The Betsy Poon Pharmacy Education Series

2025 COG Spring Meeting

CHILDREN'S ONCOLOGY GROUP

Methotrexate Pharmacokinetics and Toxicity Management in Pediatric and Adolescent Young Adult Patients

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Conflicts of Interest/Disclosures

NAME	COMPANY	RELATIONSHIP
Jennifer Young	Nothing to disclose	

All relevant financial relationships listed for the individual have been mitigated by the ACPE accredited provider (St. Jude Continuing Pharmacy Education Program).

Learning Objectives

- Understand principles of high-dose methotrexate (HD MTX) and limitations of leucovorin rescue at certain methotrexate concentrations and timepoints
- Recognize modifiable and unmodifiable risk factors for delayed methotrexate elimination including genomic alterations
- Identify when to appropriately initiate glucarpidase in the setting of delayed methotrexate elimination
- Recommend leucovorin dosing post-glucarpidase administration
- Recall when mtxpk.org may add value when ascertaining delayed methotrexate elimination

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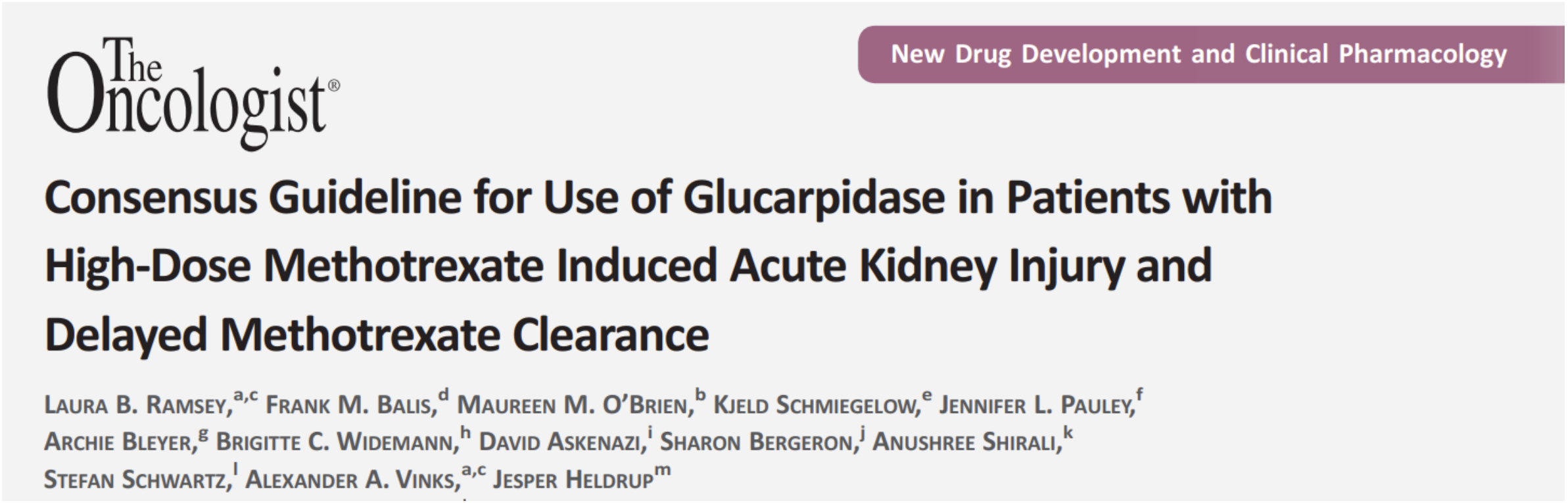
Off-label Use Disclosure: This session does not include a discussion of off-label treatment and investigational agents not approved by the FDA for use in the US.

Recommended Reading



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Ramsey LB. *Oncologist.* 2018; 23(1): 52-61.

Methotrexate Level Conversions

µM	µg/mL
120 µM	54.5 µg/mL
50 µM	22.7 µg/mL
30 µM	13.6 µg/mL
10 µM	4.54 µg/mL
5 µM	2.27 µg/mL

Concentrations in µM can be converted to µg/mL by dividing by 2.2005

Ramsey LB. *Oncologist.* 2018; 23(1): 52-61.

Section 1 – HD MTX and Leucovorin

Learning objective: Understand principles of high-dose methotrexate (HD MTX) and limitations of leucovorin rescue at certain methotrexate concentrations and timepoints

High-Dose Methotrexate (HD MTX)

Definition: Methotrexate ≥ 500 mg/m^2 per dose

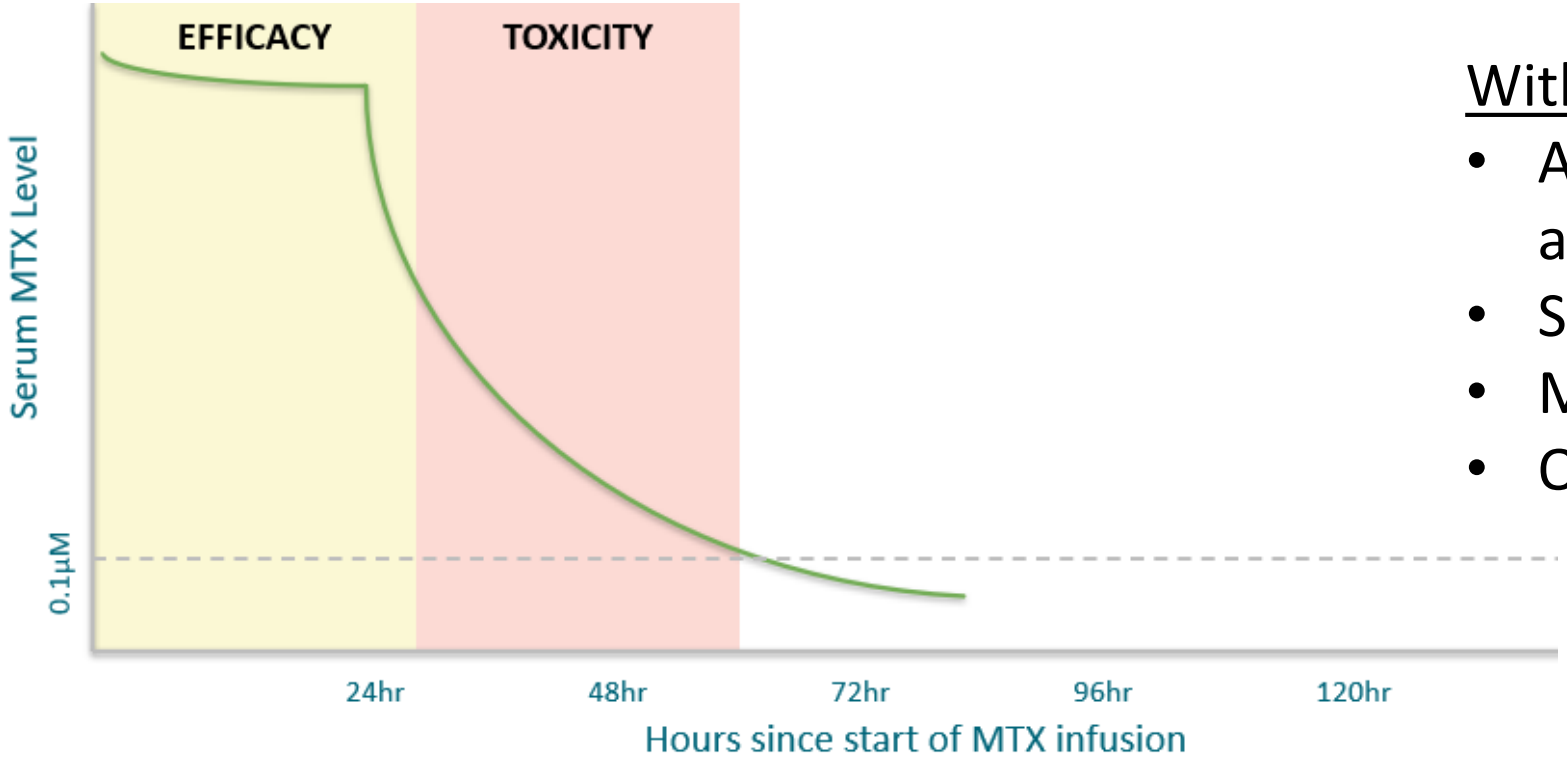
Required supportive care:

- Hyperhydration while maintaining euvolemia
- Urinary alkalinization for urine pH ≥ 7
- Leucovorin rescue
- Therapeutic drug monitoring
- Vigilance regarding drug-drug interactions

Ramsey LB. *Oncologist*. 2018;23(1):52-61.

High-Dose Methotrexate (HD MTX)

- Despite strict supportive care measures, significant interpatient + intrapatient variability exists

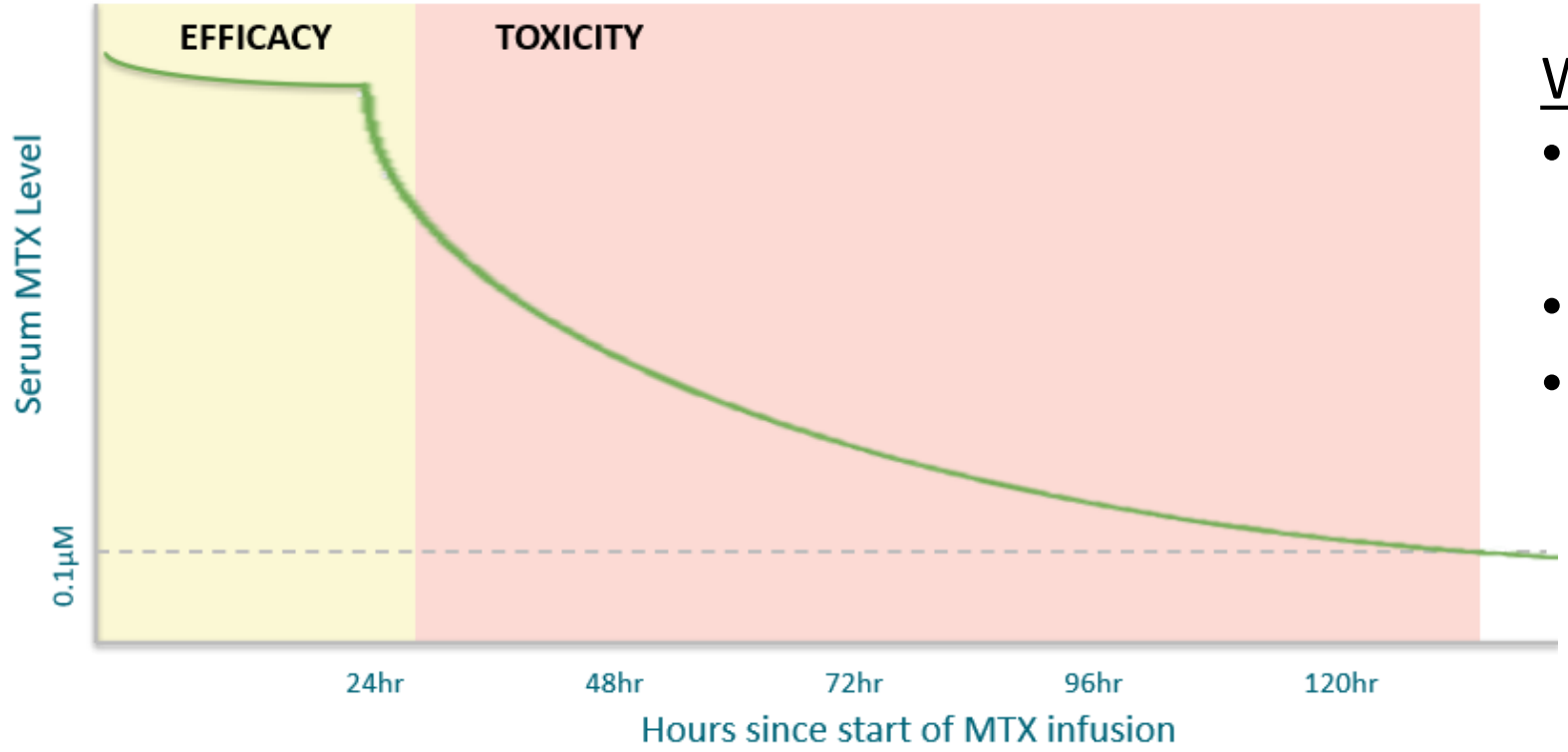


<u>With appropriate clearance</u>

- Adequate efficacy achieved
- Short clearance tail
- Minimal toxicity
- Often well tolerated

High-Dose Methotrexate (HD MTX)

- Despite strict supportive care measures, significant interpatient + intrapatient variability exists



<u>With delayed clearance</u>

- Adequate efficacy achieved
- Prolonged exposure
- Increased risk of toxicity

HD MTX-Induced AKI

MTX Administration	Rate of AKI
5 g/m^2 over 24 hours in children	0.5-1%
12 g/m^2 over 4 hours in children + AYA	1.8%
Adults	2-12%

Mechanisms of AKI –

- pH-dependent precipitation within the renal tubules
- Reduced renal perfusion with afferent arteriolar vasoconstriction
- Uptake of MTX into renal tubules with direct tubular toxicity

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Ramsey LB. *Oncologist*. 2018;23(1):52-61.

AKI = acute kidney injury
AYA = adolescent and young adult

Mechanism of Action

Role of folate (normal physiology):

- Enzyme cofactor mediating one-carbon unit transfer
- Involved in synthesis of pyrimidines, purines, amino acid metabolism, mitochondrial protein synthesis

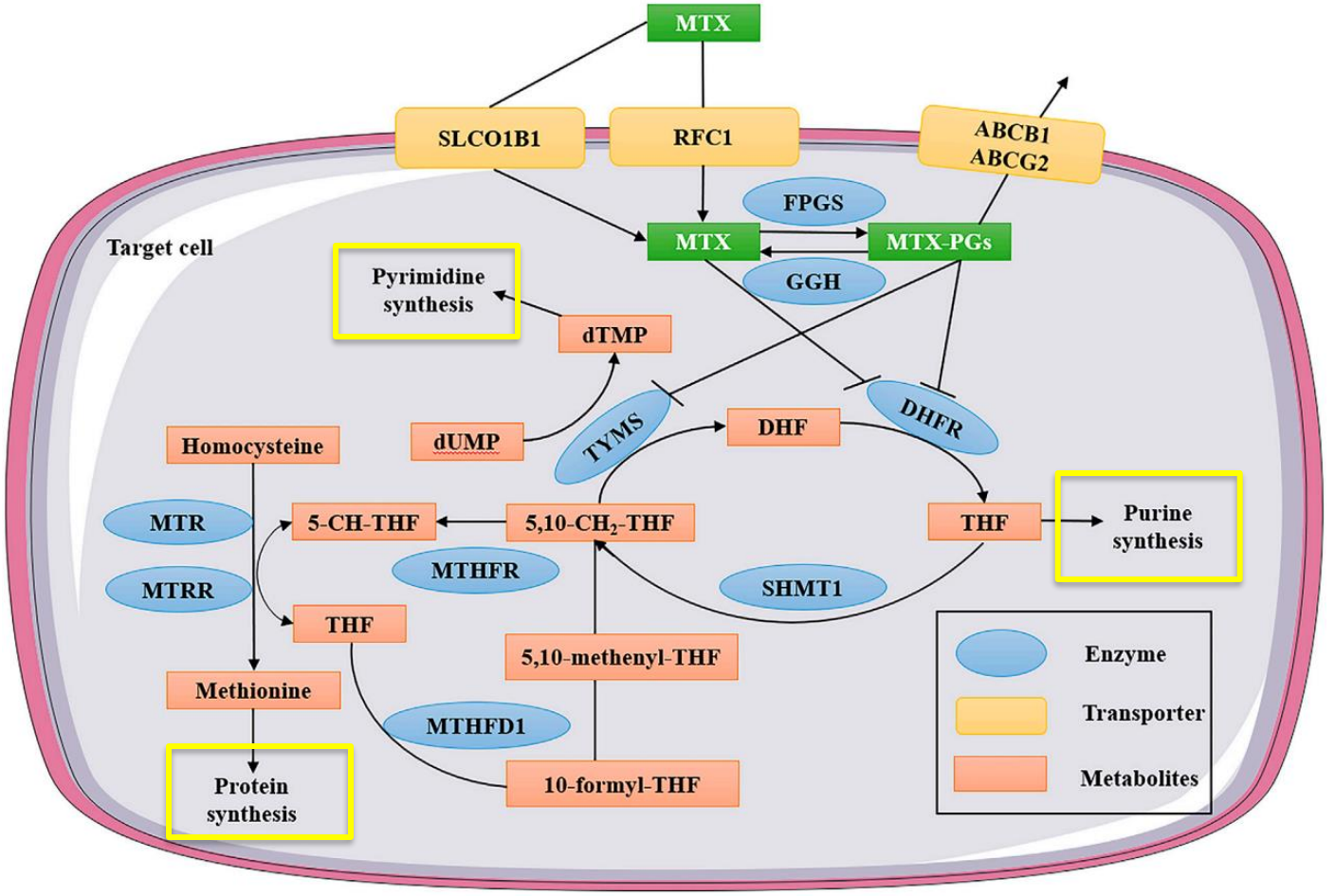
Role of methotrexate (folate antagonist):

- Inhibits dihydrofolate reductase (DHFR)

  → downstream inhibition of purine / pyrimidine synthesis, DNA synthesis and repair, and ultimately cell death

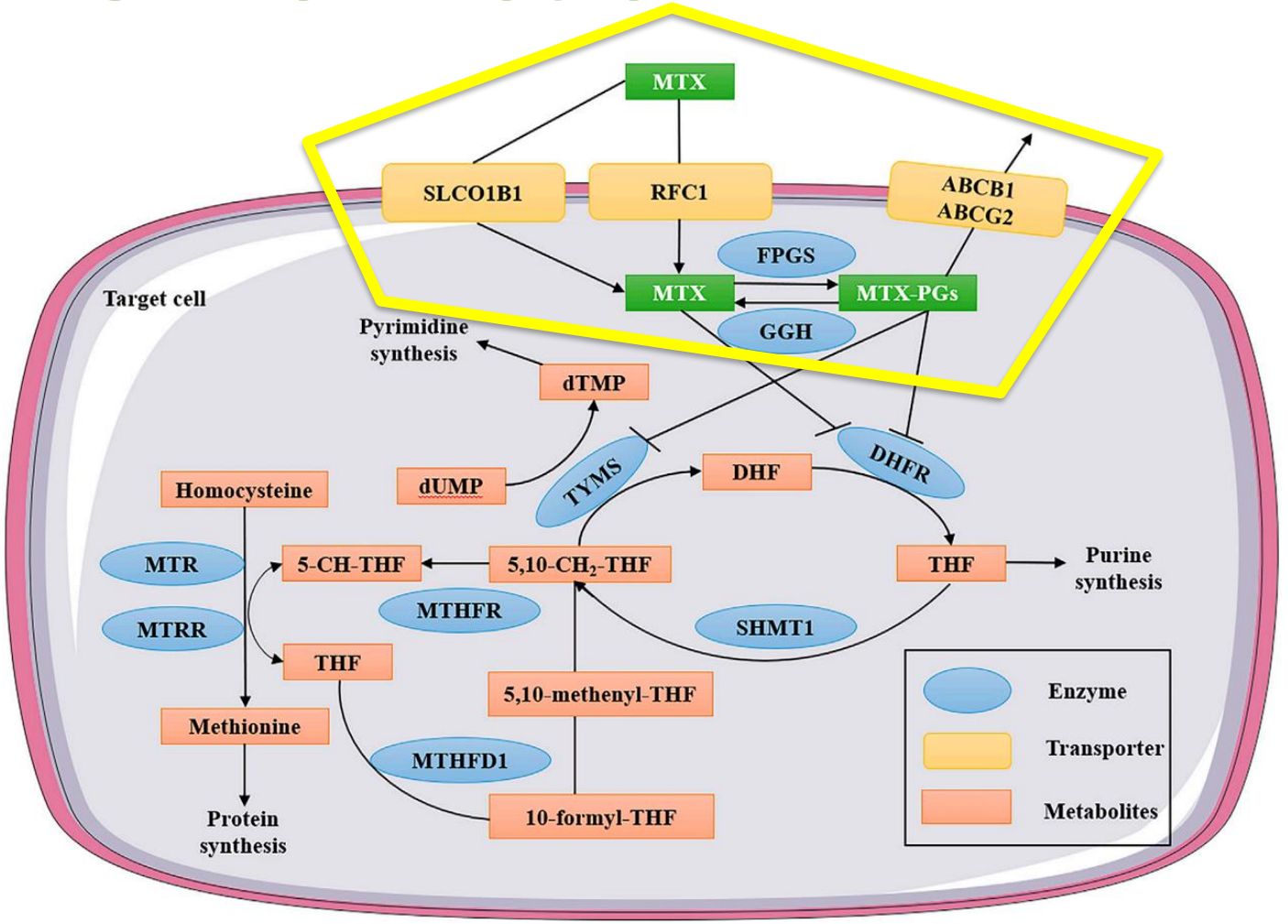
  -Methotrexate is cell-cycle specific to the synthesis phase

Mechanism of Action



Xu M, et al. Front Pharmacol. 2022; 13: 1003812.

Mechanism of Action



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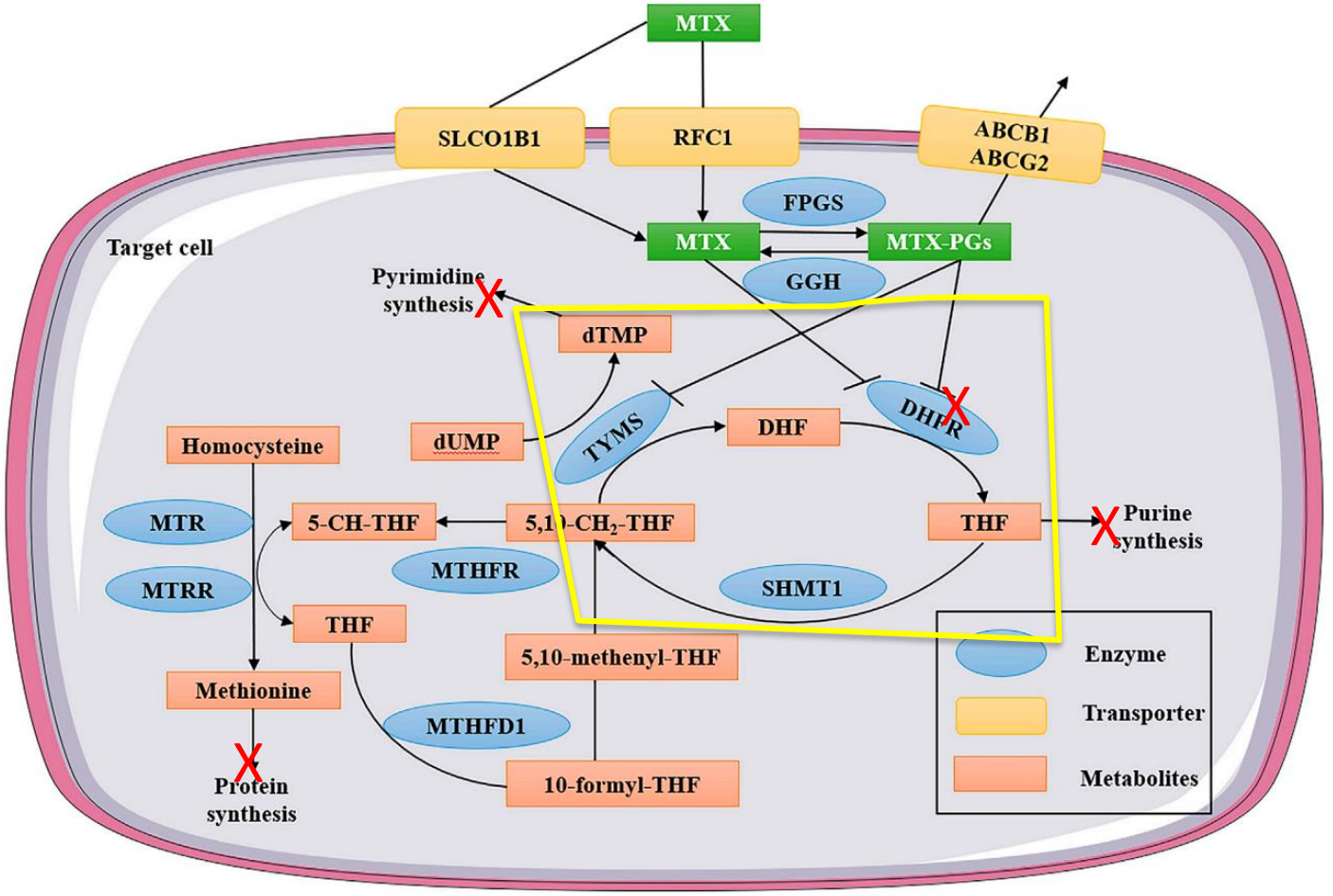
Xu M, et al. Front Pharmacol. 2022; 13: 1003812.

RFC1 = reduced folate carrier 1
SLCO1B1 = solute carrier organic anion transporter 1B1
MTX-PGs = methotrexate polyglutamates

Mechanism of Action



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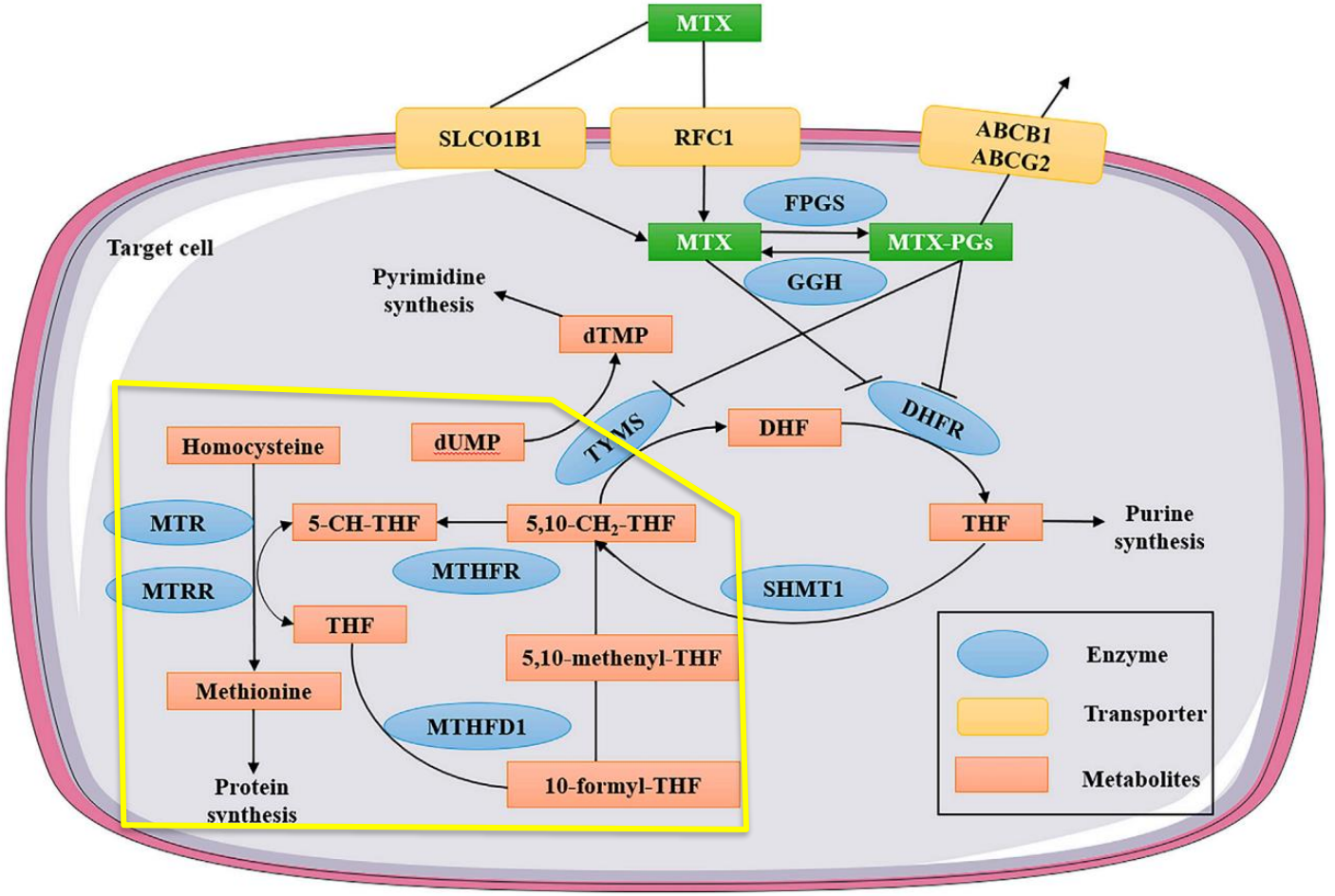
Xu M, et al. Front Pharmacol. 2022; 13: 1003812.

DHFR = dihydrofolate reductase
THF = tetrahydrofolates

Mechanism of Action



MTHFR = methylenetetrahydrofolate reductase
THF = tetrahydrofolate

Xu M, et al. Front Pharmacol. 2022; 13: 1003812.

Mechanism of Action Summary

Methotrexate is a folate antimetabolite, functioning as a competitive reversible inhibitor of dihydrofolate reductase (DHFR)

- Functions to deplete intracellular pools of tetrahydrofolates (THFs)
- THFs function as required cofactors for the synthesis of methionine, thymidine and purines → all required for DNA synthesis and repair

Ramsey LB. *Oncologist*. 2018;23(1):52-61.

Leucovorin Overview

Goal: "Rescue" healthy tissues by replacing tetrahydrofolates and restarting the folic acid cycle and enabling DNA synthesis + repair

Practical considerations:

- Upfront dosing: 10-15 mg/m^2 IV / PO Q6H
- Oral absorption is saturable, doses > 50 mg must be given IV
- Levoleucovorin may be used at 50% dosing

Leucovorin Dose	Bioavailability
25 mg	97%
50 mg	75%
100 mg	37%

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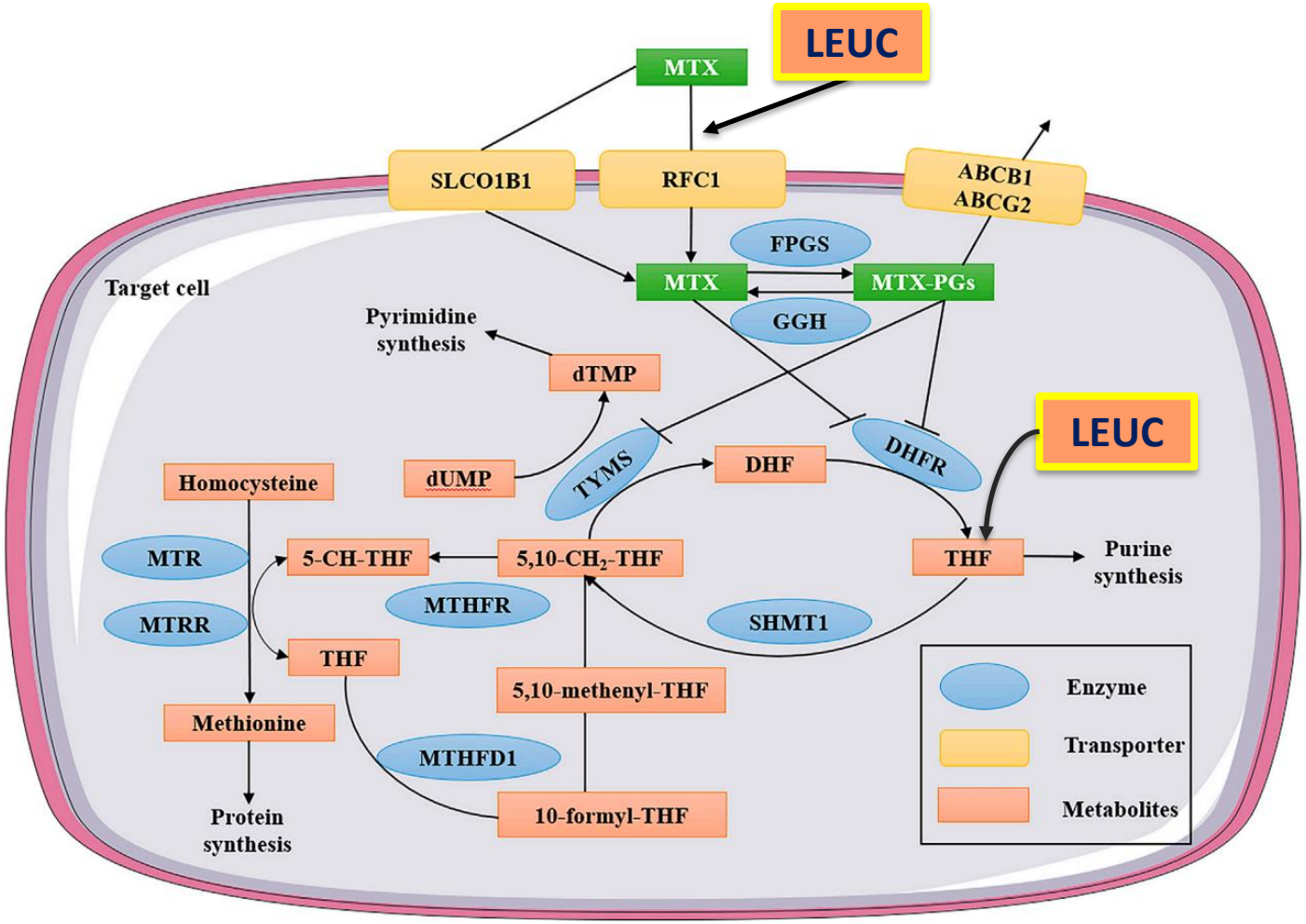
Source: COG Chemotherapy Administration Guidelines
Zelcher S, et al. Pediatr Blood Cancer. 2008; 50(6): 1176-1180.
Straw, et al. Cancer Research. 1984; 44: 3114-3119.

Role of Leucovorin Rescue



Leucovorin efficacy dependent on proper timing + proper concentrations

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LEUC = leucovorin

Xu M, et al. Front Pharmacol. 2022; 13: 1003812.

Limitations of Leucovorin - Competition

- Avoid competition during efficacy phase of HD MTX
- Once efficacy achieved, capitalize on competition to limit toxicity
  - In normal elimination, MTX levels decrease rapidly. Leucovorin adequately restarts downstream synthesis
  - In delayed elimination, leucovorin dosing needs to be escalated to adequately compete for cell entry and polyglutamation

Leucovorin Escalation Example – AOST0331

Excretion / Toxicity	24hr MTX Level	48hr MTX Level	72hr MTX Level	Leucovorin Dosing
Expected Excretion	≤ 10 µM	≤ 1 µM	≤ 0.1 µM	Maintain hydration + maintain initial leucovorin dosing
Grade 1 (Mild toxicity)	> 10 µM and < 50 µM and / or SCr ↑ 25-50%	≥ 1 µM and < 5 µM and / or SCr ↑ 25-50%	0.5-5 µM and / or SCr ↑ 25-50%	Increase hydration + maintain initial leucovorin dosing
Grade II (Moderate toxicity)	> 10 µM and < 50 µM and / or SCr ↑ 50-100%	≥ 1 µM and < 5 µM and / or SCr ↑ 50-100%	0.5-5 µM and / or SCr ↑ 50-100%	Increase hydration + **increase leucovorin to 15 mg/m² IV Q3H**
Grade III (Severe toxicity)	≥ 50 µM and < 500 µM or SCr ↑ > 100%	≥ 5 µM and < 100 µM or SCr ↑ > 100%	≥ 5 µM – 50 µM or SCr ↑ > 100%	Increase hydration + **increase leucovorin to 150 mg/m² IV Q3H**
Grade IV (Life threatening)	≥ 500µM	≥ 100µM	≥ 50µM	Increase hydration + **increase leucovorin to 1500 mg/m² IV Q6H (maximum dose 1500 mg)**

Always refer to your protocol for specific recommendations based on MTX levels and timepoints

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Algorithm source: AOST0331

Note: Leucovorin contains 0.004 mEq calcium per mg of leucovorin. Maximum rate of leucovorin is 160 mg per minute due to calcium content. Use caution with administration of escalated doses.

Limitations of Leucovorin – Over-Rescue

High leucovorin doses during high-dose methotrexate treatment may reduce the cure rate in childhood acute lymphoblastic leukemia

TVCh Skärby[1,2], H Anderson[3], J Heldrup[1], JA Kanerva[4], H Seidel[5] and K Schmiegelow[6], on behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO)

High leucovorin doses during HD MTX treatment may reduce the cure rate in childhood acute lymphoblastic leukemia	
Purpose:	To explore the relationship between time to relapse and serum methotrexate levels, MTX elimination time, and leucovorin dosing in children with acute lymphoblastic leukemia
Intervention:	N=445 HD MTX 5 g/m^2 (non-HR) or 8 g/m^2 (HR) over 24 hours +Leucovorin dose adjusted based on serum MTX concentration
Results:	High dose leucovorin related to higher risk for relapse • Doubling the leucovorin dose increased relapse risk by 22% (p=0.037) • High leucovorin doses correlated with high MTX levels at hours 24, 36, 42 and longer elimination time

No current consensus on optimal leucovorin approach

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Skarby TV. *Leukemia.* 2006; 20(11):1955-1962.

Section 2 – Risk Factors for Delayed Methotrexate Elimination

Learning objective: Recognized modifiable and unmodifiable risk factors for delayed methotrexate elimination including genomic alterations

ARS Question #1

Which of the following is a modifiable risk factor for delayed methotrexate elimination?

A. Down Syndrome
B. SLCO1B1 polymorphisms
C. Concurrent dasatinib
D. Obesity

Delayed Methotrexate Elimination

- Risk factors:
  - Drug-drug interactions
  - Concurrent nephrotoxics
  - Third spacing
  - Inadequate urinary alkalinization
  - Pharmacogenomics
  - Hypoalbuminemia

HD MTX – Drug-Drug Interactions

Agent	Mechanism	Management
Sulfamethoxazole / Trimethoprim	SMX displaces MTX from serum proteins and competes for renal tubular excretion TMP is a folate inhibitor	Contraindicated
Proton Pump Inhibitors	Inhibit renal tubular excretion of MTX	Contraindicated
Penicillins	Compete for renal tubular excretion	Contraindicated
Fluoroquinolones	Inhibit tubular absorption of MTX	Contraindicated
Imatinib / Dasatinib[1]	Undefined, possibly mediated by effects at SLCO1B1	Hold TKI 24hr prior through MTX clearance
Vitamin C	Inhibit renal tubular excretion of MTX, acidifies urine	Contraindicated
NSAIDs	Displaces MTX from serum proteins; decreases renal perfusion	Contraindicated
Salicylates	Displaces MTX from serum proteins, competes for renal tubular secretion, inhibits prostaglandins, decreases renal perfusion	Contraindicated, salicylates should be held 7 days prior to MTX through MTX clearance
Phenytoin / Fosphenytoin	Displaces MTX from serum proteins	Contraindicated
Probenecid	Displaces MTX from serum proteins, inhibits renal tubular transport	Contraindicated
Nephrotoxic Agents	These agents do not directly inhibit MTX clearance, but may impair renal function	Avoid when possible

1. Ramsey LB. *Pediatr Blood Cancer*. 2019;66(5):e27618.

Third-Spacing

- Methotrexate distributes into third space areas (ascites, effusions, edema)
  - Slower clearance from these sites, prolonged elimination

Challenges:

- Impact of hyperhydration
- Goal to keep patients net even

Inadequate Urinary Alkalinization

- Methotrexate solubility increases with increasing pH of the urine
  - pH 6 to 7 yields 10-fold increase in MTX solubility

Ramsey LB. *Oncologist*. 2018;23(1):52-61.

Hypoalbuminemia

- MTX is 50-60% albumin-bound
  - Low serum albumin → increased free MTX
  - Increased free MTX → increased diffusion into peripheral compartments (liver, target tissues, less vascular tissues)
- Hypoalbuminemia affects oncotic pressure, contributing to risk of third-spacing

- Challenging in setting of concurrent asparaginase exposure and asparaginase-induced hypoalbuminemia

Hypoalbuminemia

Study	Albumin Threshold	Association with MTX Outcomes	Additional Info
Reiss, et al. Single center	Albumin ≤ 3.4 g/dL	Longer clearance in low albumin group (96hr vs 72hr, p=0.004)	Reported confounders - Increased rates of third spacing, concurrent nephrotoxics in hypoalbuminemia group
Khera S, et al.	Albumin ≤ 3.5 g/dL	Increased rates of MTX-induced nephrotoxicity with low albumin group (OR 4.71)	
Barakat, et al.	Albumin ≤ 3.5 g/dL	Increased myelosuppression, febrile neutropenia and mucositis in low albumin group	Did not report kinetics
Mirza, et al. Single center	Albumin ≤ 3.5 g/dL	No association	
Taylor, et al. Multicenter	Albumin < 2.5 g/dL	Slower MTX clearance by 2% in severe hypoalbuminemia	

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Barakat S. *J Egypt Natl Canc Inst*. 2022; 34(1): 17.
Mirza MA. *Int J Health Sci*. 2023; 17(2): 3-9.
Taylor ZL. *Clin Transl Sci*. 2023; 16(11): 2130-2143.
Reiss SN. *Ann Hematol*. 2016; 95(12): 2009-2015.
Khera S. *Pediatr Blood Cancer*. 2022; 69(9):e29738
.

Pharmacogenomics

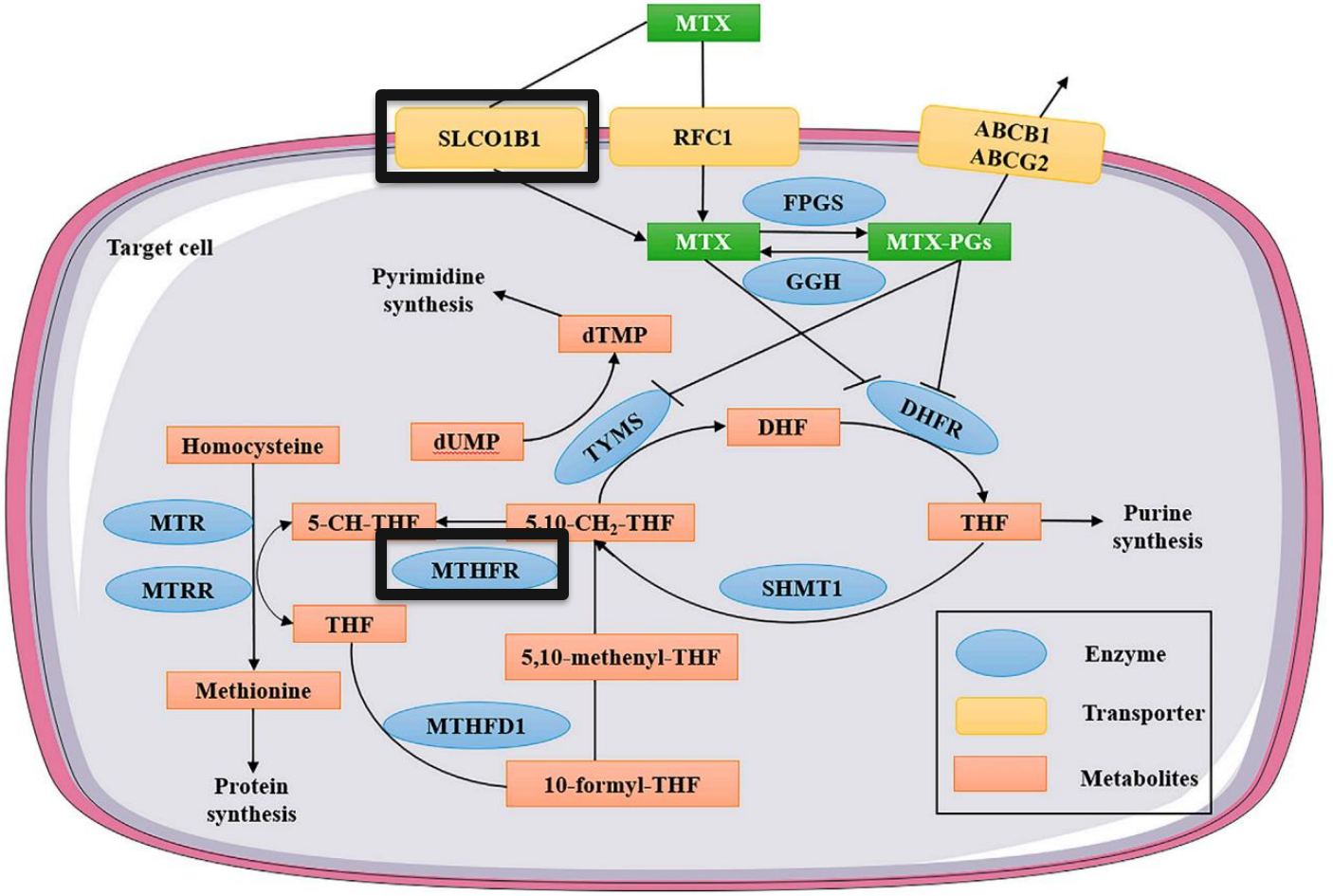
- Significant research, somewhat conflicting, currently insufficient for adjusting management

- Genes of interest:
  - Transport / Efflux genes: SLCO1B1
  - Folate pathway genes: MTHFR

No current actionable data. Watch CPIC (CPICPGX.org) for future guidance.

SLCO1B1 = solute carrier organic anion transporter 1B1
MTHFR = methylenetetrahydrofolate reductase
CPIC = Clinical Pharmacogenetics Implementation Consortium

Mechanism of Action



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Xu M, et al. Front Pharmacol. 2022; 13: 1003812.

SLCO1B1 = solute carrier organic anion transporter 1B1
MTHFR = methylenetetrahydrofolate reductase

Pharmacogenomics – SLCO1B1

- SLCO1B1 - encodes an organic anion-transporting polypeptide 1B1 (OATP1B1)
  - Transporter expressed primarily in the liver, responsible for hepatic uptake of methotrexate
  - Enterohepatic circulation plays a substantial role in MTX pharmacokinetics

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SLCO1B1 = solute carrier organic anion transporter 1B1

Taylor ZL. *Cancers*. 2021;13(11):2837.

SLCO1B1

Review

Systematic Review of Pharmacogenetic Factors That Influence High-Dose Methotrexate Pharmacokinetics in Pediatric Malignancies

Zachary L. Taylor [1,2,3], Jesper Vang [4,5], Elixabet Lopez-Lopez [6,7], Natanja Oosterom [8], Torben Mikkelsen [9] and Laura B. Ramsey [2,3,*]

Systematic Review of Pharmacogenetic Factors that Influence High-Dose Methotrexate Pharmacokinetics in Pediatric Malignancies	
Purpose:	Systematic review; to provide a comprehensive overview of available pharmacogenetic factors that influence HD MTX pharmacokinetics in pediatric malignancies
Scope:	Identified 58 studies, inclusive of 9695 patients 3 genome-wide association studies + 55 candidate gene studies
Findings:	SLCO1B1 is the only gene that reliably demonstrates an effect on MTX pharmacokinetics • *5 and *15 alleles associated with reduced MTX clearance due to reduced transporter expression • *14 and *35 alleles associated with increased MTX clearance

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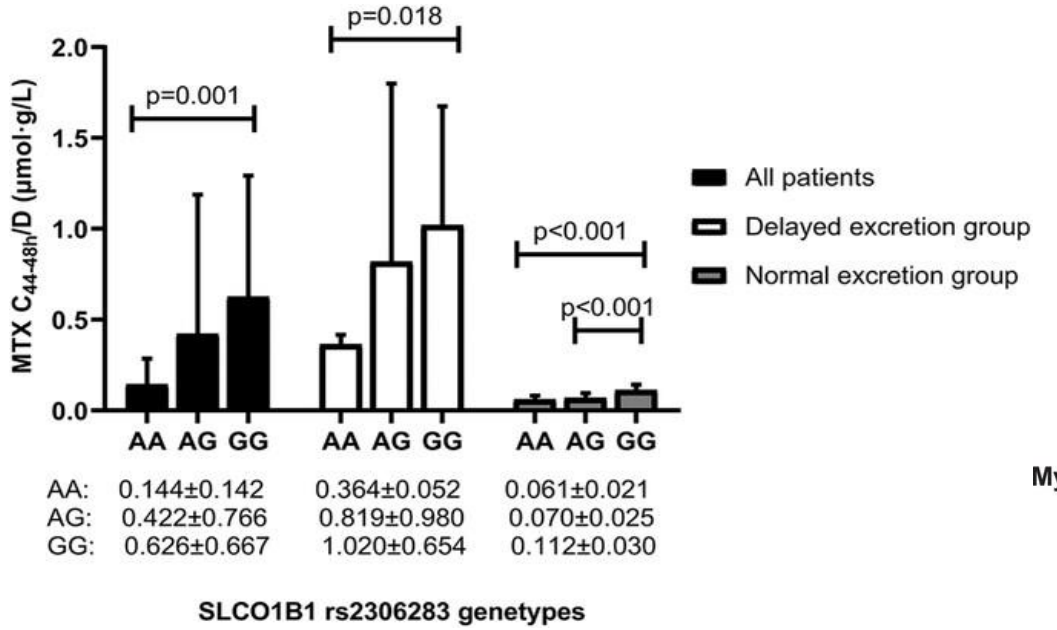
SLCO1B1 = solute carrier organic anion transporter 1B1

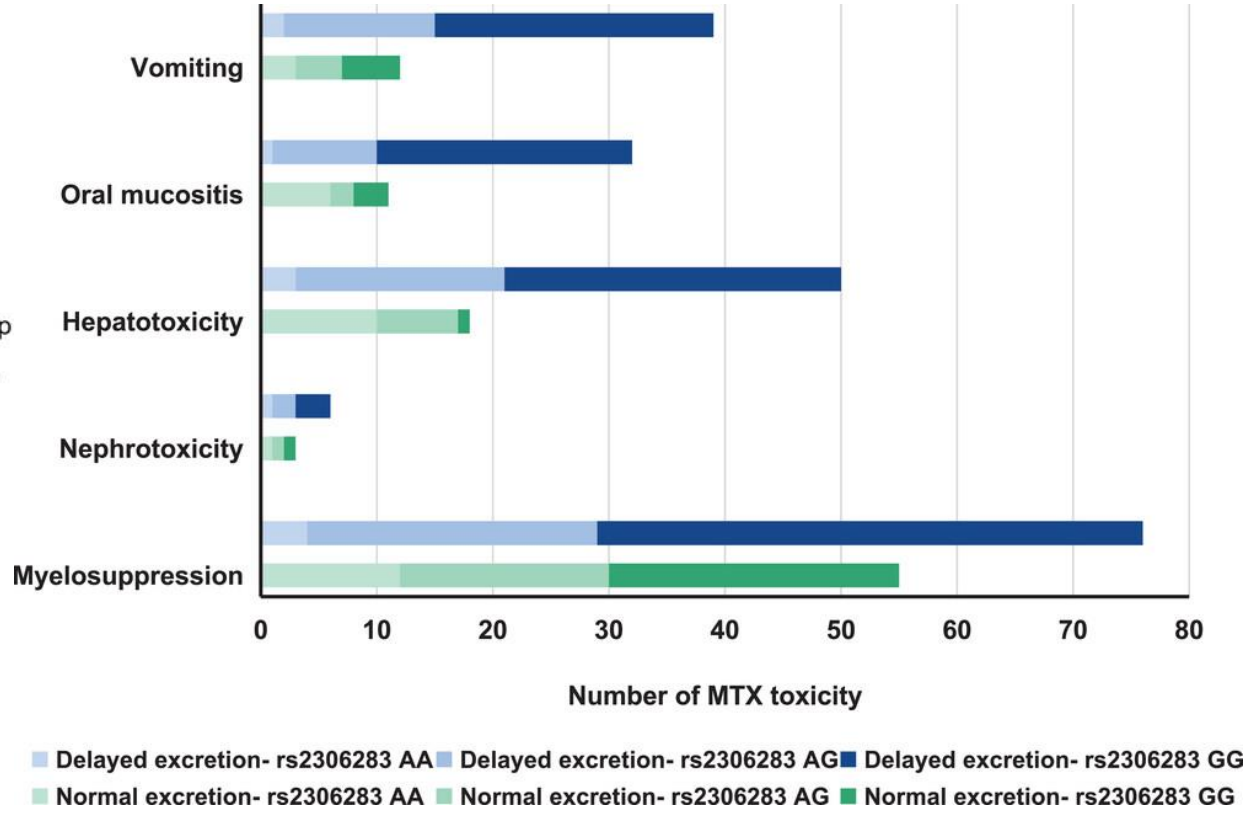
Taylor ZL. *Cancers*. 2021;13(11):2837.

SLCO1B1

rs2306283

AA	Homozygous wild-type
AG	Heterozygous mutation
GG	Homozygous mutation





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SLCO1B1 = solute carrier organic anion transporter 1B1

Cheng Y. *Pediatr Blood Cancer*. 2021; 68(5): e28858.

MTHFR

CC	Homozygous wild-type
CT	Heterozygous mutation
TT	Homozygous mutation

- Critical enzyme for folate metabolism. Genetic mutations cause decreased enzyme activity, leading to altered folate metabolism and increased homocysteine levels
- Conflicting data -
  - C677T single-nucleotide polymorphism (CT or TT genotype) may be associated with increased MTX levels and decreased MTX clearance
  - TT genotype may be associated with increased risk of hematologic toxicity and mucositis

Song Z. *Br J Clin Pharmacol*. 2022; 88(5): 2456-2472.
Taylor ZL. *Cancers*. 2021;13(11):2837.

MTHFR = methylenetetrahydrofolate reductase

Section 3 – Glucarpidase

Learning objectives:

-Identify when to appropriately initiate glucarpidase in the setting of delayed methotrexate elimination

-Recommend leucovorin dosing post-glucarpidase administration

ARS Question #2

Audience Poll – Have you given glucarpidase to a patient?

A. Yes

B. No

Glucarpidase

Mechanism of Action:

- Exogenous enzyme, rapidly hydrolyzes MTX into two inactive metabolites (DAMPA + glutamate) that are eliminated via renal and non-renal pathways
  - Reduces MTX concentrations by > 90% within 15 minutes

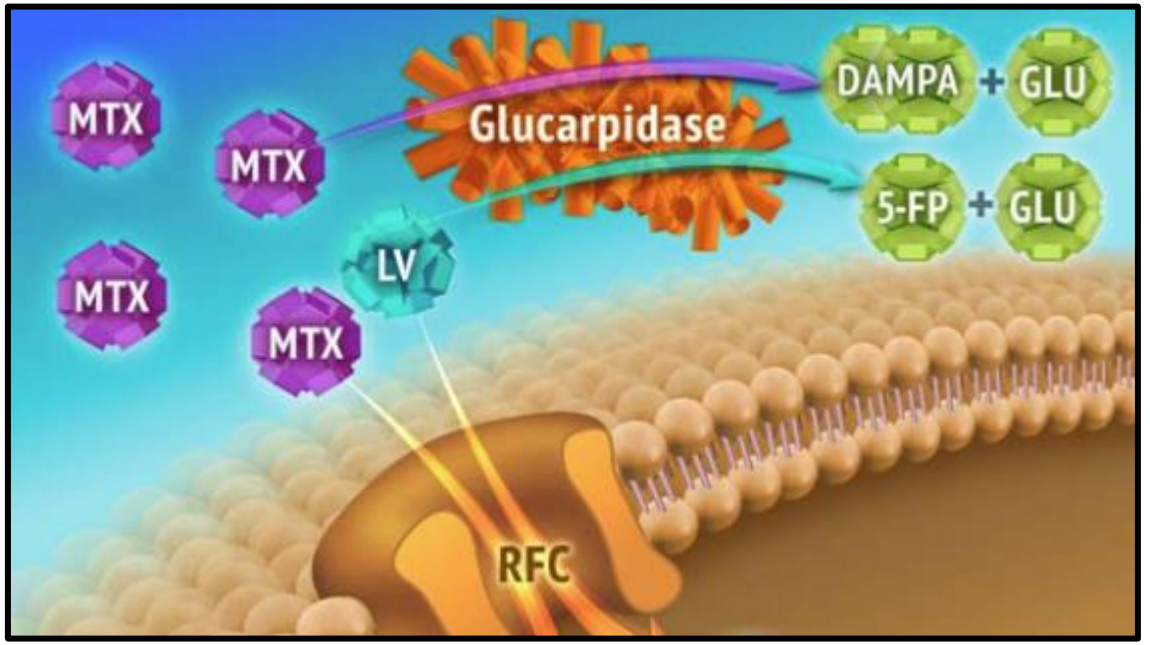

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Image source: Ramsey LB. *Oncologist*. 2018;23(1):52-61.

DAMPA = 4-deoxy-4-amino-N10-methylpteroic acid

Glucarpidase – FDA Labeling

Indication: Indicated for the treatment of toxic plasma methotrexate concentrations (>1 μM/L) in patients with delayed methotrexate clearance due to impaired renal function.

Limitations of use: Not indicated for use in patients who exhibit the expected clearance of methotrexate or those with normal or mildly impaired renal function because of the potential risk of subtherapeutic exposure to methotrexate.

Glucarpidase package insert. BTG International, Inc. Brentwood, TN. Accessed 12/2024.

Glucarpidase – FDA Labeling

Challenges with interpreting / applying labeled indication:

- Labeling does not define time points
- Labeling does not define impaired renal function
- How to calculate standard deviations in real time?
- How to know the specific curve for the HD MTX dose given?

ARS Question #3

MP is a 5-year-old with B-ALL receiving HD MTX 5 g/m^2 over 24 hours per AALL1732. Which of the following methotrexate levels would warrant consideration of glucarpidase administration?

A. 24hr level = 150 µM

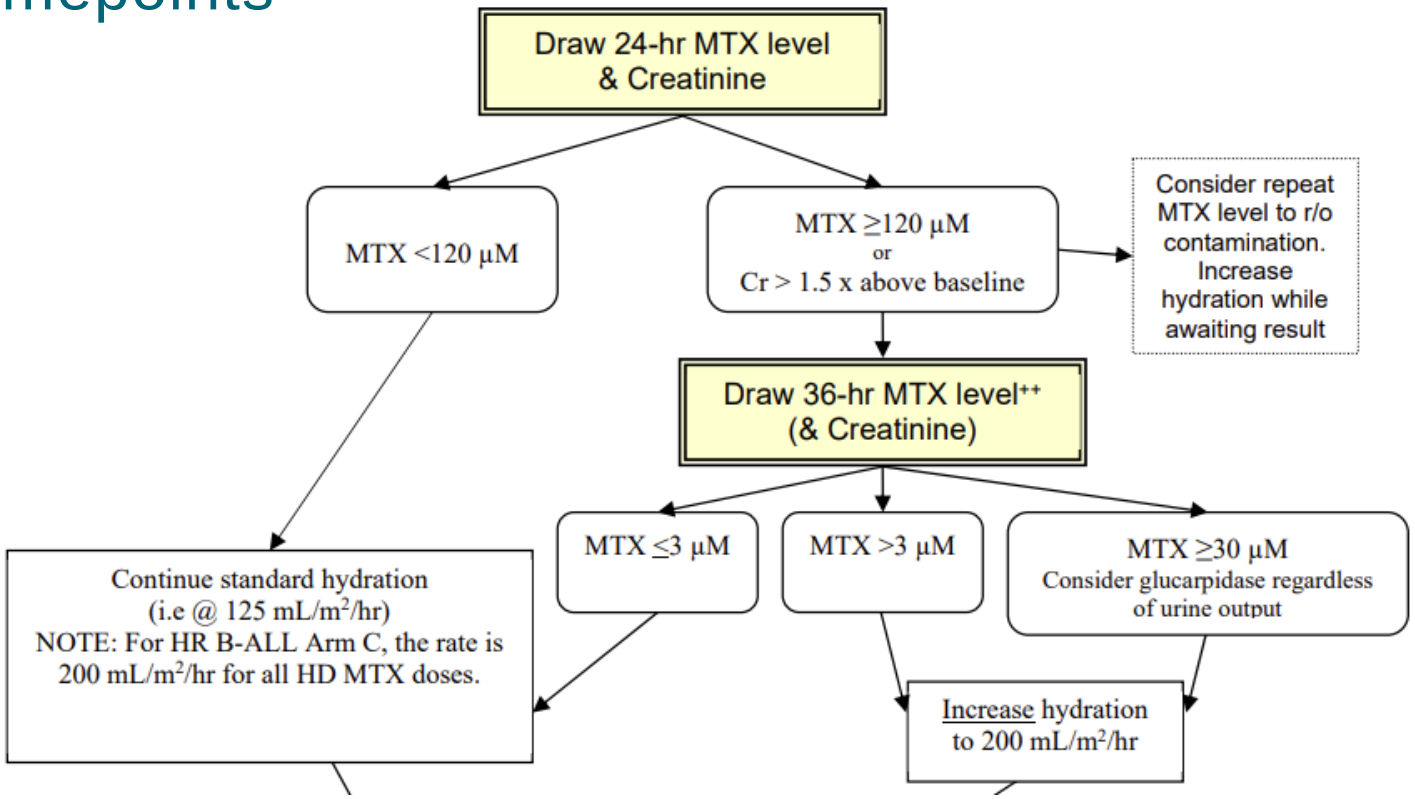
B. 36hr level = 25 µM

C. 42hr level = 12 µM

D. 48hr level = 0.9 µM

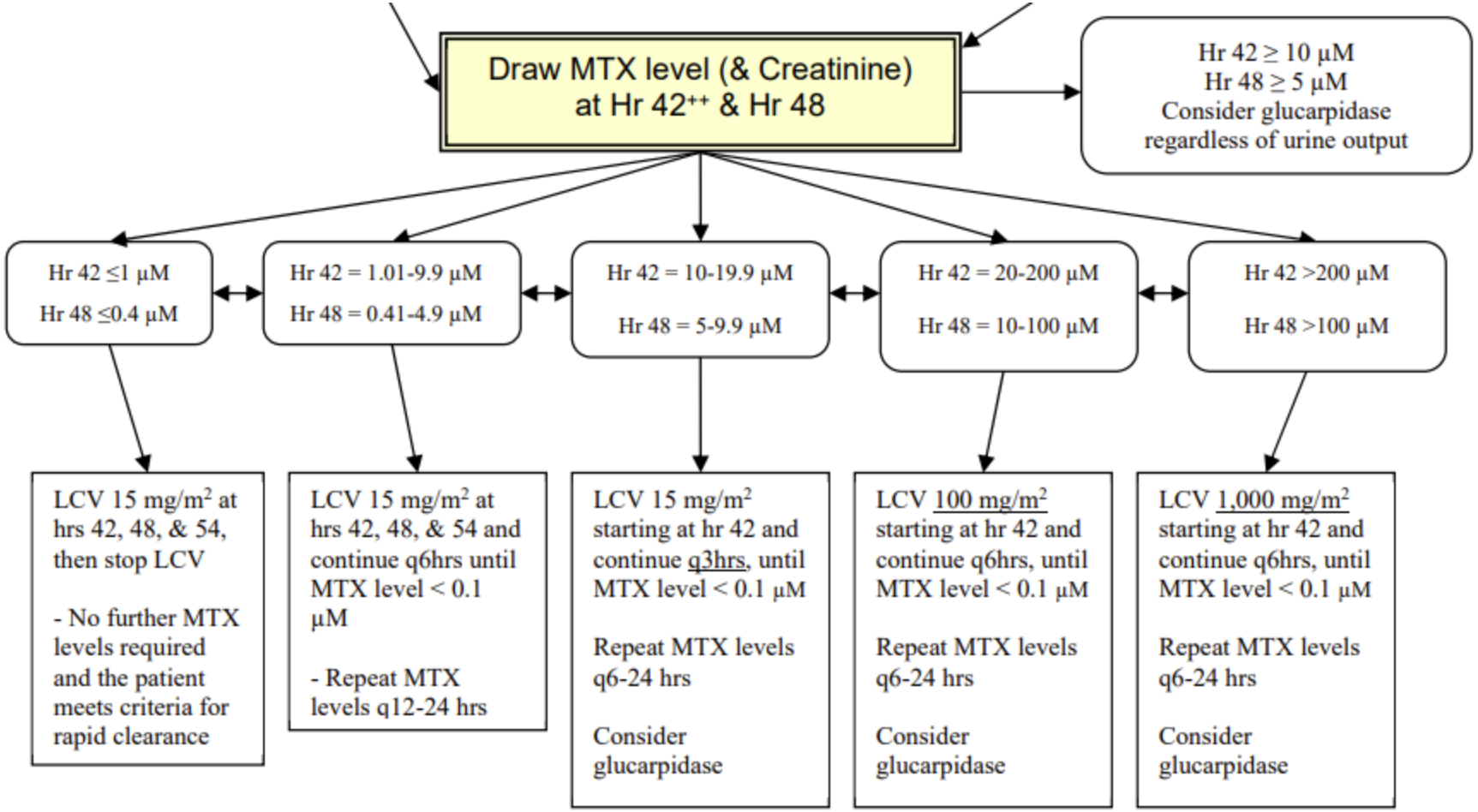
Methotrexate Therapeutic Drug Monitoring

- Always refer to your protocol for specific recommendations based on MTX levels and timepoints



Algorithm source: AALL1732

Methotrexate Therapeutic Drug Monitoring



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Algorithm source: AALL1732

Consensus Guideline Recommendations

Thresholds for Glucarpidase Administration in Setting of Rising Serum Creatinine				
	24 hour	36 hour	42 hour	48 hour
HD MTX ≤ 1 g/m^2 over 36-42hr	-	-	-	> 5 µM
MTX 1-8 g/m^2 over 24hr	*	> 30 µM	> 10 µM	> 5 µM
MTX 8-12 g/m^2 over ≤ 6hr	> 50 µM	> 30 µM	> 10 µM	> 5 µM

*If 24hr value > 120 µM, obtain 36hr level

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Ramsey LB. *Oncologist*. 2018;23(1):52-61.

Glucarpidase Dosing

Labeled dosing: 50 units/kg x 1

*COG protocols do not define dosing

Medication	Formulation	AWP Price	Price per Unit	Cost per Dose*
Glucarpidase	1,000 unit vial	$49,408.80 per vial	$49.41 per unit	20 kg patient: $49,410 40 kg patient: $98,820 60 kg patient: $148,320 80 kg patient: $197,640

*Dosing 50 units / kg x 1

Some institutions may choose to stock glucarpidase
If not, emergency expedited orders available from manufacturer same day

Glucarpidase package insert. BTG International, Inc. Brentwood, TN. Accessed 12/2024.

Utility of Capped Glucarpidase Dosing?

Small volume of distribution, glucarpidase remains within the blood

Comparable Efficacy With Varying Dosages of Glucarpidase in Pediatric Oncology Patients

Jeffrey R. Scott, PharmD[1,*], Yinmei Zhou, MS[2], Cheng Cheng, PhD[2], Deborah A. Ward, PharmD[1], Hope D. Swanson, PharmD[1], Alejandro R. Molinelli, PhD[1], Clinton F. Stewart,

Comparable Efficacy with Varying Doses of Glucarpidase in Pediatric Oncology Patients	
Purpose:	Explore relationship between glucarpidase dose and patient outcomes in pediatric oncology patients
Scope:	Retrospective, single institution St. Jude
Findings:	• 42% of patients received < 50 units/kg • 5 patients received a capped dose of 2,000 units (range 13.7-39.9 units/kg) • Similar reduction in MTX concentration in patients receiving < 50 units/kg versus >/= 50 units/kg (both 99.4% reduction)
Conclusion:	Efficacy of glucarpidase is not dose-dependent

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Scott JR, et al. Pediatr Blood Cancer. 2015; 62(9): 1518-1522.

ARS Question #4

MP's methotrexate levels are as shown below. In consultation with you as the clinical pharmacist, the team would like to administer glucarpidase in response to his 36hr level. What do you recommend?

24hr level	220 µM	Action: Recheck + increase hydration rate
24hr level (recheck)	211 µM	Action: Check 36hr level
36hr level	45 µM	?

A. Order glucarpidase STAT and administer once available
B. Order glucarpidase STAT and administer 2 hours before or after leucovorin
C. Recommend waiting until 42hr MTX level results
D. Hold further leucovorin and switch to glucarpidase

Glucarpidase Pearls

- When indicated, glucarpidase should be initiated within 48-60 hours after the start of HD MTX
  - Beyond this point life-threatening toxicities may not be preventable

- All supportive care (leucovorin, hyperhydration, alkalinization) should be continued post-glucarpidase administration
  - Continue escalated leucovorin dosing per protocol
  - Leucovorin acts as a substrate for glucarpidase. Do not give a glucarpidase dose within 2 hours (before or after) of leucovorin.

Glucarpidase Pearls

Glucarpidase: MTX → DAMPA + Glutamate

Know how your institution measures MTX levels

- Immunoassay method: Reports MTX + DAMPA together
- High-performance liquid chromatography: Accurately measures MTX without DAMPA interference

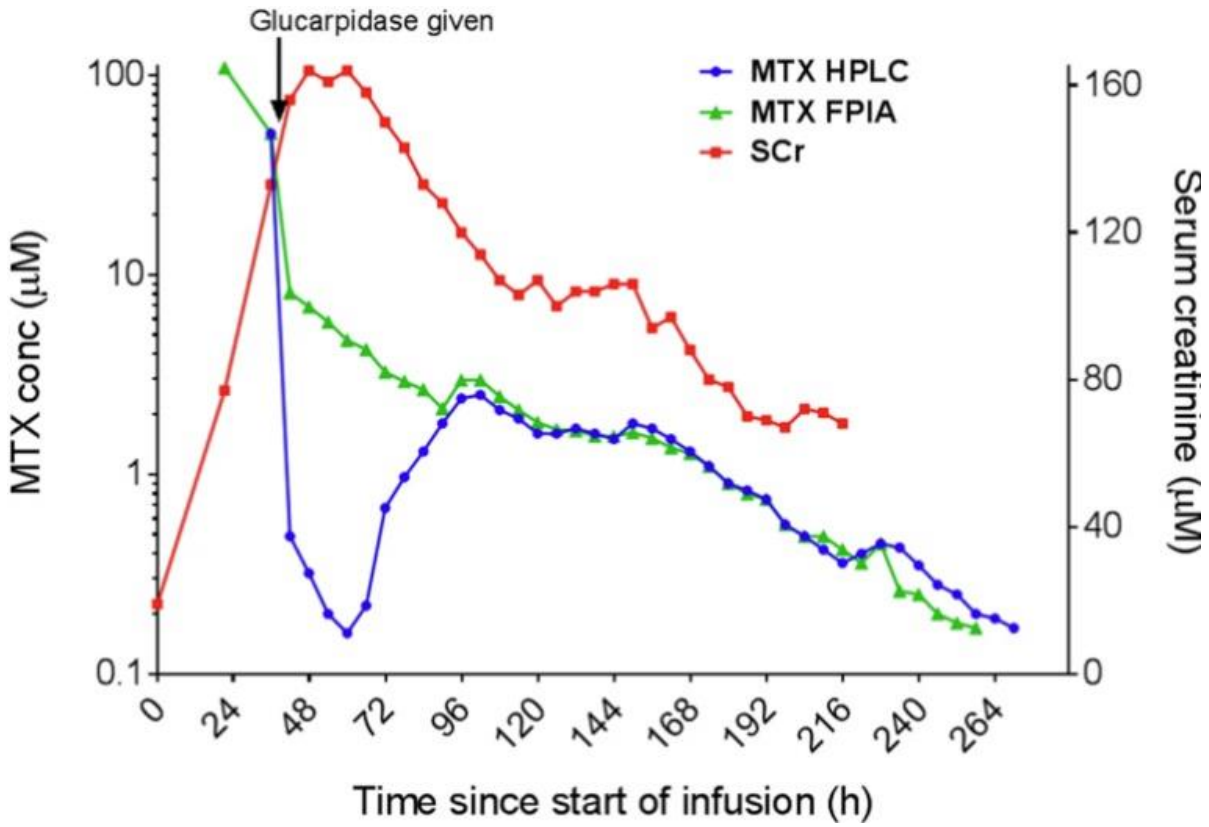
Glucarpidase Pearls

Glucarpidase: MTX → DAMPA + Glutamate

Glucarpidase only cleaves MTX within the bloodstream

- No impact on MTX within cells
- No impact on MTX in third-space areas
- No impact of MTX within urinary collecting system

Following glucarpidase effect, MTX from these reservoirs will re-enter the blood stream following the activity of glucarpidase and may cause MTX level to rebound



CHILDREN'S ONCOLOGY GROUP

Ramsey LB. *Oncologist*. 2018;23(1):52-61.

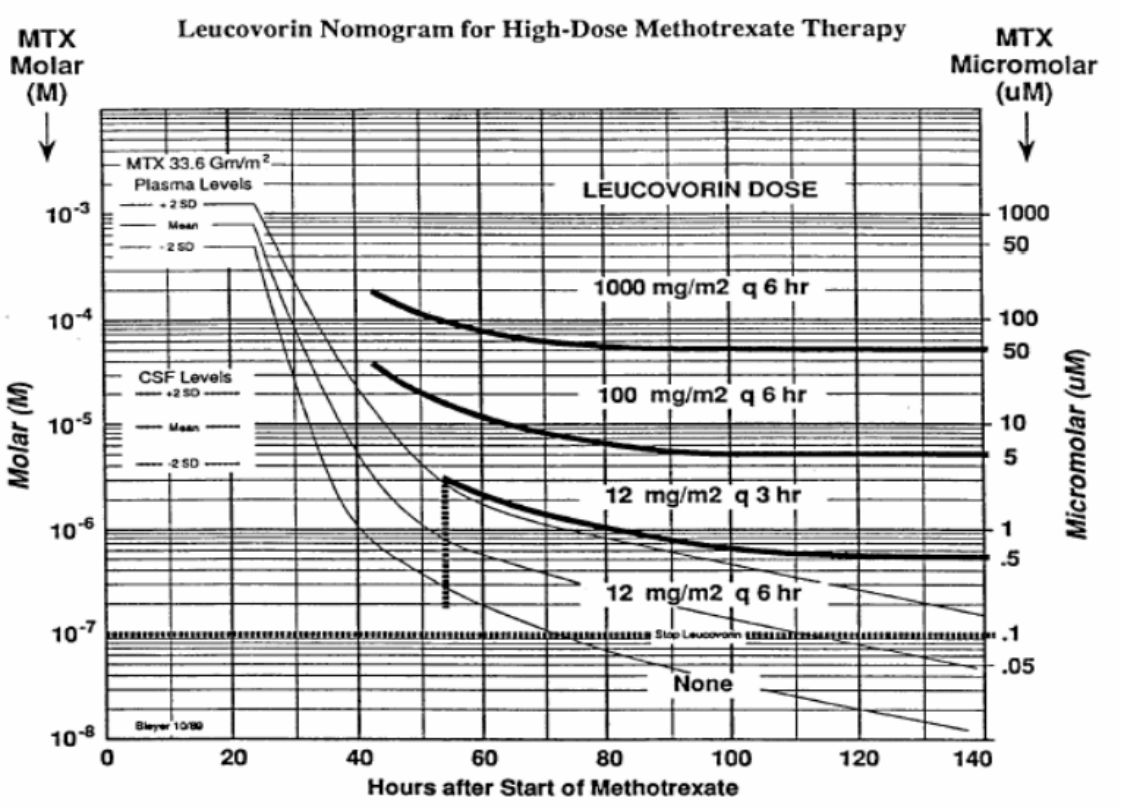
HPLC = high performance liquid chromatography
FPIA = fluorescence polarization immunoassay
SCr = serum creatinine

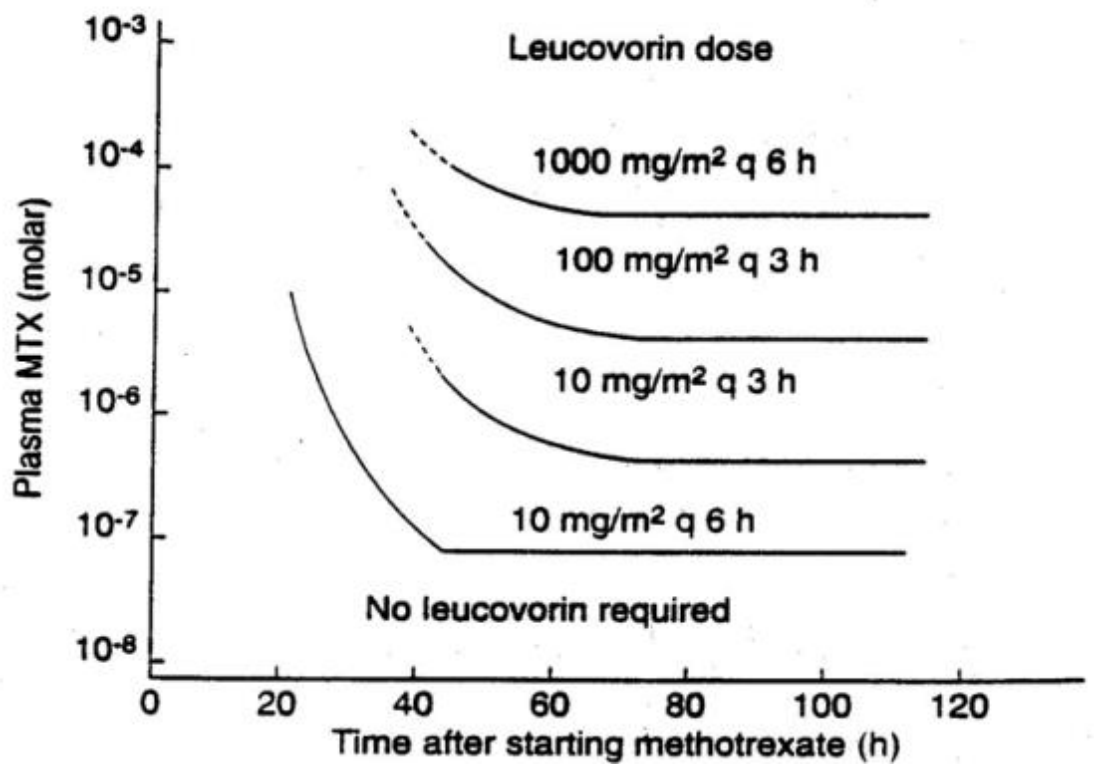
ARS Question #5

RJ is a 15-year-old boy with osteosarcoma currently clearing HD MTX. His 24hr MTX level was lost in the hospital's tube system, which wasn't recognized until hour 30. A STAT MTX level is drawn at hour 30. How would you approach interpreting a 30hr level?

A. No guidance available for the 30 hour level, wait and redraw at 48 hours
B. Utilize 24hr level thresholds in protocol to evaluate 30 hour level
C. Chart 30 hour level on population clearance curves to evaluate
D. Phone a friend

Leucovorin Nomograms





Bleyer WA, et al. Cancer. 1989; 63: 995-1007.

Section 4 – MTXPK.org

Learning objective: Recall when MTXPK.org may add value when ascertaining delayed methotrexate elimination

MTXPK.ORG

Free online clinical decision support tool

Tool provides a MTX population pharmacokinetic model with concurrent depiction of the standard deviation curve to facilitate decisions regarding glucarpidase.

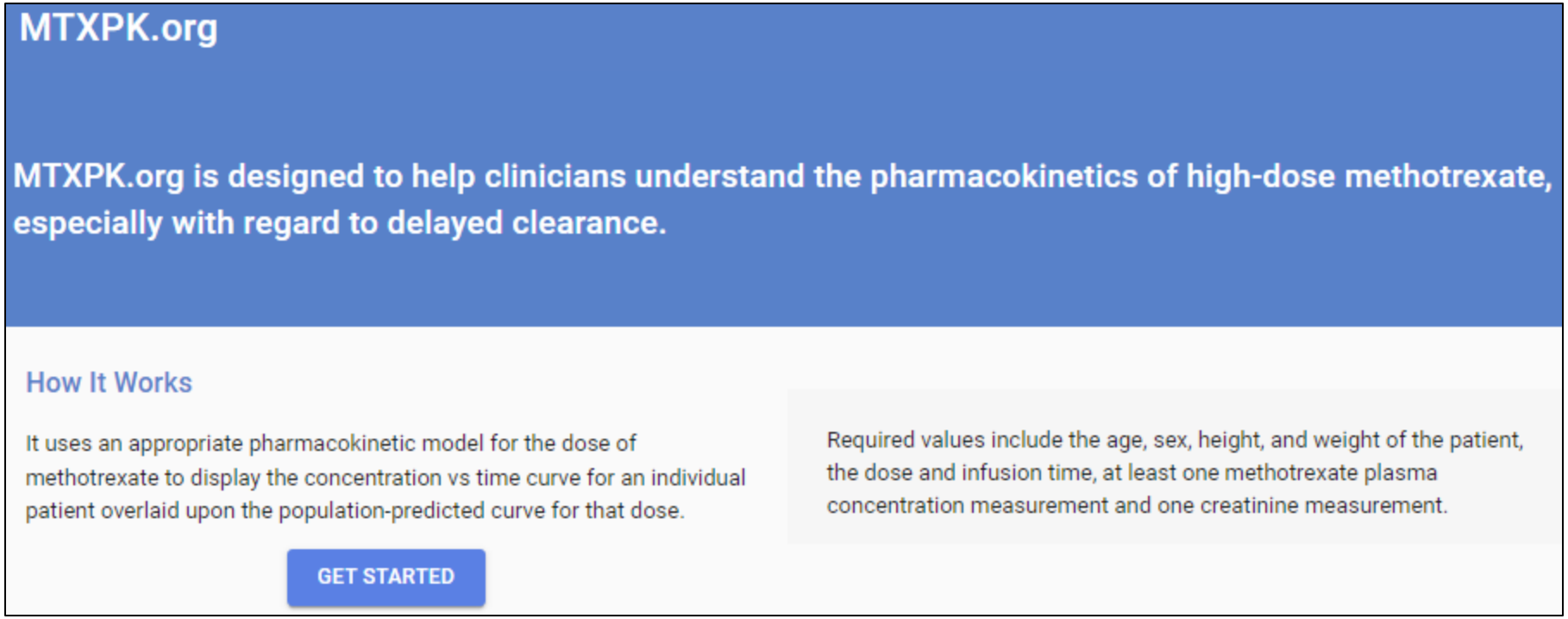
Utility:

- Utilizes individual demographics, serum creatinine, and real-time drug concentrations
- Provides visual depiction of individual patient elimination
- Estimates time to clearance
- Useful for evaluating levels drawn outside of defined timepoints

CHILDREN'S ONCOLOGY GROUP

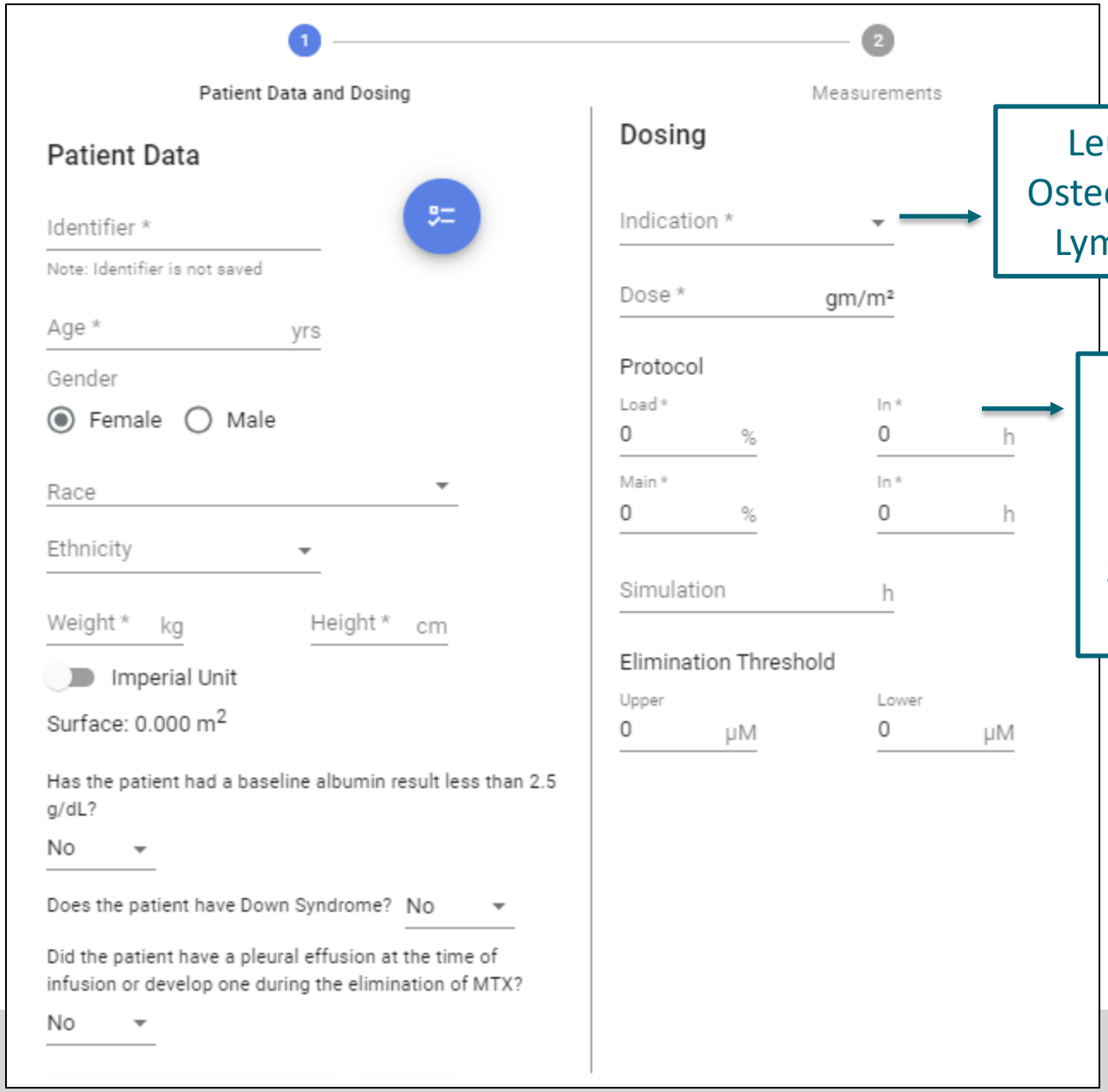
Taylor ZL. *Clin Pharmacol Ther.* 2020; 108(3): 635-643.
Taylor ZL. *Clin Transl Sci.* 2023; 16(11): 2130-2143.

MTXPK.ORG



Source: MTXPK.org

MTXPK.ORG



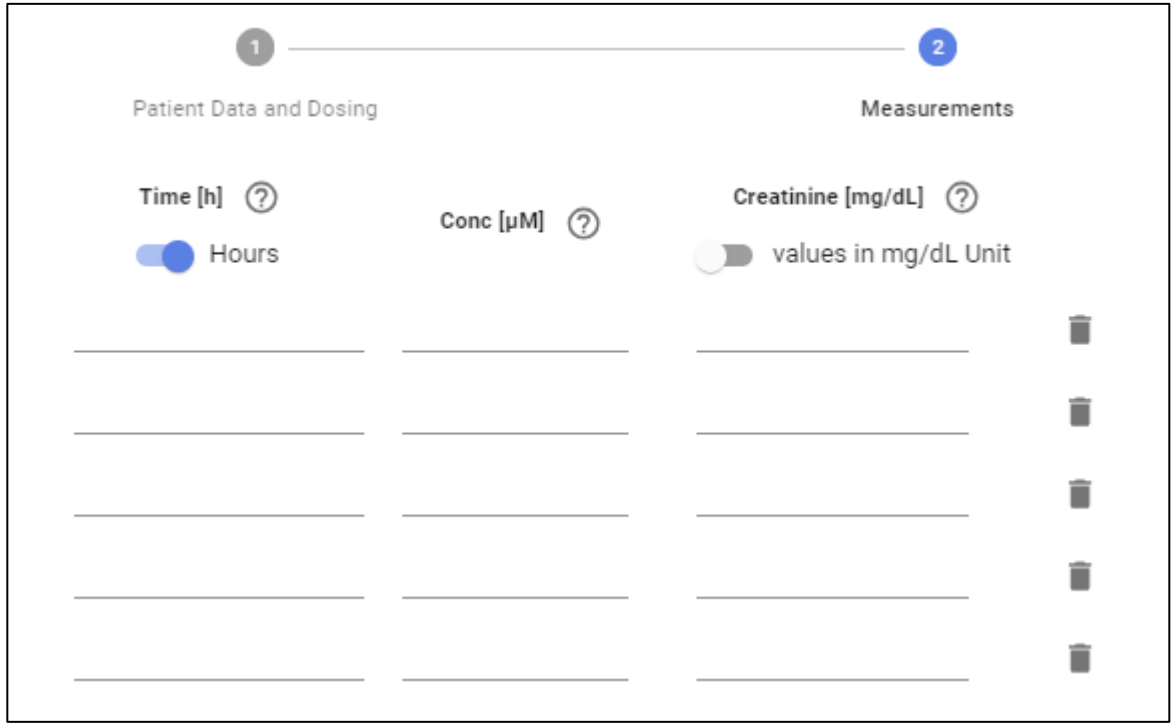
Leukemia
Osteosarcoma
Lymphoma

If leukemia selected, defaults to 10% over 30min + 90% over 23.5hr

CHILDREN'S ONCOLOGY GROUP

Source: MTXPK.org

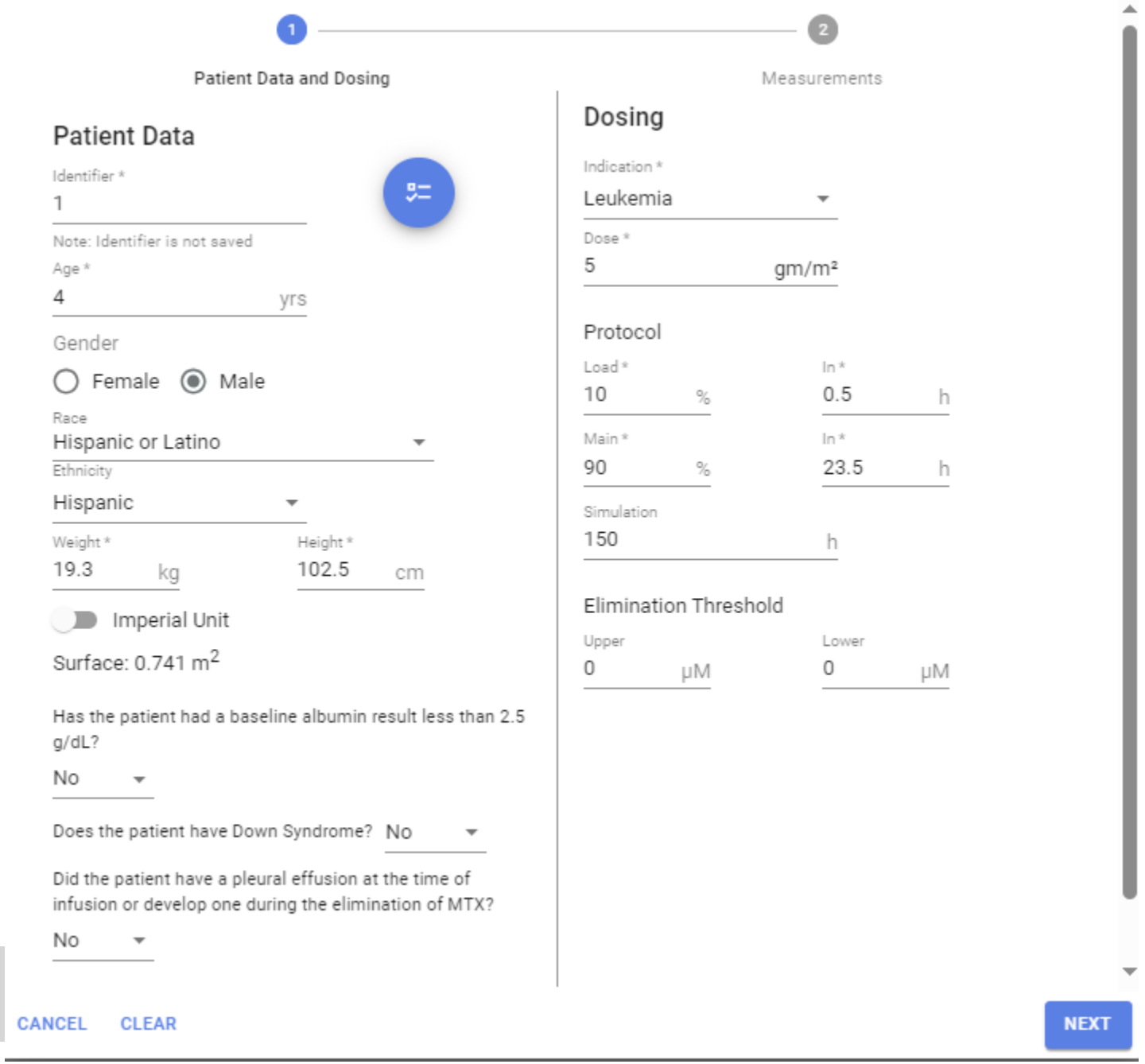
MTXPK.ORG



Source: MTXPK.org

Example

4-year-old boy with
B-ALL receiving HD MTX
5 g/m^2 over 24 hours



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Source: MTXPK.org

Example

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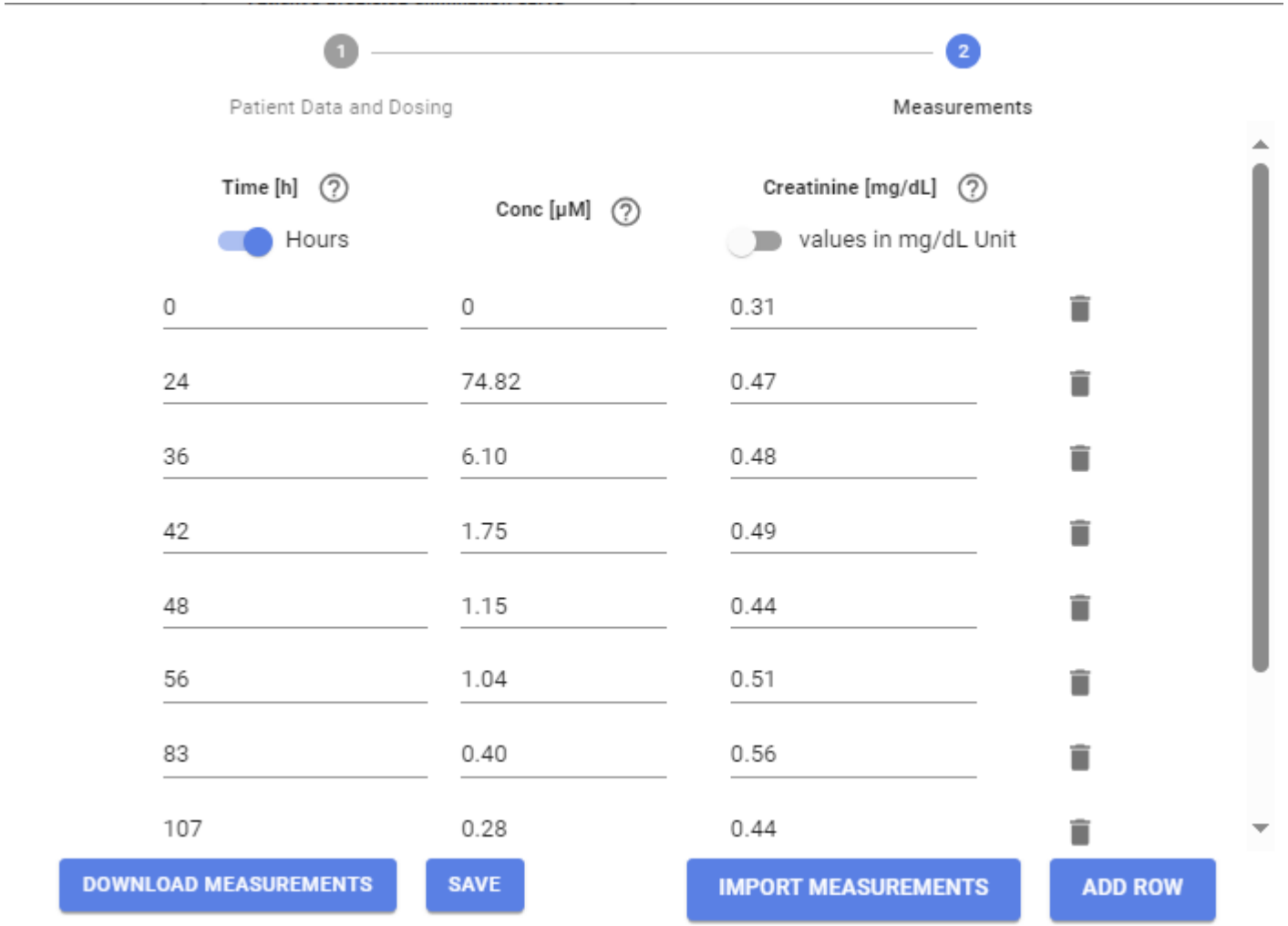
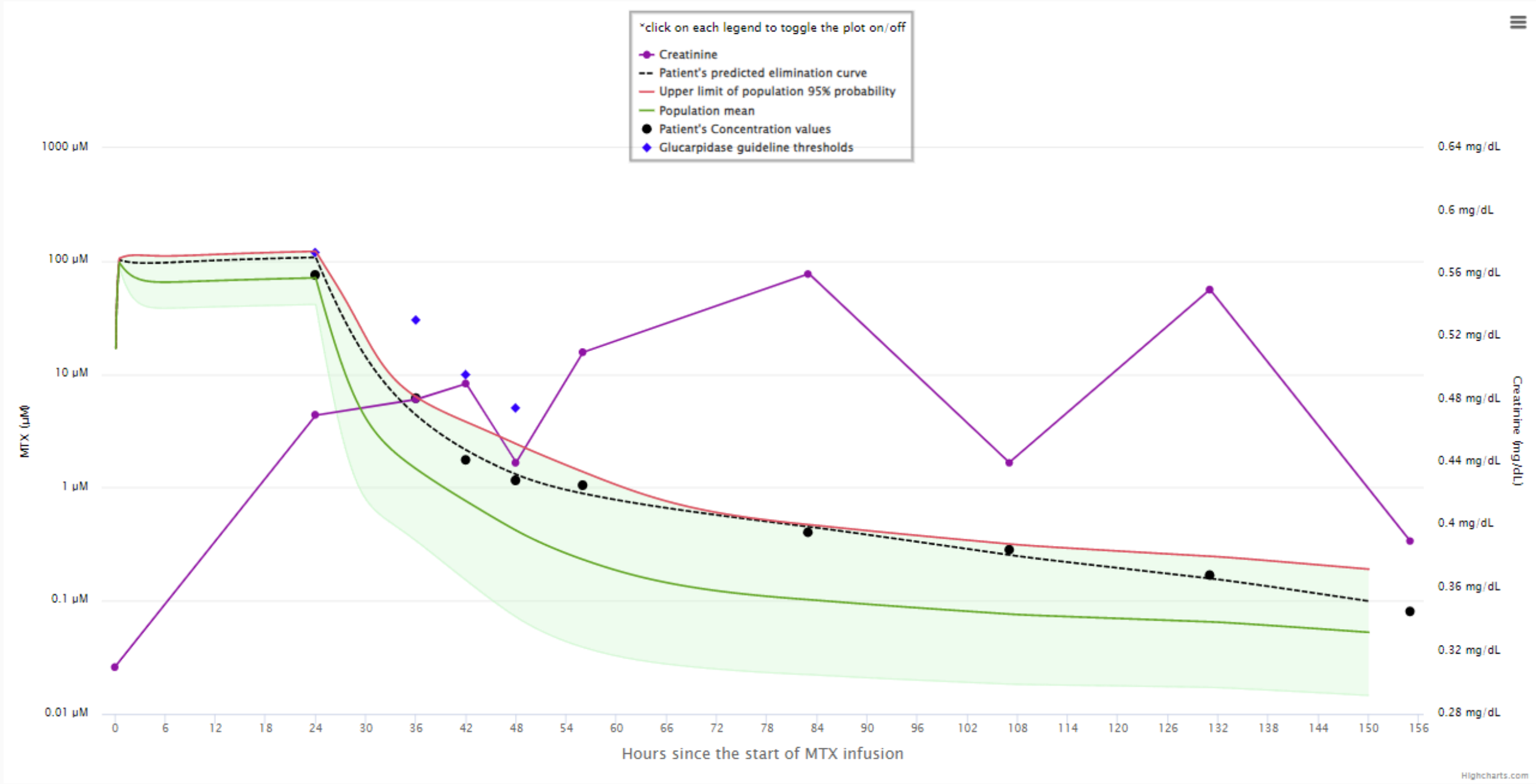


Source: MTXPK.org



Source: MTXPK.org

MTXPK.ORG

- History:
  - Originally launched in 2019 with population dataset derived from Nordic patients with pediatric ALL
  - Subsequent validity cohort supported application of the model across ALL, osteosarcoma and lymphoma protocols
  - Concern regarding limited ancestry

Taylor ZL. *Clin Transl Sci.* 2023; 16(11): 2130-2143.

MTXPK.ORG

- History:
  - Originally launched in 2019 with population dataset derived from Nordic patients with pediatric ALL
  - Subsequent validity cohort supported application of the model across ALL, osteosarcoma and lymphoma protocols
  - Concern regarding limited ancestry

    → Multisite collaboration between Cincinnati Children's Hospital Medical Center, Texas Children's Hospital and Children's Healthcare of Atlanta established to investigate the PK and toxicity in a broader population

Taylor ZL. *Clin Transl Sci.* 2023; 16(11): 2130-2143.

MTXPK.ORG

Clinical covariates that improve the description of high dose methotrexate pharmacokinetics in a diverse population to inform MTXPK.org

Zachary L. Taylor[1,2] | Tamara P. Miller[3,4] | Ethan A. Poweleit[1,5,6,7] | Nicholas P. DeGroote[4] | Lauren Pommert[2,8] | Oluwafunbi Awoniyi[4] | Sarah G. Board[1,5]

Clinical covariates that improve the description of high dose methotrexate pharmacokinetics in a diverse population to inform MTXPK.org

Purpose:	Describe the pharmacokinetics of HD MTX from a diverse population to identify factors contributing to variability to improve the model • Age, ethnicity, indication for HD MTX, variable infusion durations	
Design:	Retrospective analysis of PK data, 2010-2020	
Patients:	N=1758 patients, 8105 administrations Age 1 month - 32 years	ALL, osteosarcoma, NHL Sites: CCHMC, CHOA, TCH
Findings:	Quantify impact of infusion duration, Down Syndrome, pleural effusion, severe hypoalbuminemia on MTX PK • Short infusion (≤8hr) cleared 5% faster than long infusion (>8hr) • Down Syndrome patients with 17% slower clearance • Severe hypoalbuminemia (< 2.5mg/dL) showed 2% slower clearance	

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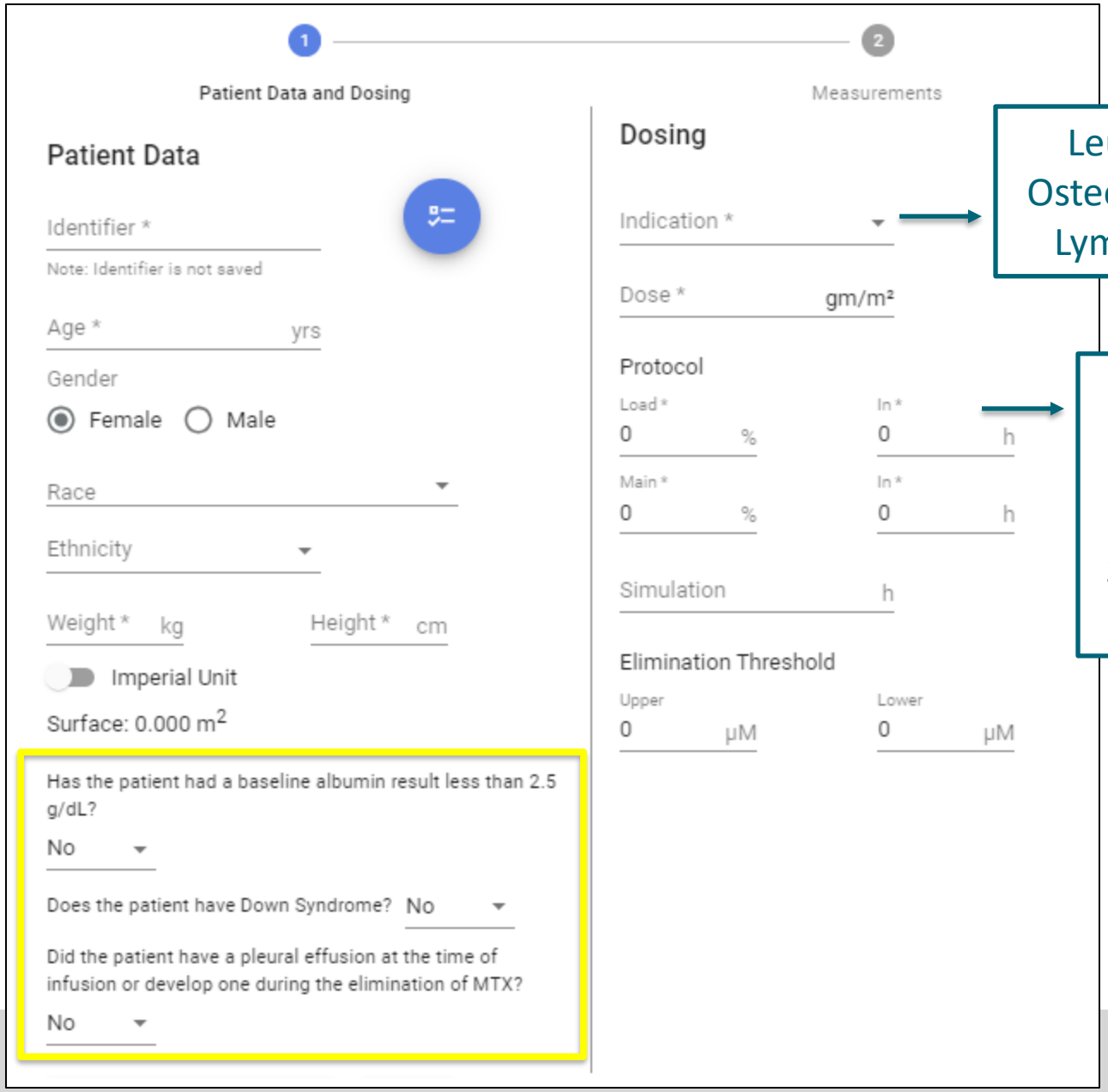
Taylor ZL. *Clin Transl Sci.* 2023; 16(11): 2130-2143.

CCHMC = Cincinnati Children's Hospital Medical Center
CHOA = Children's Healthcare of Atlanta
TCH = Texas Children's Hospital

MTXPK.ORG



Leukemia
Osteosarcoma
Lymphoma

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CHILDREN'S ONCOLOGY GROUP

Source: MTXPK.org

Unique Integration of MTXPK.org into EMR

- Cincinnati Children's Hospital Medical Center developed a dashboard which automates data entry into embedded MTXPK.org tool
  - Overcomes risk of errors with manual data entry
  - Increased efficiency with less time to output
  - Allows easy comparison to past elimination curves for individual patients

Unique Integration of MTXPK.org into EMR

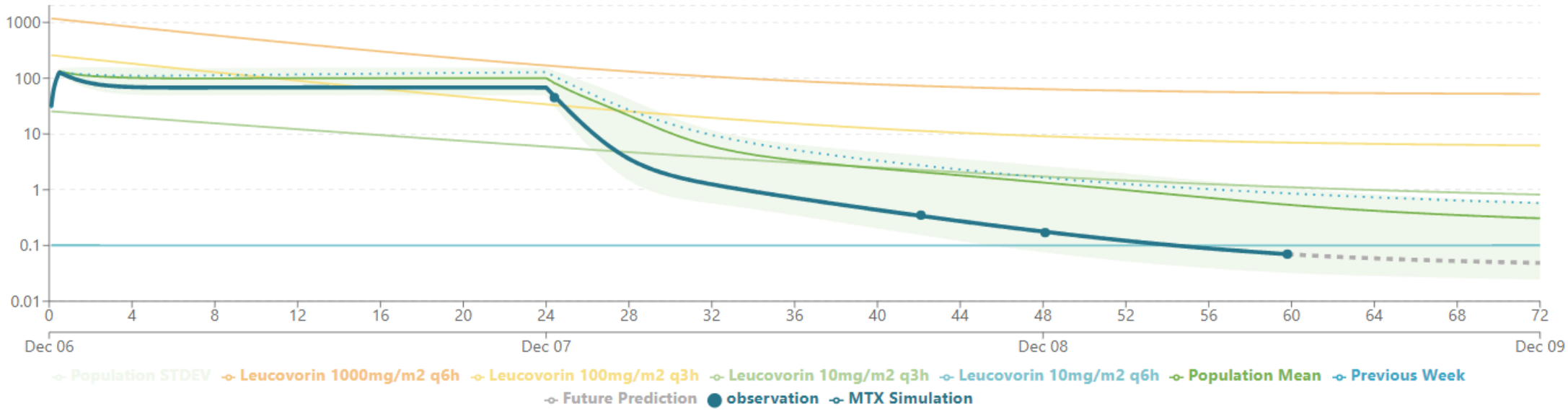
Viewing: 12/6/2024 - 12/12/2024

Hour Zero:	12/6/2024 | 5:44:00 PM	Estimated Discharge:	12/9/2024 | 12:05:51 AM
Elapsed Time:	0m		
Weight:	18.8 kg	Height:	102.9 cm
BSA:	0.733 m^2		

Methotrexate (µM)

Latest: 0.07 µM

Dose: 5047.4 mg/m^2 Length: 24 hours



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Summary Points

- HD MTX requires diligent supportive care measures with therapeutic drug monitoring. Leucovorin is necessary to mitigate toxicities but may be inadequate in settings of AKI and delayed clearance.
- A proactive approach for avoidance of risk factors associated with delayed clearance improves outcomes. Pharmacogenomics are not yet actionable, but a promising future opportunity for individualization of HD MTX therapy.
- When indicated, glucarpidase therapy is life-saving. Diligence with timing of glucarpidase administration and continued supportive care with leucovorin is required to minimize toxicity.
- MTXPK.org is a useful tool to characterize an individual patient's clearance and clarify when glucarpidase may be considered.

Question & Answer Session

Jennifer Young, PharmD, BCOP
Jennifer.Young@CCHMC.org

CHILDREN'S ONCOLOGY GROUP

For full instructions on how to claim CE credit visit:
https://stjude.cloud-cme.com/COG