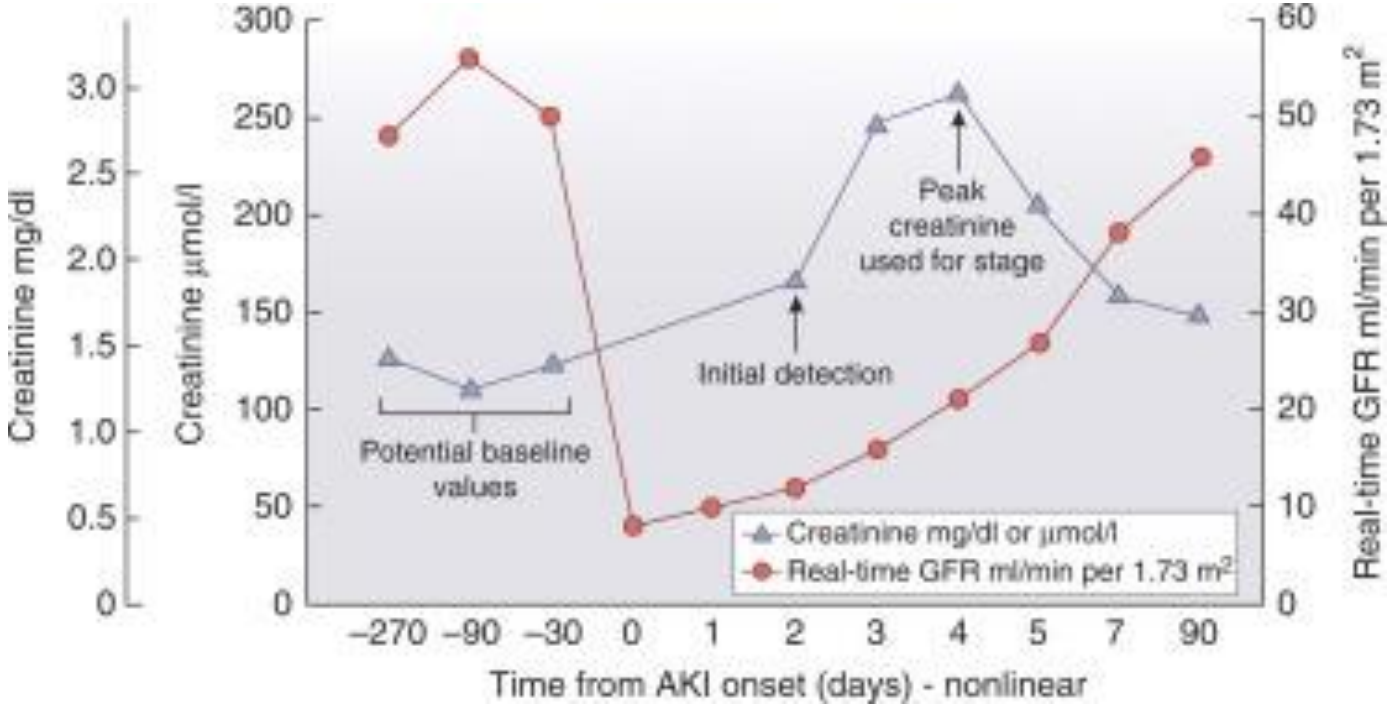
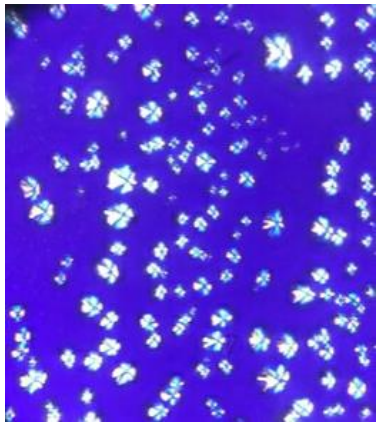


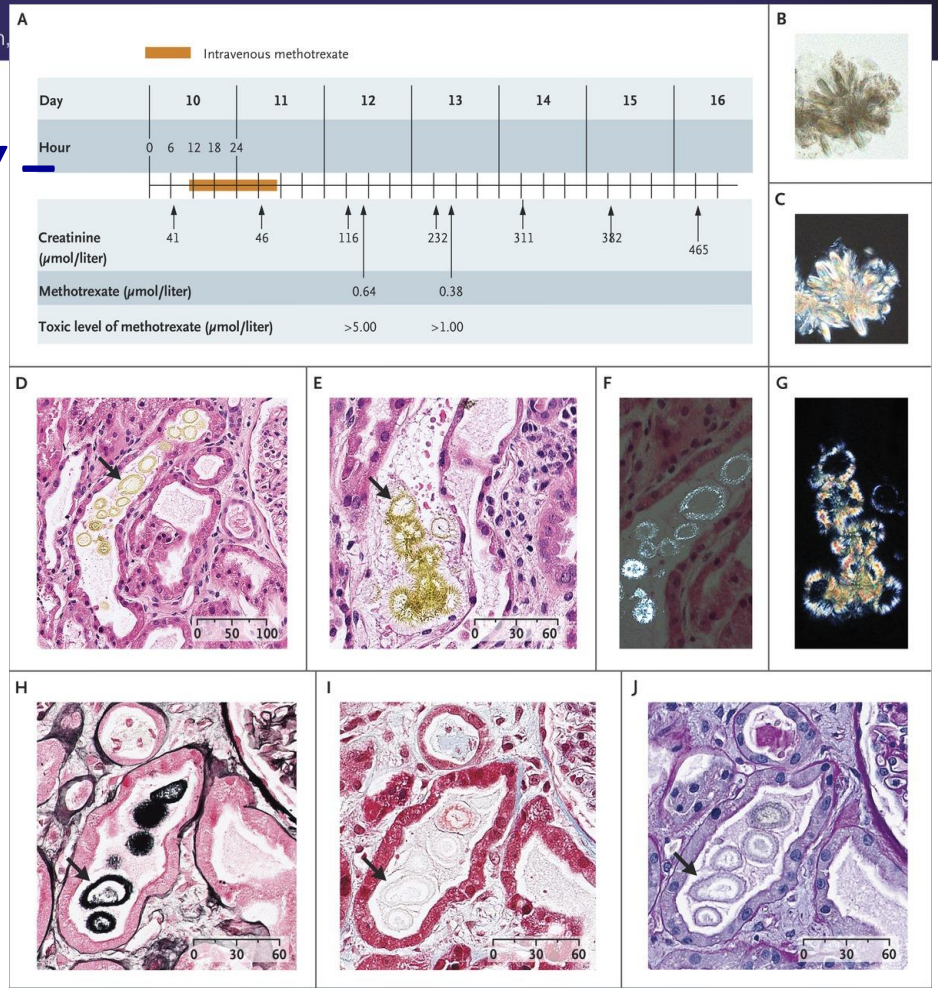
Thomas ME, Blaine C, Dawnay A, Devonald MA, Ftouh S, Laing C, Latchem S, Lewington A, Milford DV, Ostermann M. The definition of acute kidney injury and its use in practice. Kidney Int. 2015 Jan;87(1):62-73

MECHANISM OF TOXICITY – RENAL

Timeline and Microscopic Imaging.



Garneau AP et al. N Engl J Med 2015;373:2691-2693.



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RISK FACTORS LEADING TO TOXICITY

Risk Factor
Nephrotoxic comedication
Body mass index ≥ 25 kg/m^2
Urine pH < 7
CrCl < 60 mL/min
Renal insufficiency prior to HDMTX
Prior toxicity with HDMTX
Volume depletion due to vomiting, diarrhea, or other factors
Adult and Elderly Patients
Third Spacing (i.e. pleural effusions, ascites, intracranial fluid)
Polyuria

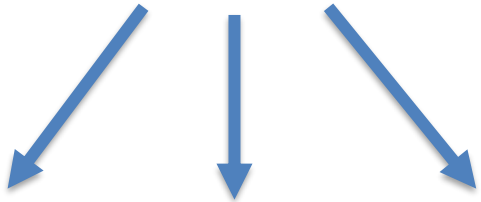
Table 2. Drugs that impair methotrexate clearance

Agents	Mechanism of inhibition
Nonsteroidal anti-inflammatory drugs, penicillin and penicillin derivatives, salicylates, probenecid, gemfibrozil, trimethoprim-sulfamethoxazole	Direct inhibition of renal excretion
Amphotericin, aminoglycosides, radiographic contrast dyes	Nephrotoxicity that leads to decreased glomerular filtration with consequent inhibition of renal excretion
Proton-pump inhibitors	Unclear; potential inhibition of methotrexate BCRP-mediated renal transport
P-glycoprotein/ABCB1 inhibitors	Inhibition of methotrexate transport in multiple organs, including kidney
Levetiracetam, chloral hydrate	Unclear, potential competition for tubular secretion

References [10–15].
Abbreviations: ABCB1, ATP-binding cassette B1; BCRP, breast cancer resistance protein, also known as ABCG2 (ATP-binding cassette) G2.

Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and Managing Toxicities of High-Dose Methotrexate. Oncologist. 2016 Dec;21(12):1471-1482.

TREATMENT OF HDMTX TOXICITY



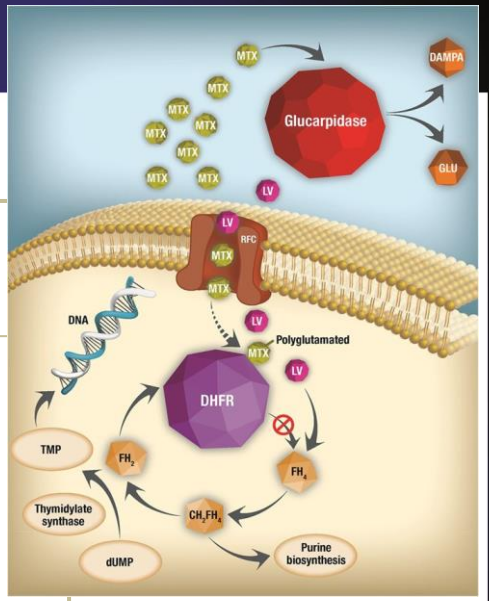
TREATMENT OF HDMTX TOXICITY

Glucarpidase

- Glucarpidase reduces extracellular MTX levels by rapid enzymatic breakdown to nontoxic DAMPA and glutamate, facilitating nonrenal MTX elimination
- No effect on intracellular MTX
- Does not affect MTX levels in the CNS when administered systemically
- Hydrolyzes all folate and folate-like substances (i.e. leucovorin)

Leucovorin

- Acts intracellularly
- Does not affect plasma clearance
- At very high MTX concentrations:
  - No plasma LV concentration may be sufficient to fully reverse toxicity
  - Competition for binding to receptors for transport into the cell may play a role



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1. Ramsey LB, Balis FM, O'Brien MM, et al. Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance. Oncologist. 2018 Jan;23(1):52-61
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TREATMENT OF HDMTX TOXICITY

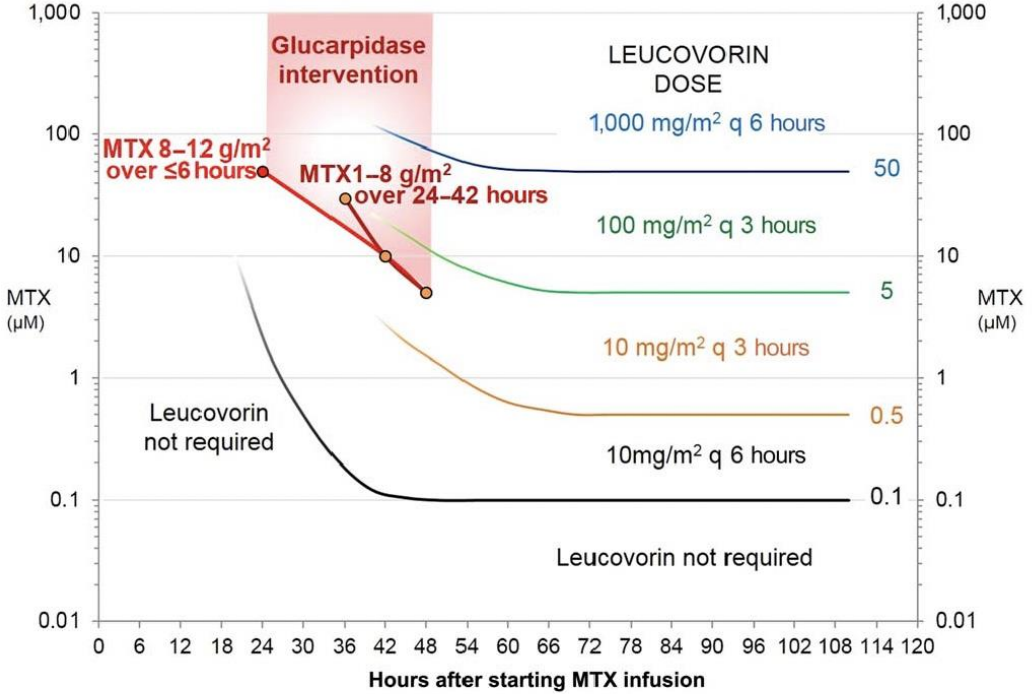


Figure 6. Standard leucovorin nomogram used in the U.S. Glucarpidase use may be indicated when MTX concentrations are within the shaded area.
Abbreviation: MTX, methotrexate.

Indication for Glucarpidase: ***to reduce toxic plasma methotrexate concentration in adults and children (aged 28 days and older) with delayed methotrexate elimination or at risk of methotrexate toxicity.***

Ramsey LB, Balis FM, O'Brien MM, et al. Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance. Oncologist. 2018 Jan;23(1):52-61.

TREATMENT OF HDMTX TOXICITY - DIALYSIS

MODALITIES STUDIED IN LITERATURE

- Hemodialysis
- High-flux hemodialysis
- Charcoal hemoperfusion or hemofiltration

Rebound ↑ in post-dialysis MTX concentrations of 90-100% observed.

Median Decrease in Plasma MTX Concentrations

Most Dialysis-Based Modalities	High-Flux Hemodialysis
52% (range, 26-82%)	76% (range, 42-94%)

Kitchlu A, Shirali AC. High-flux hemodialysis versus glucarpidase for methotrexate-associated acute kidney injury: What's best? *Journal of Onco-Nephrology*. 2019;3(1):11-18

Extracorporeal Treatment for Methotrexate Poisoning

Systematic Review and Recommendations from the EXTRIP Workgroup

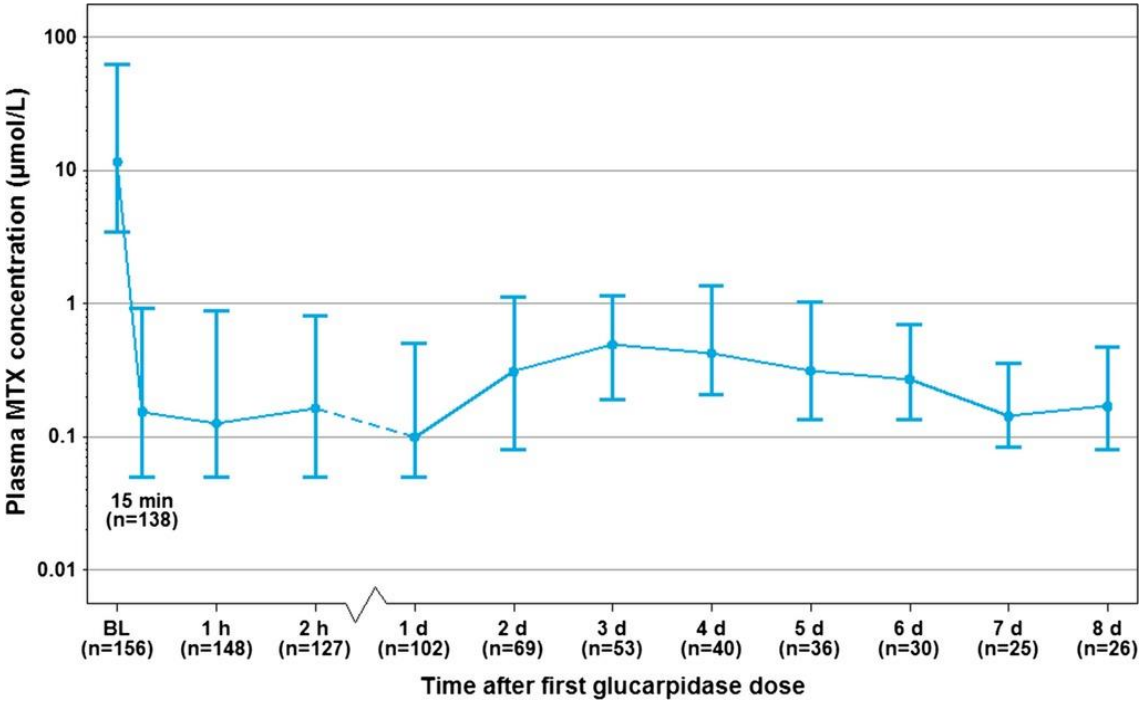
Marc Ghannoum,[1,2] Darren M. Roberts,[3] David S. Goldfarb,[4] Jesper Heldrup,[5] Kurt Anseeuw,[6] Tais F. Galvao,[7] Thomas D. Nolin,[8] Robert S. Hoffman,[9] Valery Lavergne,[1] Paul Meyers,[10] Sophie Gosselin,[11] Tudor Botnaru,[12] Karine Mardini,[13] and David M. Wood,[14] for the EXTRIP workgroup*

Box 1. General recommendations of extracorporeal treatments in methotrexate poisoning In patients with severe methotrexate poisoning receiving standard care treatments including folinic acid rescue therapy:

1) We suggest AGAINST performing extracorporeal treatments when glucarpidase is not administered (weak recommendation; very low–quality evidence) (median: 2; upper quartile: 5.25; disagreement index: 0.61)
2) We recommend AGAINST performing extracorporeal treatments when glucarpidase is administered (strong recommendation; very low–quality evidence) (median: 1; upper quartile: 3; disageement index: 0.13)
3) We recommend AGAINST performing extracorporeal treatments instead of administering glucarpidase (strong recommendation; very low–quality evidence) (median: 1; upper quartile: 3; disagreement index: 0.29)

Ghannoum M, Roberts DM, Goldfarb DS, et al; EXTRIP workgroup. Extracorporeal Treatment for Methotrexate Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup. Clin J Am Soc Nephrol. 2022 Apr;17(4):602-622.

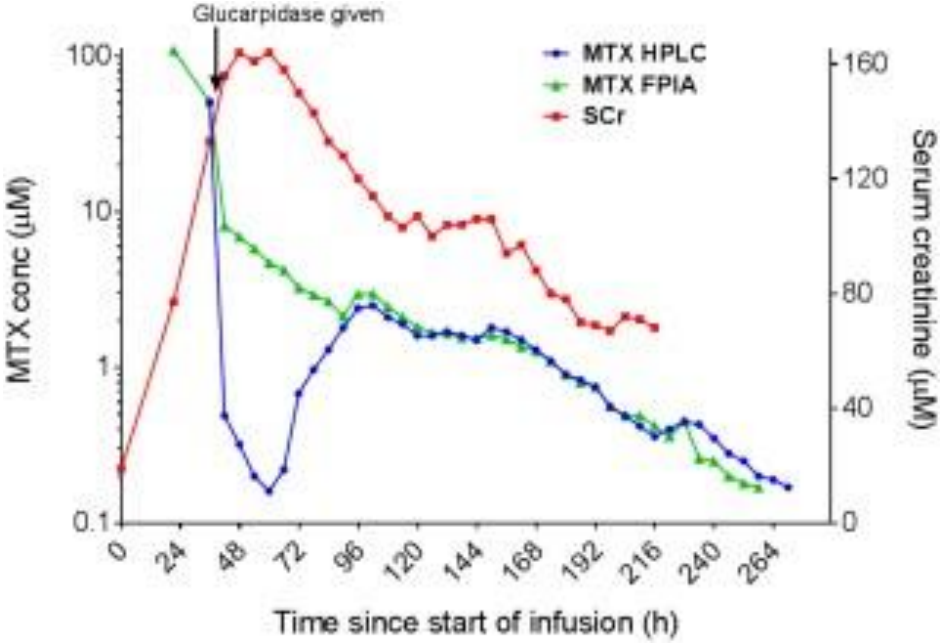
TREATMENT OF HDMTX TOXICITY - GLUCARPIDASE



Efficacy of Glucarpidase (Carboxypeptidase G2) in Patients with Acute Kidney Injury After High-Dose Methotrexate Therapy

Pharmacotherapy, Volume: 34, Issue: 5, Pages: 427-439, First published: 17 October 2013, DOI: (10.1002/phar.1360)

TREATMENT OF HDMTX TOXICITY



Concentrations of MTX and SCr in a patient enrolled on the Nordic Society of Paediatric Haematology.

Oncologist, Volume 23, Issue 1, January 2018, Pages 52–61, https://doi.org/10.1634/theoncologist.2017-0243

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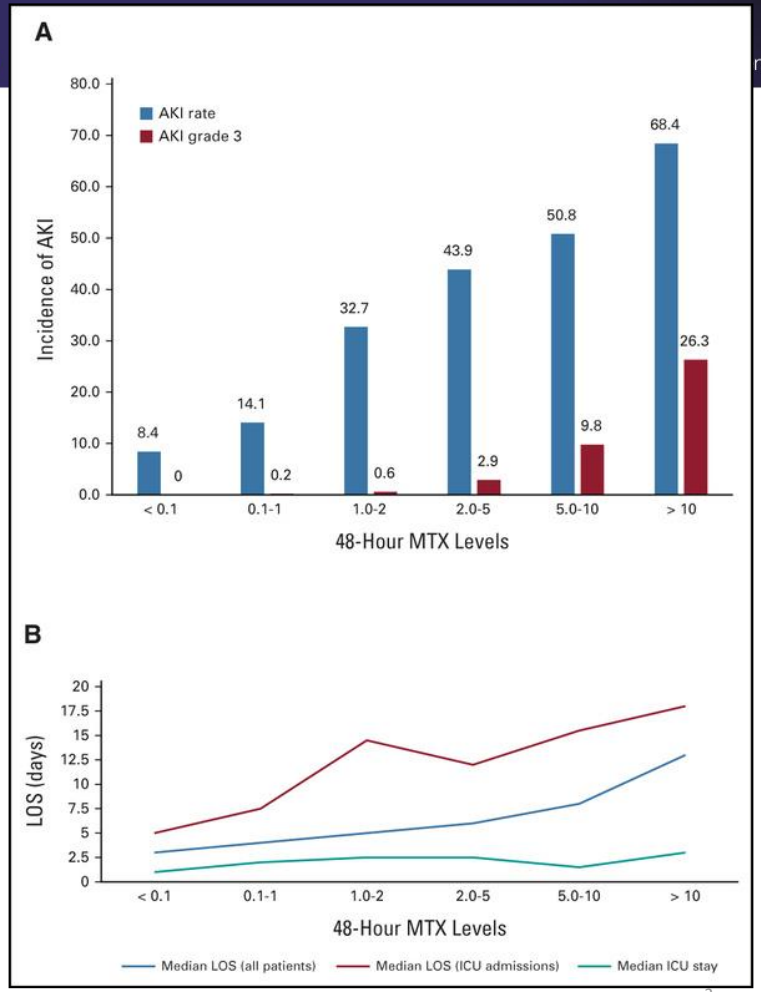
(A) The incidence of AKI compared across predefined groups of 48-hour MTX levels

(B) The effect of ICU admission on LOS compared across predefined groups of 48-hour MTX levels.



High-Dose Methotrexate in Patients With Lymphoma: Predictors of a Complicated Course.
ODonoghue, Darragh; Truong, Huong; Finnes, Heidi; et al. JCO Oncology Practice. 18(12):e1908-e1917,

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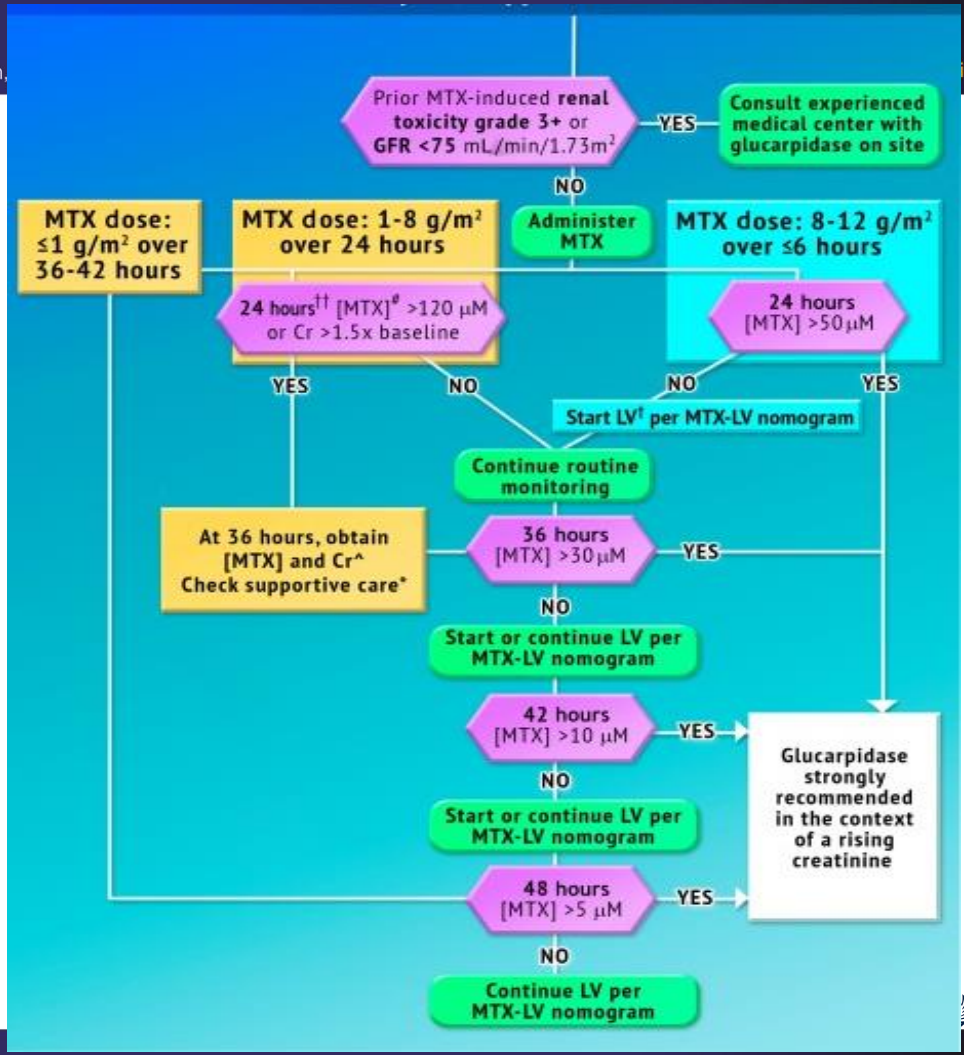
TREATMENT OF HDMTX TOXICITY



Oncologist, Volume 23, Issue 1, January 2018, Pages 52–61,
https://doi.org/10.1634/theoncologist.2017-0243

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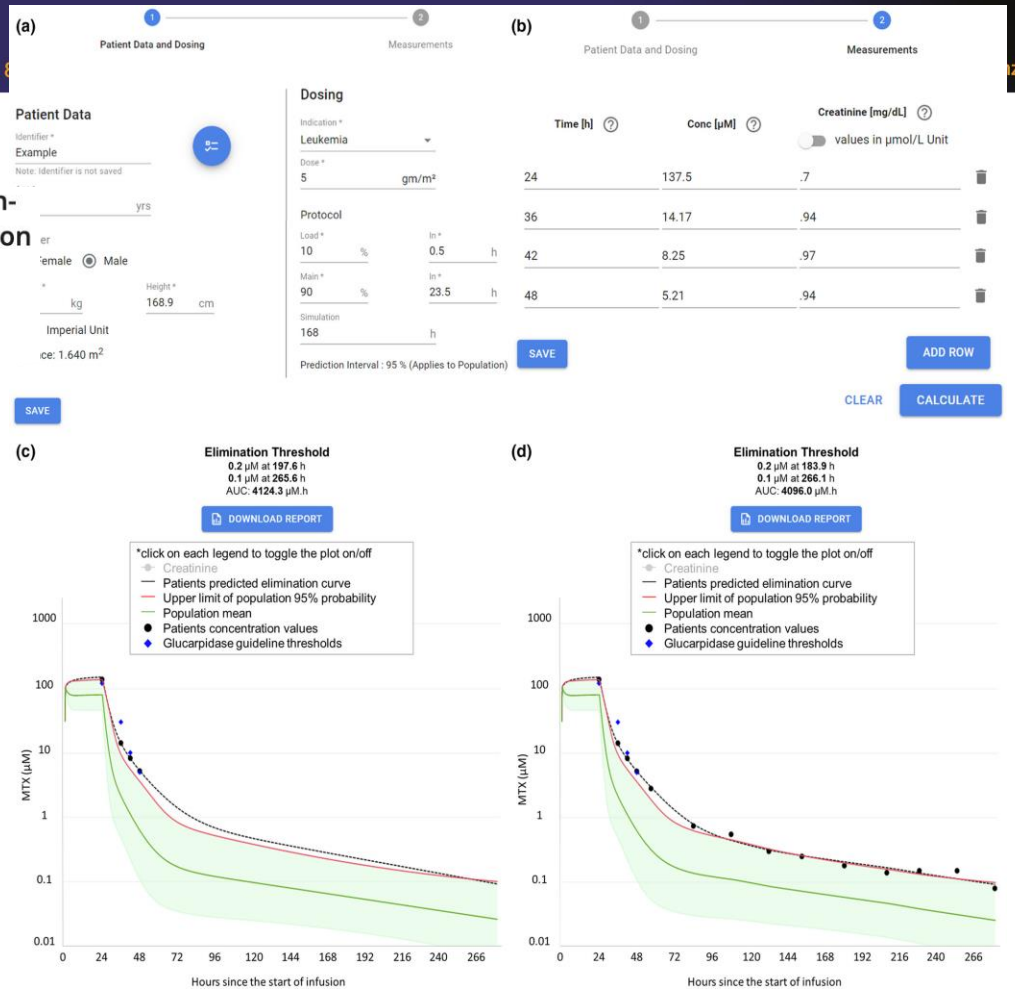
MTXPK.org: A Clinical Decision Support Tool Evaluating High-Dose Methotrexate Pharmacokinetics to Inform Post-Infusion Care and Use of Glucarpidase

Zachary L. Taylor, Tomoyuki Mizuno, Nieko C. Punt, Balaji Baskaran, Adriana Navarro Sainz, William Shuman, Nicholas Felicelli, Alexander A. Vinks, Jesper Heldrup, Laura B. Ramsey



Clin Pharma and Therapeutics, Volume: 108, Issue: 3, Pages: 635-643, First published: 19 June 2020, DOI: (10.1002/cpt.1957)

THANK YOU