Glucarpidase

NZHPA CNO SIG MEETING 2025

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Methotrexate

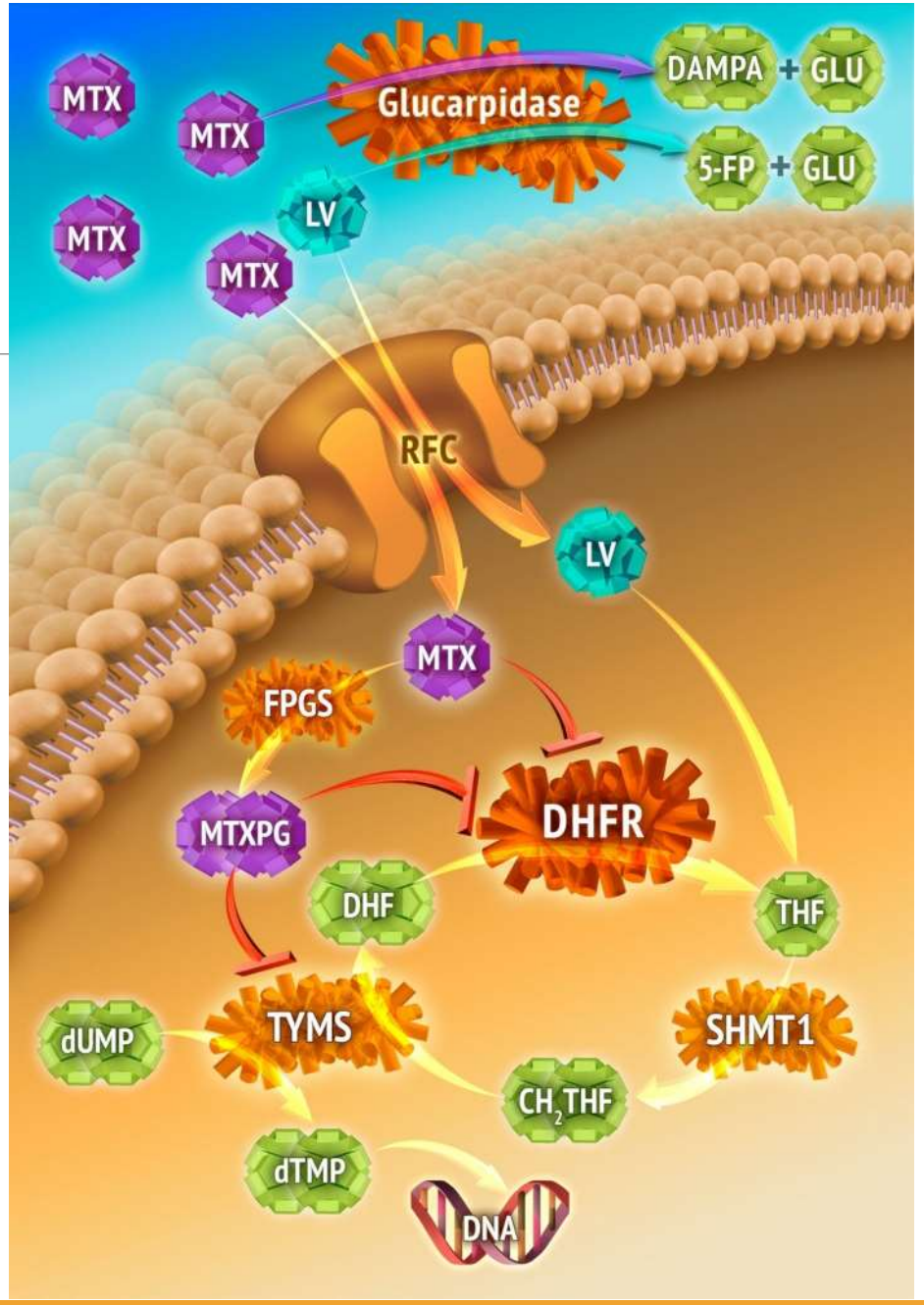
High Dose Methotrexate

- Methotrexate dose ≥500mg/m2 administered by IV infusion

Disease	Usual infusion time	Usual dose
ALL	Long (24-36h)	1-5 g/m^2
CNS lymphoma	Short (2-4h)	≥3 g/m^2
Osteosarcoma	Short (4h)	8-12 g/m^2
CNS prophylaxis (lymphoma)	Short (4h)	≥3 g/m^2

Mechanism of action

- Folate antagonist
- Enters cells via RFC (reduced folate carrier)
- Undergoes polyglutamation → MTX-PG
- Inhibition of dihydrofolate reductase and thymidylate synthetase
  - Inhibits production of purine and thymidylate (building blocks / precursors to DNA and RNA)
  - Inhibition of DNA and RNA synthesis → cell death



Pharmacokinetics

Distribution

- Vd 0.4-0.8 L/kg (non fatty tissues)
- 50% protein bound
- Penetrates into third space fluids (eg. pleural effusion, ascites)

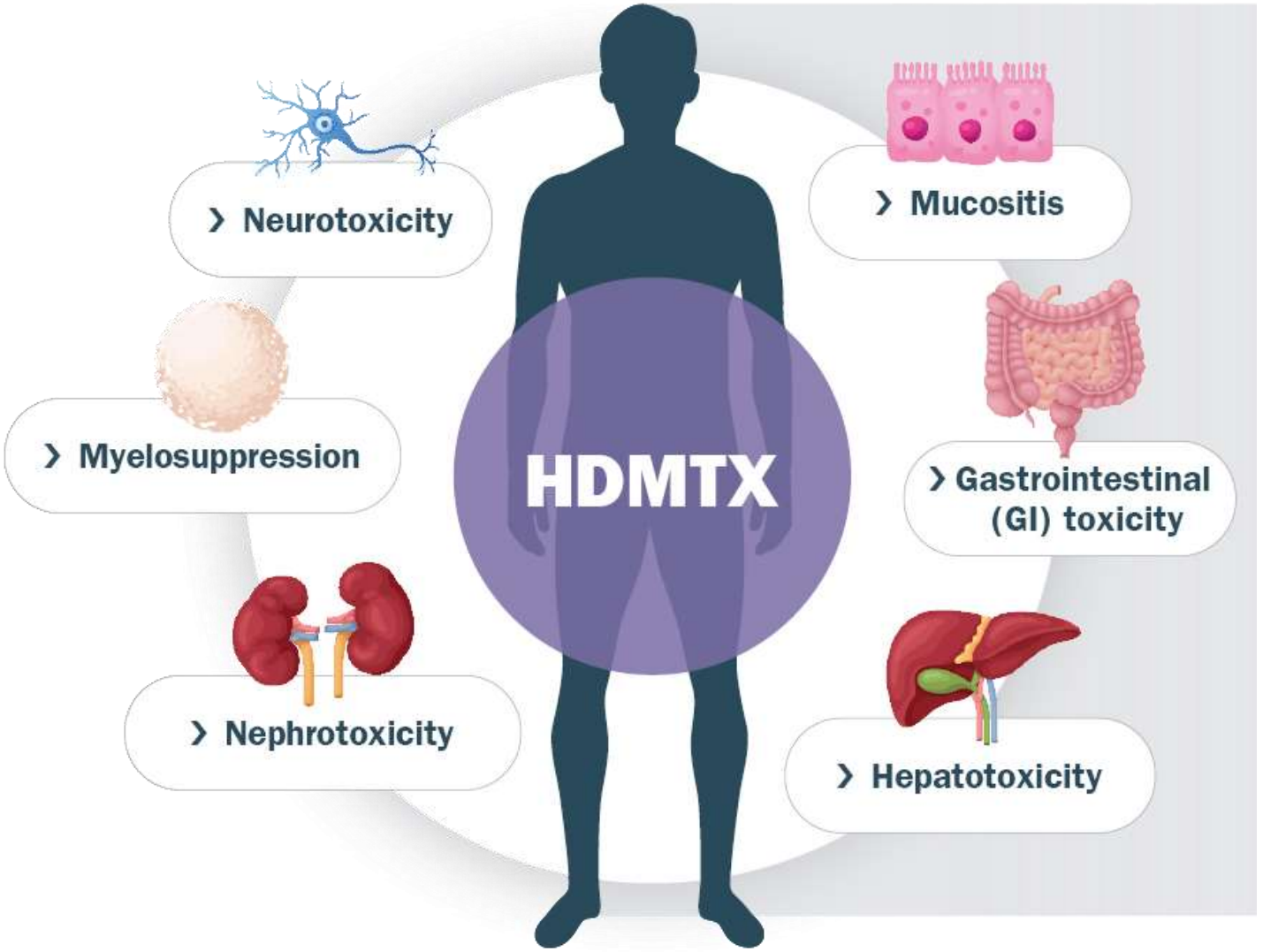
Metabolism

- Active metabolites: MTX polyglutamates, 7-hydroxyl-MTX
- Inactive metabolite: 4-amin0-deoxy-N-methylpteric acid (DAMPA)

Elimination

- 80-90% in urine
- 10% biliary (excreted in faeces)
- 8-15h half life (for high dose MTX)

Methotrexate toxicity



Risk factors for toxicity

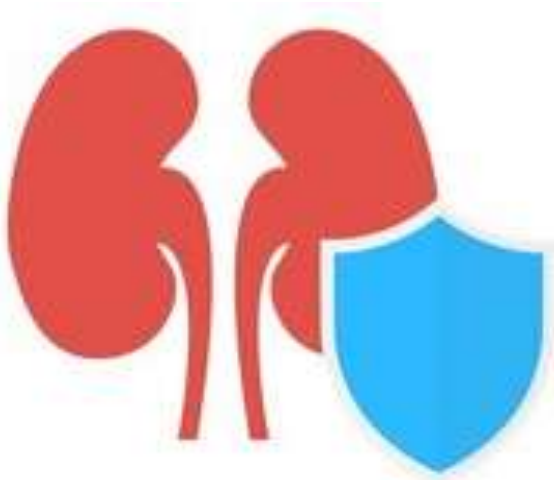
- Concomitant interacting +/- nephrotoxic medicines
- BMI ≥25
- Renal insufficiency (CrCl <60ml/min)
- Prior toxicity with HD MTX
- Elderly / frail
- Third spacing (pleural effusions, ascites, intracranial fluid)
- Volume depletion
- Polyuria
- Urine pH <7
- Hypoalbuminaemia
- Delay between recognition of toxicity and initiation of treatment

Drug interactions

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

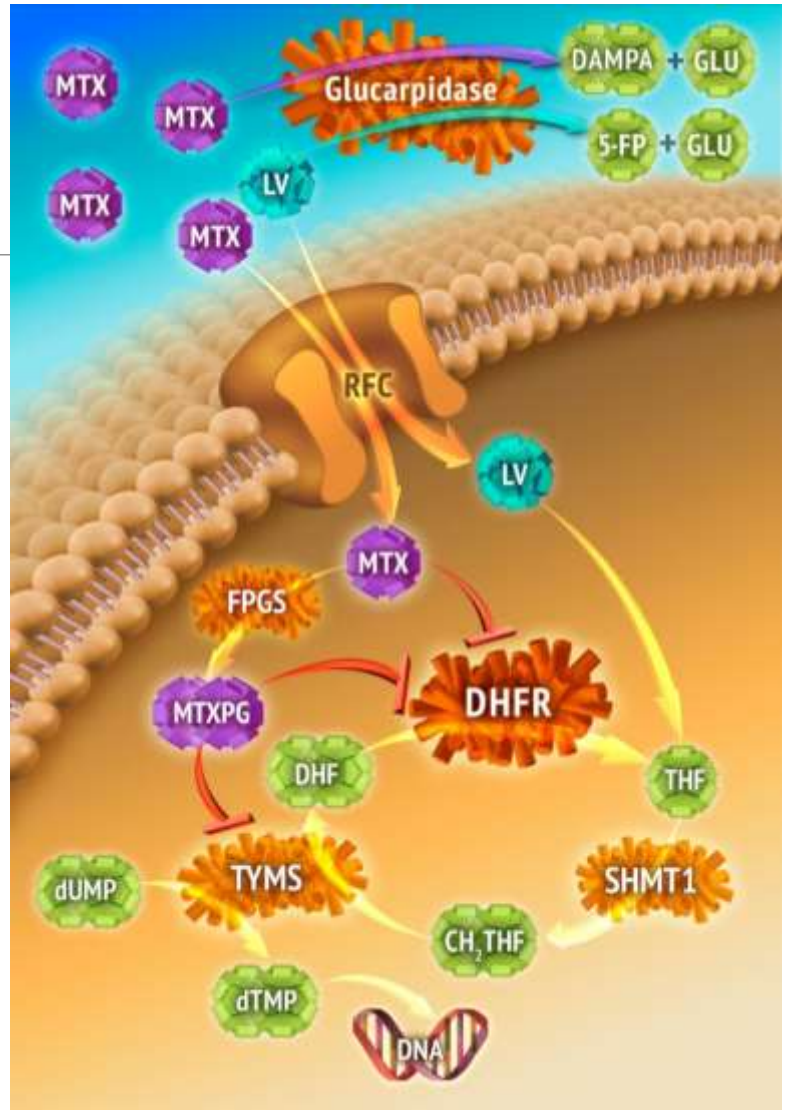
Early warning signs of nephrotoxicity

- Elevated plasma methotrexate level (prior to change in serum creatinine)
- Increase in serum creatinine (lagging indictor of AKI)
- Decreased urine output
- Positive fluid balance
- Weight change



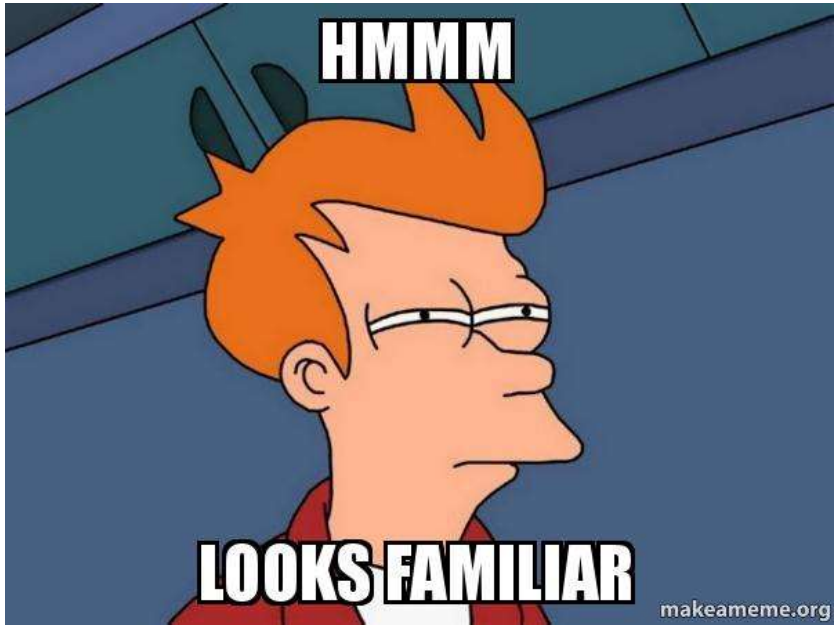
Prevention of MTX toxicity

- Hydration + maintain urine output
- Urinary alkalinisation
- Administration of calcium folinate/leucovorin
- Close monitoring of labs
  - Serum creatinine and electrolytes
  - Plasma MTX levels
- Avoid interacting + nephrotoxic drugs
- Dose adjustments



Management of MTX toxicity

- Hydration + forced diuresis
- Urinary alkalinisation
- Calcium folinate/leucovorin rescue
  - Increase dose + frequency
- Close monitoring of labs
  - Serum creatinine and electrolytes
  - Plasma MTX levels
- ? Dialysis
- ? Glucarpidase



Dialysis for MTX toxicity

Clin J Am Soc Nephrol. Ghannoum et al 2022

- Included analysis of 92 articles
- Data clinically analysed on 109 patients (91 had HDMTX ≥500 mg/m^2)
- Found MTX to be moderately dialyzable by intermittent haemodialysis
- Haemodialysis most effective out of all forms of extracorporeal treatment
  - Median MTX half life of 4h (compared to usual MTX half life 8-15h)

Ghannoum M, 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.

Dialysis for MTX toxicity

Clin J Am Soc Nephrol. Ghannoum et al 2022

Recommendation

- Recommended against extracorporeal treatment, whether glucarpidase is used or not

Rationale

- Poor intracellular clearance
- Removal of leucovorin
- Glucarpidase is more effective (if available)
- Lack of clinical benefit (doesn’t decrease incidence or severity of MTX toxicity)

Ghannoum M, 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.

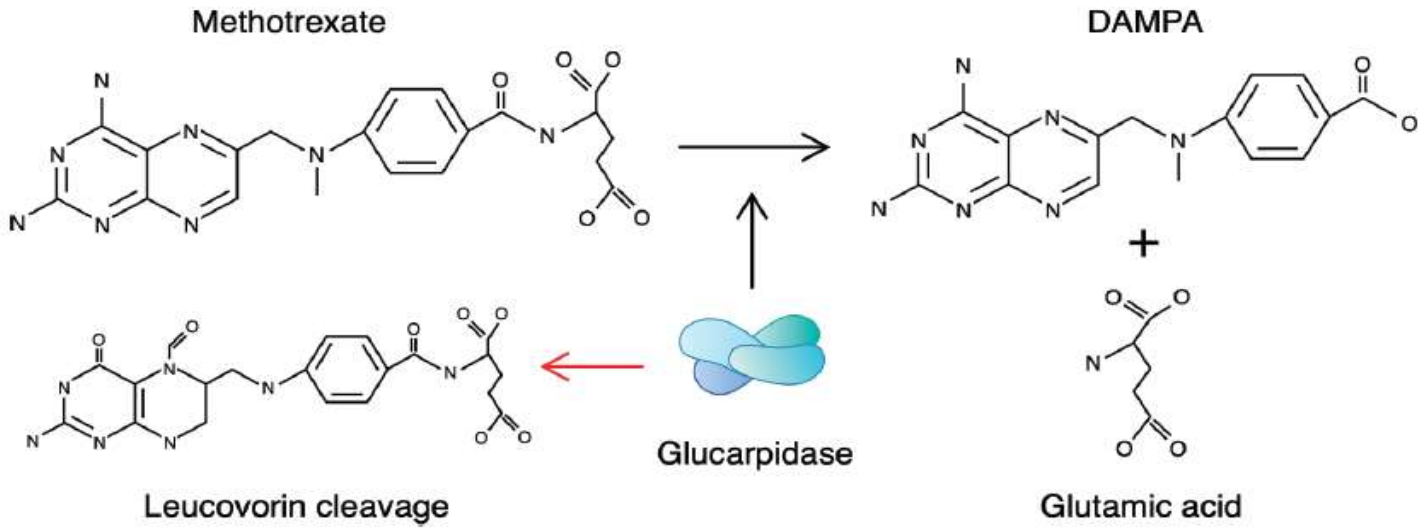
Glucarpidase

History

- 1970s
  - Carboxypeptidase G_1 (CPG_1) isolated from *Pseudomonas stutzeri*
  - Studies in mice and a small number of patients found administration after MTX prevented subsequent toxicity
  - Bacterial source subsequently lost ☹
- 1980s
  - Carboxypeptidase G_2 (CPG_2) isolated and purified from *Pseudomonas* strain RS-16
  - Cloned into and now produced by recombinant DNA technology in genetically modified *Escherichia coli* → glucarpidase

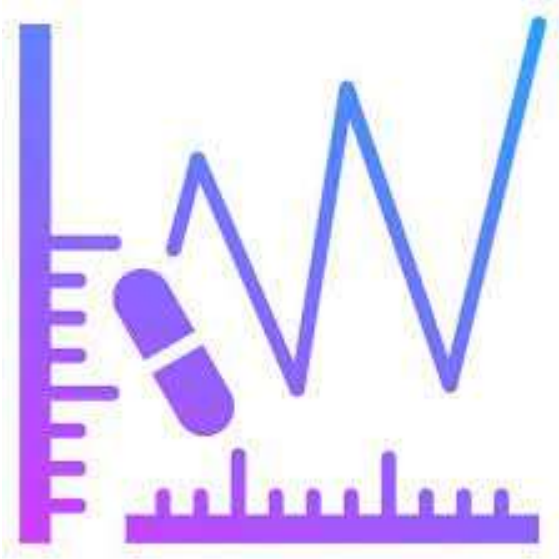
Mechanism of action

- Recombinant bacterial enzyme
- Catalyses the conversion of methotrexate to inactive metabolites
  - Hydrolyses the glutamate residue from folate analogues
- Works on circulating methotrexate only (not intracellular)

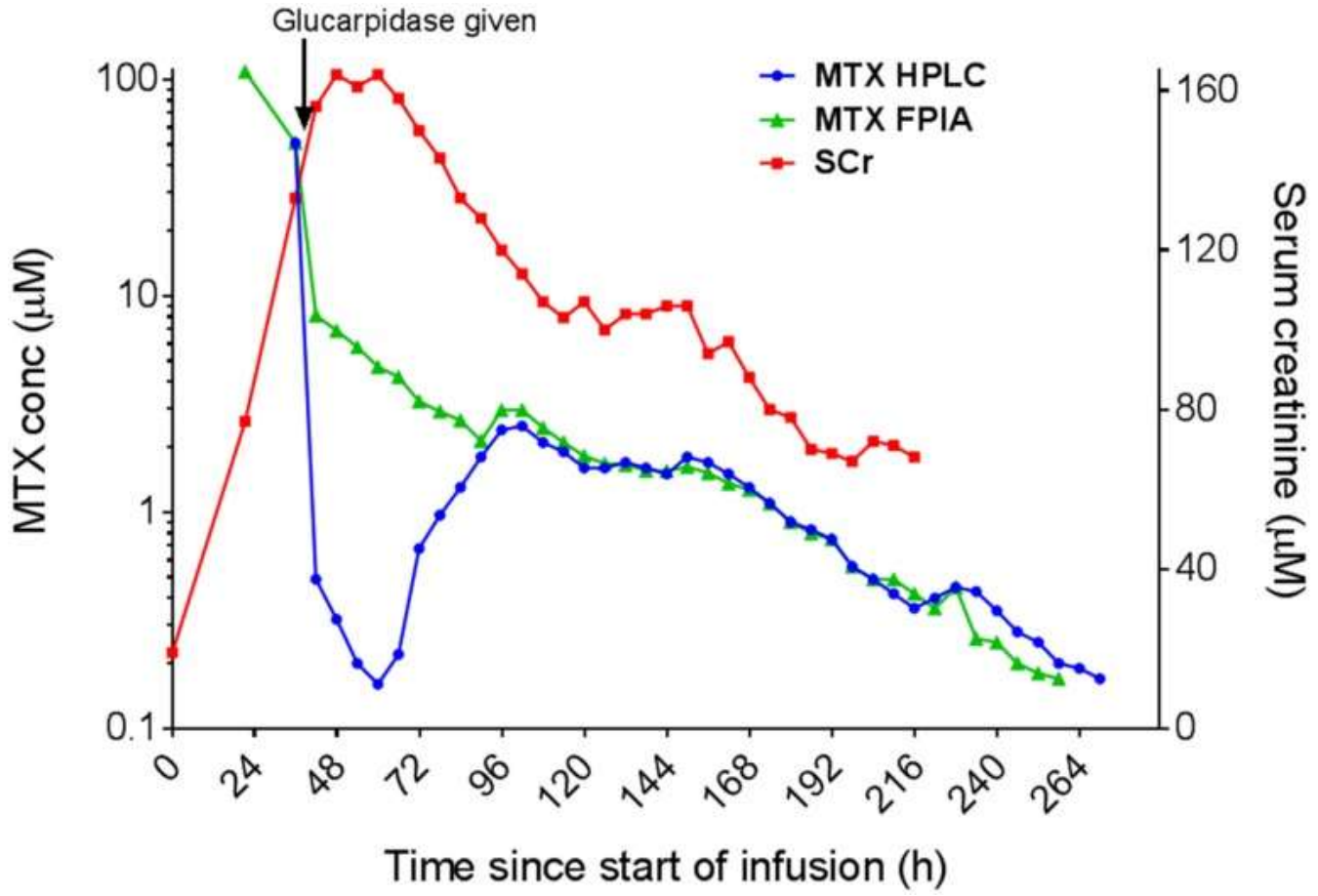


Pharmacokinetics

- V_d = 42 mL/kg (~3.6L)
  - ONLY distributed in the bloodstream
- Elimination half life
  - Plasma concentration half life: 9h
  - Enzyme activity half life: 5.6h
  - Closer to 9h in renal impairment



MTX monitoring post glucarpidase



Safety

- Nausea/vomiting
- Hypotension
- Paraesthesia
- Flushing
- Headache

- Anti-glucarpidase antibodies may develop in as many as 50% of patients who receive glucarpidase
  - May limit future utility of glucarpidase

Dosing

- 50 units/kg as a single dose
  - Powder for injection
  - Reconstituted with 1mL sodium chloride 0.9%
  - IV bolus over 5 minutes
  - Within 48 – 60h from the start of MTX infusion
- > $50,000 for 1000 units

Efficacy of glucarpidase

- Single-arm, open-label study from glucarpidase manufacturer (BTG Pharmaceuticals)
- 22 patients who had markedly delayed MTX clearance due to impaired renal function
- All patients received glucarpidase 50 units/kg
  - Continued hyperhydration, urinary alkalinisation and leucovorin alongside glucarpidase treatment (leucovorin not administered within 2 hours of glucarpidase)
- Main outcome measure: proportion of patients who achieved a rapid and sustained clinically important reduction (RSCIR) in plasma MTX concentration
  - Plasma MTX level ≤1 umol/L at 15 minutes post glucarpidase, that was sustained for up to 8 days
- Median age 15.5y, 59% male, and most patients had either osteogenic sarcoma, leukemia or lymphoma

Efficacy of glucarpidase

Pre-VORAXAZE Methotrexate Concentration (µmol/L)	Patients n	Patients Achieving RSCIR n (%)	Patients with >95% Rapid Reduction in Methotrexate Concentration and Maintained up to 8 Days n (%)
>1	22	10 (45%)	20 (91%)
>1 to ≤50	13	10 (77%)	11 (85%)
>50 to ≤100	2	0	2 (100%)
>100	7	0	7 (100%)

RSCIR: rapid and sustained clinically important reduction in methotrexate concentration.

Glucarpidase for treatment of high-dose methotrexate toxicity

Blood, Gupta et al 2025

- Target trial emulation (retrospective) across 28 cancer centres in the US from 2000 to 2022 (708 patients in total)
- Included adults (≥ 18y) who received HD MTX (≥ 1g/m^2) and developed MTX-AKI (≥ 1.5-fold increase in SCr (from baseline) within 4 days after initiation of MTX
- Excluded patients with ESRF and those who were moribund (likely to die within 2 days) at the time of MTX initiation
- Glucarpidase vs no glucarpidase within 4 days following initiation of MTX

Glucarpidase for treatment of high-dose methotrexate toxicity

Blood, Gupta et al 2025

- Primary outcome: kidney recovery at discharge from hospital
  - Survival to discharge with SCr <1.5-fold compared to baseline and without dialysis dependence
- Secondary outcomes:
  - Time to kidney recovery in the first 14 days
  - Incidence and severity of neutropenia, transaminitis and mucositis assessed on day 7
  - MTX rechallenge within 30 days
  - Persistent kidney impairment or death at day 90
  - Time to death

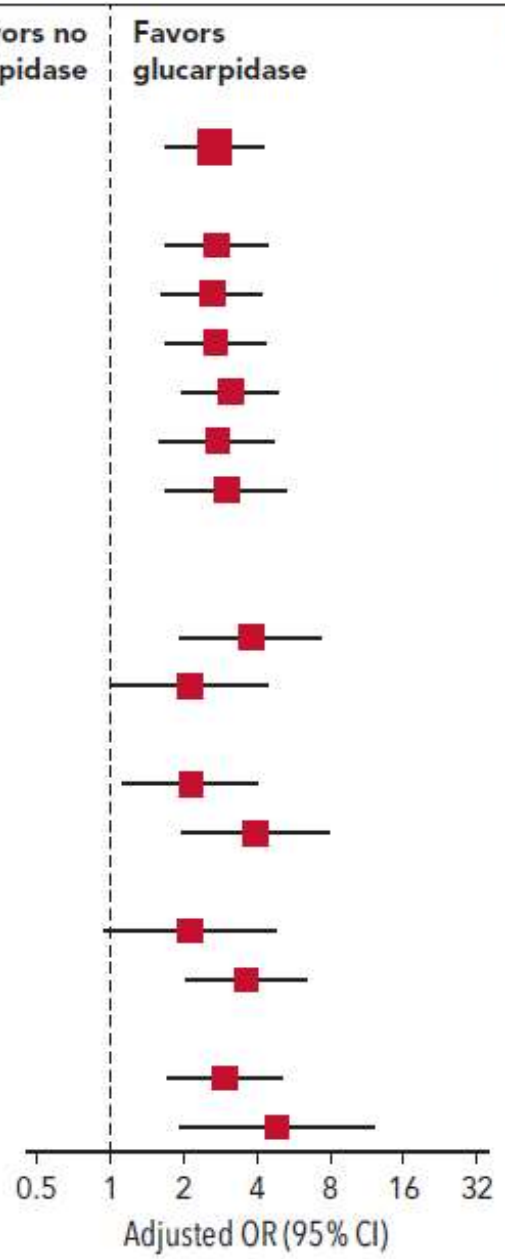
Baseline characteristics

Blood, Gupta et al 2025

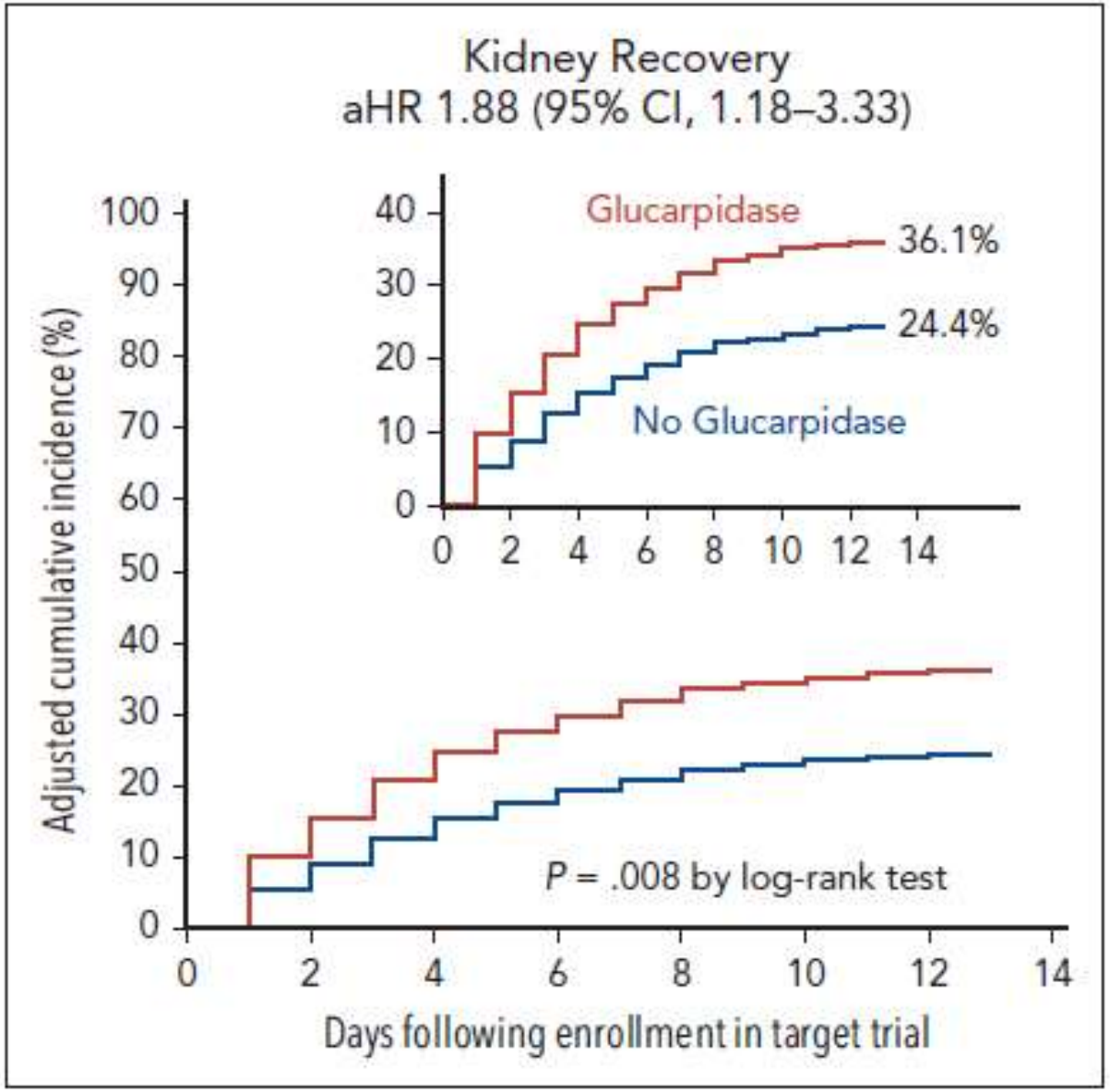
- Similar in glucarpidase-treated versus non-glucarpidase-treated patients with respect to age, sex, race, duration and dose of MTX infusion, and most baseline lab results
- Glucarpidase treated patients
  - More likely to have comorbidities (eg. hypertension, diabetes) and more likely to have received concomitant nephrotoxic medications
  - Had higher 24-, 36- and 28-hour plasma methotrexate concentrations
  - Had greater severity of AKI
  - Received larger amounts of IV fluids and leucovorin

Primary endpoint

	No. Events/ No. Patients (%)	Adjusted OR (95% CI)	*P* value for interaction
Primary analysis	384/1645 (23.3)	2.70 (1.69–4.31)	NA
Sensitivity analyses			
1. Glucarpidase in the first 3 days	384/1645 (23.3)	2.74 (1.69–4.43)	NA
2. Adjusted for site[a]	384/1645 (23.3)	2.64 (1.64–4.23)	NA
3. Adjusted for site[b]	384/1645 (23.3)	2.71 (1.68–4.35)	NA
4. Limited to 2012 or later	365/1509 (24.2)	3.11 (1.97–4.90)	NA
5. Limited to MTX infusion <12h	343/1369 (25.1)	2.75 (1.61–4.70)	NA
6. Limited to glucarpidase ≥50 U/kg	371/1572 (23.6)	3.00 (1.69–5.28)	NA
Subgroup analyses			
Age (years)			.30
<65	194/858 (22.6)	3.79 (1.95–7.37)	
≥65	190/787 (24.1)	2.13 (1.03–4.42)	
Sex			.02
Male	278/1183 (23.5)	2.14 (1.13–4.05)	
Female	106/462 (22.9)	3.96 (1.98–7.94)	
Baseline eGFR (ml/min/1.73m2)			.16
<90	183/598 (30.6)	2.13 (0.94–4.81)	
≥90	201/1047 (19.2)	3.61 (2.05–6.36)	
AKI stage			.14
Stage 1 or 2	354/1240 (28.5)	2.95 (1.72–5.07)	
Stage 3	30/405 (7.4)	4.83 (1.93–12.04)	

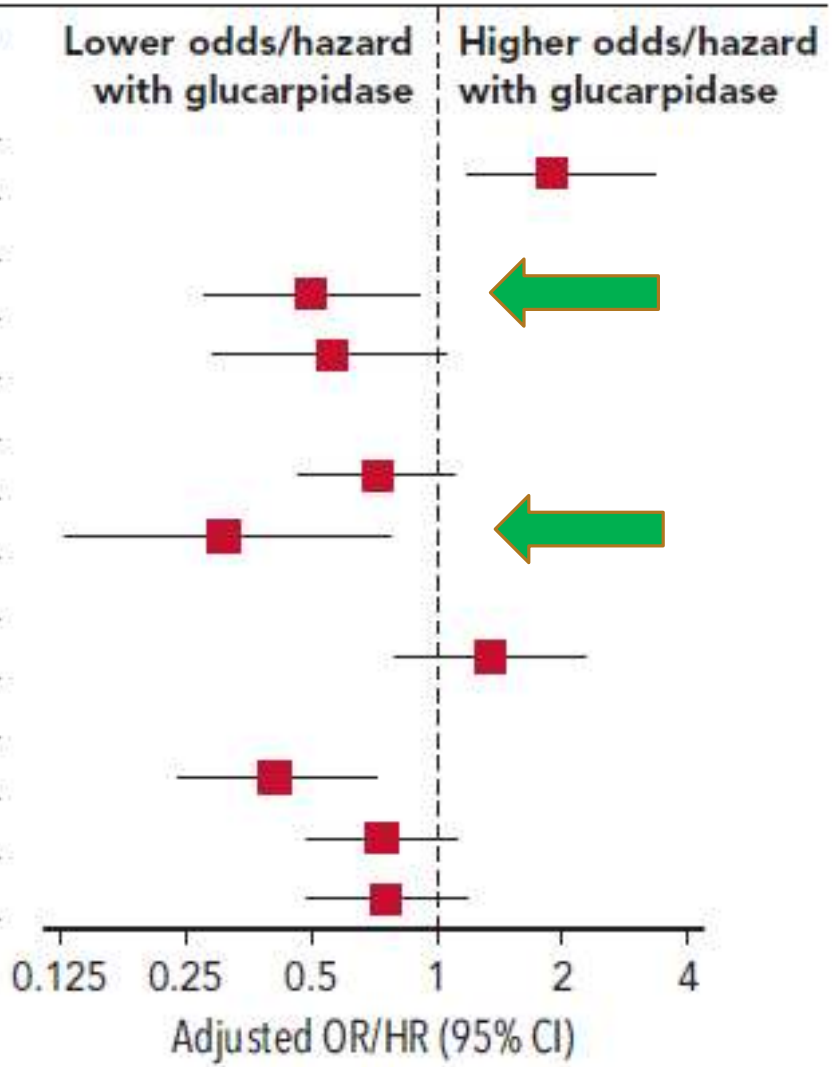


Time to kidney recovery
(secondary endpoint)



Secondary endpoints

Outcome	No. Events/ No. Patients (%)	Adjusted OR/HR[a] (95% CI)
Time-to-kidney recovery[a]	390/1645 (23.7)	1.88 (1.18–3.33)
Neutropenia on day 7		
Grade ≥2 (ANC <1500/mm^3)	266/1502 (17.7)	0.50 (0.28–0.91)
Grade ≥3 (ANC <1000/mm^3)	169/1573 (10.7)	0.56 (0.29–1.06)
Transaminitis on day 7		
Grade ≥1 (ALT ≥ULN)[b]	389/1167 (33.3)	0.72 (0.47–1.10)
Grade ≥2 (ALT ≥3x ULN)[c]	113/1167 (9.7)	0.31 (0.13–0.77)
Mucositis on day 7		
Any grade	177/1644 (10.8)	1.34 (0.80–2.26)
MTX Rechallenge		
Within 30 days following index MTX infusion	466/1645 (28.3)	0.41 (0.24–0.72)
Persistent kidney impairment or death at day 90	388/1349 (32.0)	0.74 (0.49–1.11)
Time-to-death[a]	232/1645 (14.1)	0.76 (0.49–1.18)



Glucarpidase dose optimisation

- Scott et al, Pediatr Blood Cancer 2015
  - 26 paediatric patients received glucarpidase 13 – 90 units/kg (42% of patients had <50 units/kg)
  - No statistically significant difference in MTX reduction or renal recovery with doses <50 units/kg versus >50 units/kg

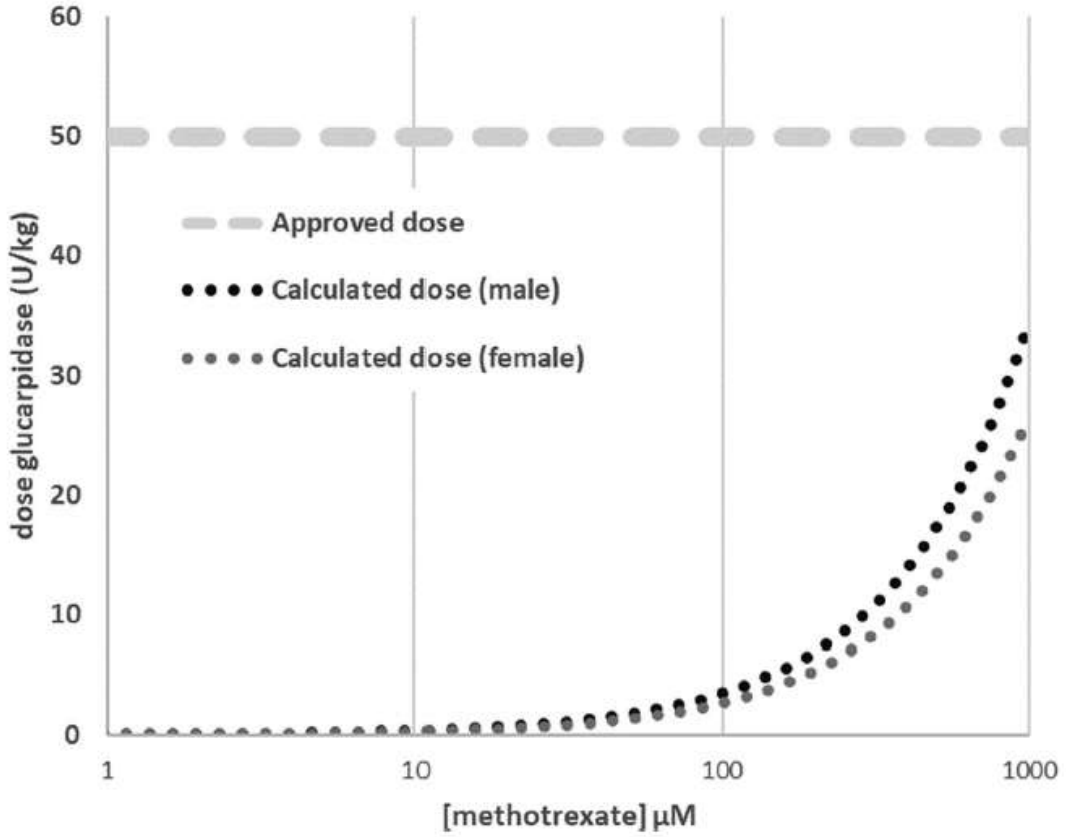
- Heuschkel et al, Cancer Chemother Pharmacol 2022
  - 7 patients (age range 19-71) received glucarpidase 25 units/kg
  - Within 1 day of glucarpidase, MTX plasma concentrations decreased by ≥ 97.7%

- Schaff et al, BMC Cancer 2022
  - 8 PCNSL patients received prophylactic glucarpidase 1000 or 2000 units, 24h after MTX dose
  - Glucarpidase didn't appear to compromise efficacy of HD MTX
  - >95% reduction in plasma MTX in 97.1% of patients receiving 2000 units, and 75% of patients receiving 1000 units glucarpidase

Methotrexate toxicity and glucarpidase: A call for dose optimization

Br J Clin Pharmacol, Koppen et al 2025

- One unit of glucarpidase cleaves 1 umol of methotrexate in 1 min at 37°C
  - In an 80kg male with a plasma volume of 2.8L and a methotrexate concentration of 100 umol/L – 280 units of glucarpidase would reduce the plasma MTX concentration to <1 umol/L in 1 min



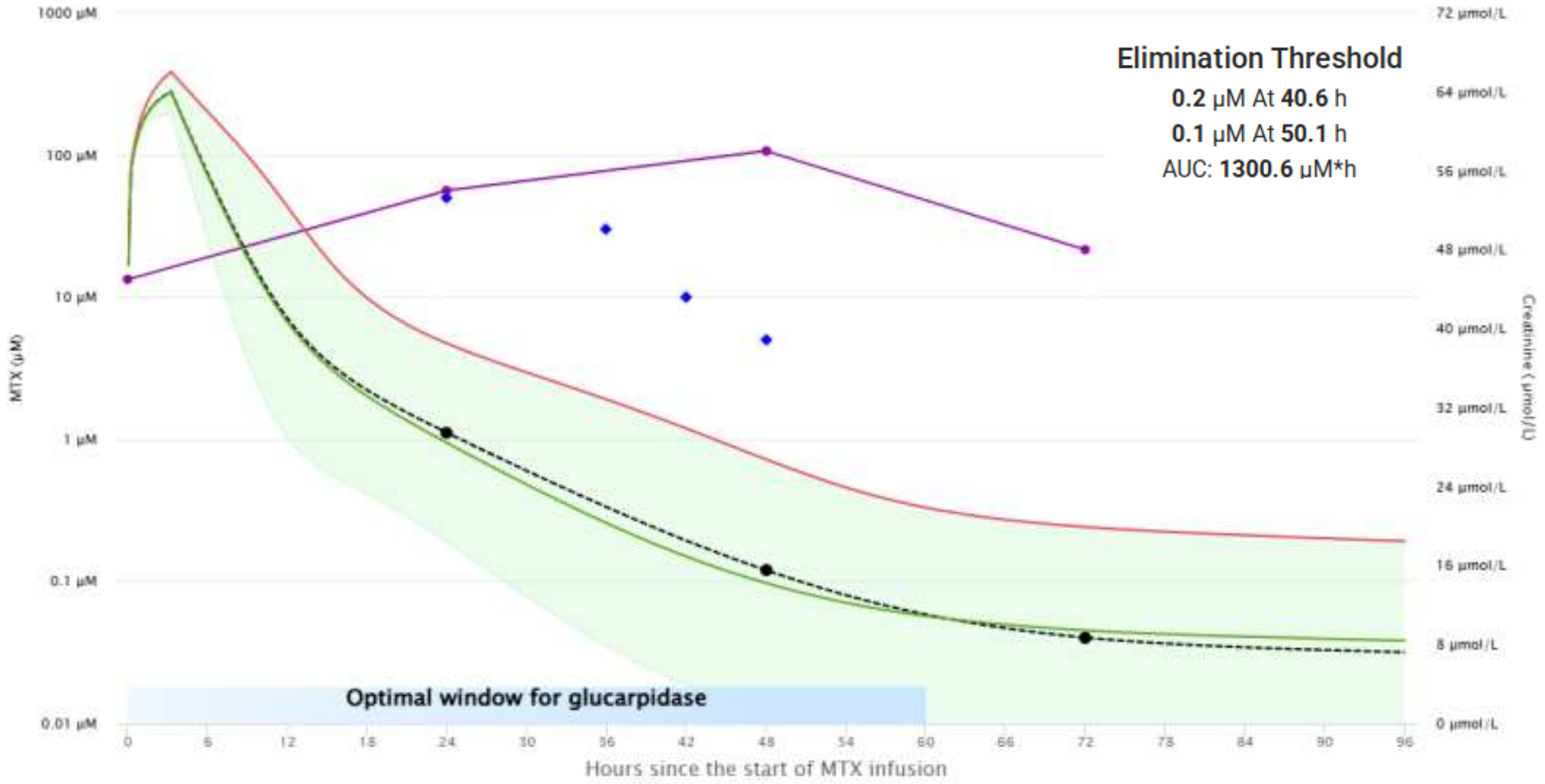
Methotrexate toxicity and glucarpidase: A call for dose optimization

Br J Clin Pharmacol, Koppen et al 2025

- Benefits of using lower glucarpidase doses
  - Lower cost
  - ?Increased efficacy of leucovorin
  - ?Less formation of glucarpidase neutralising antibodies
  - Fewer side effects

Methotrexate PK simulator

- https://mtxpk.org/
- PK model to display concentration vs time curve for an individual patient, overlaid on the population-predicted curve for that dose
- Input required
  - Age
  - Gender
  - Height
  - Weight
  - Dose + infusion time
  - ≥1 MTX level + creatinine



= Population mean	= Patient's concentration values	--- = Patient's predicted elimination	= Creatinine	= Consensus glucarpidase guideline threshholds

Barriers to access in NZ

Cost

Availability

Funding

Takeaway messages / food for thought

Methotrexate toxicity and delayed elimination can be life threatening

Hydration, urinary alkalinisation and leucovorin rescue are essential for the prevention and treatment of methotrexate toxicity

- TDM is important to guide prescription of these measures

Glucarpidase has proven effective in rapidly reducing plasma methotrexate levels, and beneficial in reducing toxicity associated with DME

- Important to understand the continued management of methotrexate toxicity and monitoring of levels post glucarpidase

?May be utility in holding stock of glucarpidase somewhere in NZ?

- ?Using fixed dosing may be more cost effective?
- ?MTX PK simulator may be helpful in guiding use of glucarpidase?

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