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Bedside treatment algorithm for safe administration of 24-hour high-dose methotrexate in adult acute lymphoblastic leukemia

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Bedside algorithm for safe dosing of HD-MTX in ALL

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Data acquisition

Original data are available from the corresponding author upon reasonable request.

Author Contributions

Anna-Karin Hamberg: conceptualization, methodology, formal analysis, writing, review and editing. Jessica Schubert: writing, review and editing. Emma Bergfelt Lennmyr: writing, review and editing. Helene Hallböök: conceptualization, methodology, writing, review and editing. All authors have read and agreed to the final version of the manuscript.

Conflict of interest

None of the authors (Anna-Karin Hamberg, Jessica Schubert, Emma Bergfelt Lennmyr or Helene Hallböök) have any disclosures.

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Therapeutic drug monitoring (TDM) including within-cycle dose adjustment of high-dose methotrexate (HD-MTX), has been described in pediatric acute lymphoblastic leukemia (ALL) (1-3), but has, to our knowledge, not been previously reported for adults with ALL. We developed and implemented a bedside dosing algorithm that facilitated safe administration of HD-MTX achieving therapeutic plasma concentrations while reducing the risk of nephrotoxicity, over-rescue with folinic acid and prolonged hospitalization.

HD-MTX remains an important component of therapy in the era of new treatments for ALL, owing to its proven efficacy and central nervous system (CNS) penetration. While generally well tolerated, the treatment is associated with significant inter- and intra-individual variability in drug excretion, resulting in challenges for safe and effective dosing. Plasma MTX concentration monitoring is routinely used to guide folinic acid rescue and to determine the need for glucarpidase in cases of delayed excretion or nephrotoxicity.

The aim of this study was to develop, implement and evaluate a bedside decision tool consisting of an algorithm for optimized HD-MTX administration in adult ALL. The algorithm was designed to enable safe and individualized administration of the drug to achieve target steady-state plasma concentrations (20–80µM), with the possibility of within-cycle dose adjustment for high steady state concentrations.

We conducted a single-center study at Uppsala University Hospital including adult ALL patients aged 18-55 years treated according to Swedish national guidelines including pediatric protocols, mainly NOPHO ALL 2008 (4), with dose reductions for patients older than 45 years. HD-MTX was defined as 1.5–5 g/m^2 and in most patients given with mercaptopurine and intrathecal therapy. HD-MTX was administered over 24 hours, with 10% of the dose given during the first hour. All patients received standard supportive care with intravenous hydration (≥3000mL/m^2), sodium bicarbonate for urine alkalization, and folinic acid rescue starting at 42 hours.

In the first part, July 2015–December 2018, data were collected from 17 patients receiving a total of 78 cycles of HD-MTX. Plasma MTX concentrations were measured 23 hours after the start of infusion, at 36 hours, and every 6 hours thereafter until MTX-levels were < 0.2 µM, and S-creatinine was measured starting at 36 hours. From February 2017 to December 2018, extra samples for MTX and S-creatinine were collected at 2 and 6 hours after the start of infusion, covering 27 of the 78 cycles included in the first part of the study. Although dose modifications based on samples at 2 and 6 hours were not suggested, it was permitted at the treating physician's discretion.

These collected data were used to develop a bedside decision tool for dose reduction (Figure 1) in case of concentrations >75 µM at the 6-hour sample. The tool was adapted from a previously published pediatric algorithm (1-3). Steady state was generally not reached at 2 hours but was typically attained at 6 hours, and increased creatinine levels could not be detected at 2 hours. Consequently, the 6-hour time point was selected for use in the next part of the study.

In the second part, starting in March 2019, the algorithm (Figure 1) was introduced into clinical routine. Data were collected through December 2023, covering 23 adult ALL patients and a total of 106 HD-MTX cycles. To evaluate safety, the following were recorded: delayed excretion (defined as > 1 µM at 42h (2)), acute kidney injury (per KDIGO criteria (5)), total dose of folinic acid per treatment cycle, and glucarpidase administration. The time to MTX concentration <0,2 µM was used as a surrogate marker for hospital discharge. The decision tool permitted only dose reductions and was not intended to achieve higher plasma concentrations.

Categorical variables were compared using the Chi-Square and Fisher's exact tests, means were compared using one-tailed T-test, and a P-value <0.05 was considered significant. Statistical analyses were performed with MedCalc (www.medcalc.org).
Ethical approvals were obtained for all parts of the study (EPN Dnr 2017/399, 2017-399-1B and 2020-06323). Informed consent was obtained from all patients providing extra samples before the algorithm was introduced into clinical routine, in accordance with the ethical approvals.

All patients who received a planned HD-MTX dose of 1.5–5 g/m² as a 24-hour infusion were included in the comparison between non-TDM-guided treatment (part 1) and the algorithm-guided treatment (part 2). In total, 40 patients and 184 HD-MTX treatment cycles were evaluated. Use of the treatment algorithm resulted in unmodified dosing in 69% of cycles (73/106), a recommended 20% reduction in 23% (25/106), and a 50% reduction in 8% (8/106). Dose reductions were more common in patients younger than 46 years (treated according to protocols prescribing mainly 5g/m^2). Reductions were recommended in 50% (28/56) of cycles—a 20% reduction in 38% (21/56) and a 50% reduction in 12% (7/56). A similar trend was seen when looking at patients with a prescribed dose ≥ 4 g/m2, irrespective of patient age (Table S1). Dose reductions were applied during the final 12–14 hours of the infusion, due to turnaround time for the 6-hour and confirmatory samples (Figure 1). After algorithm implementation, there was a non-significant trend toward higher planned mean doses among patients aged <46 years (Table 1).

Target attainment at 23 hours (MTX 20–80 µM) was achieved in 81% of algorithm-guided cycles, compared to 68% before implementing the decision tool. Values above target occurred in 17% and 29% of cycles, respectively, while 2% and 3%, respectively, were below target (prescribed dosage 1.5 g/m^2), supporting that the algorithm did not increase the risk of subtherapeutic concentrations (Figure 2).

The safety evaluation showed that the incidence of delayed excretion (MTX >1 µM at 42 hours) and acute kidney injury was significantly lower in the algorithm-guided group compared with non-TDM-guided treatment ($p < 0.01$; Table 1). The median time to MTX <0.2 µM was also significantly shorter in the algorithm group ($p < 0.01$) after excluding one cycle in which the algorithm was not followed (Table 1, Supplementary Figures S1-2). Despite use of the algorithm, 4% of cycles (4/106) exceeded 84 hours to reach <0.2 µM, compared with 12% (9/78) with non-TDM-guided treatment (Supplementary Figures S1).

Inadequate urine alkalinization (pH <7), significant weight gain despite use of loop diuretics, and one case with concomitant omeprazole use were identified as possible contributing factors to delayed excretion.

By using this TDM-based bedside algorithm, we achieved safer HD-MTX administration with lower rates of renal toxicity, no use of glucarpidase, and shorter hospital stays.

HD-MTX remains an important component in ALL treatment in the modern era, offering the advantage of reaching extramedullary compartments. The dose calculated per body surface area is typically given as a 24-hour infusion, and pre-existing kidney failure may constitute a contraindication to treatment. In adult ALL, dosing recommendations vary between protocols and age groups, but the dose is seldom individualized within a treatment cycle to achieve a target concentration or area under the curve (AUC), as has been suggested for pediatric ALL (6, 7).

In this study of adult ALL patients, we selected a conservative upper threshold (>75 µM at 6 hours) for dose reduction (1). While pediatric studies have suggested target steady-state concentrations of >20 µM (7), 65 µM (8) or 50–80 µM (2), a recent Chinese guideline for adult ALL proposed a range of 16–40 µM (9). Information on optimal plasma concentrations for treating CNS disease in ALL remains limited across all age groups and might be further complicated by only moderate correlation between plasma and cerebrospinal fluid concentrations (10, 11).

A known complication of excessive folinic acid rescue is hypercalcemia, which can be fatal. Moreover, excessive folinic acid may reduce the efficacy of subsequent methotrexate cycles, and previous research has linked high folinic acid exposure to increased relapse risk (12). In addition, for patients who develop kidney failure and delayed methotrexate excretion, further leukemia treatment may be compromised —both due to treatment delays and because additional methotrexate cycles may be withheld.

Despite algorithm implementation, some patients still experienced delayed excretion. Monitoring urine alkalinization, vigilant urine pH adjustments, attention to concomitant medications and the presence of third-space fluid remains crucial. As a secondary observation, we noted a trend towards higher administered methotrexate doses after algorithm implementation. Previously, physicians occasionally reduced the methotrexate dose following a treatment course with delayed excretion. We hypothesize that the bedside algorithm provided confidence to maintain adequate dosing, with the knowledge that within-cycle adjustment could be made if needed.

In conclusion, implementation of a bedside methotrexate dosing algorithm facilitated safer administration of HD-MTX in adult ALL patients, achieving therapeutic plasma concentrations while reducing the risk of nephrotoxicity, over-rescue with folinic acid, and prolonged hospitalization. The main limitations of this study are the single-center design and predominantly Nordic population. The findings should therefore be interpreted within this context and confirmatory studies are necessary. With these precautions, the algorithm is applicable in routine care in similar populations of young patients, provided timely access to plasma MTX concentrations with turnaround times of less than two hours. Further research is needed to better define the optimal MTX target range in adult ALL and to refine dose individualization strategies.

References

1. Foster JH, Bernhardt MB, Thompson PA, Smith EO, Schafer ES. Using a Bedside Algorithm to Individually Dose High-dose Methotrexate for Patients at Risk for Toxicity. J Pediatr Hematol Oncol. 2017;39(1):72-76.

2. Foster JH, Thompson PA, Bernhardt MB, et al. A prospective study of a simple algorithm to individually dose high-dose methotrexate for children with leukemia at risk for methotrexate toxicities. Cancer Chemother Pharmacol. 2019;83(2):349-360.

3. Pauley JL, Panetta JC, Crews KR, et al. Between-course targeting of methotrexate exposure using pharmacokinetically guided dosage adjustments. Cancer Chemother Pharmacol. 2013;72(2):369-378.

4. Toft N, Birgens H, Abrahamsson J, et al. Results of NOPHO ALL2008 treatment for patients aged 1-45 years with acute lymphoblastic leukemia. Leukemia. 2018;32(3):606-615.

5. KDIGO.org. Acute Kidney Injury (AKI) 2012 Guideline. Kidney International Supplements. https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf. Accessed on 2012, April 2.

6. Acevedo K, Soto G, Shapiro MC, et al. Intrainfusion Drug Monitoring and Algorithm-Based Dose Adjustments for Children With ALL Receiving High-Dose Methotrexate Are Feasible and Safe in Costa Rica, a Low- and Middle-Income Country. JCO Glob Oncol. 2025;11:e2400450.

7. Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. N Engl J Med. 1998;338(8):499-505.

8. Liao C, Nie J, Xu XJ, et al. The effect of the plasma methotrexate concentration during high-dose methotrexate therapy in childhood acute lymphoblastic leukemia. Leuk Lymphoma. 2024;65(1):91-99.

9. Song Z, Hu Y, Liu S, et al. Medication therapy of high-dose methotrexate: An evidence-based practice guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. Br J Clin Pharmacol. 2022;88(5):2456-2472.

10. Milano G, Thyss A, Serre Debeauvais F, et al. CSF drug levels for children with acute lymphoblastic leukemia treated by 5 g/m2 methotrexate. A study from the EORTC Children's Leukemia Cooperative Group. Eur J Cancer. 1990;26(4):492-495.

11. Niemann A, Muhlisch J, Fruhwald MC, Gerss J, Hempel G, Boos J. Therapeutic drug monitoring of methotrexate in cerebrospinal fluid after systemic high-dose infusion in children: can the burden of intrathecal methotrexate be reduced? Ther Drug Monit. 2010;32(4):467-475.

12. Skarby TV, Anderson H, Heldrup J, Kanerva JA, Seidel H, Schmiegelow K. High leucovorin doses during high-dose methotrexate treatment may reduce the cure rate in childhood acute lymphoblastic leukemia. Leukemia. 2006;20(11):1955-1962.

Table 1 Patient characteristics and main study outcomes related to safety

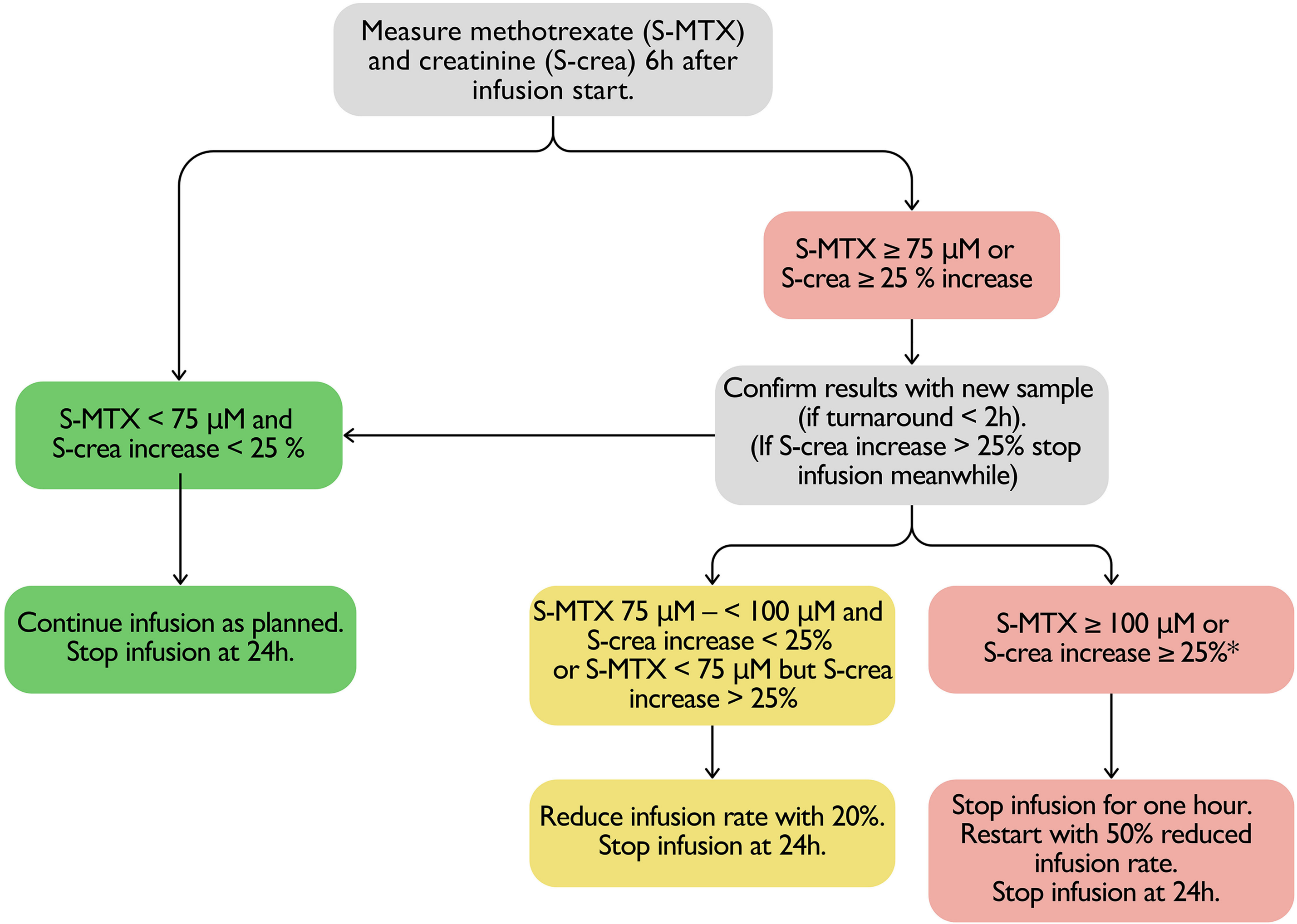
	Non-TDM group 78 treatment cycles		**Bedside algorithm 106 treatment cycles**		
	< 46 years n=12 55 cycles	**46–55 years** n=5 23 cycles	**< 46 years** n=15 56 cycles	**46–55 years** n=8 50 cycles	**p-values**
Age (years) Median (range)	25.0 (19.5–43.6)	48.6 (47.5–54.5)	31.1 (19.6–41.8)	50.6 (46.0–54.4)	p=0.6
Sex (Male/Female)	8/4	2/3	8/7	4/4	NA
MTX-dose (g/m^2) Mean±SD (range) [¤]Prescribed [§]Administered	3.8±1.1[¤] (1.8–5.3)	2.6±0.6[¤] (1.8–4.6)	4.3±0.9[¤] (1.5–5.1) 4.0±0.8[§] (1.3–5.1)	2.6±0.8[¤] (1.5–4.7) 2.5±0.7[§] (1.3-4.1)	< 46 y p=0.25 46-55 y p=0.62
Delayed excretion defined as >1 µM at 42h	44% (34/78)		19% (20/106)		p<0.01[*]
Acute Kidney Injury, all - Stage 1 - Stage 2 - Stage 3	18% (14/78) 14.1% (11/78) 2.6% (2/78) 1.3% (1/78)		4.7% (5/106) 3.8% (4/106) 0.9% (1/106) 0% (0/106)		p<0.01[*]
Glucarpidase use	2.6% (2/78)		0% (0/106)		NA
Time (h) to MTX <0.2 µM Median (range) Mean±SD	60 (42–216) 71±33		57 (42–204) 61±19 55 (42–132)[#] 60±13[#]		p<0.05[§] p<0.01[§]
Folinic acid dose per cycle (mg), Median (range), Mean±SD					
All cycles	133 (45–5328) 421±1000		101 (47–2710) 167±278		p<0.05
Only cycles with delayed excretion	276 (165–5328) 845±1415		272 (141–2710) 385±492		p=0.11

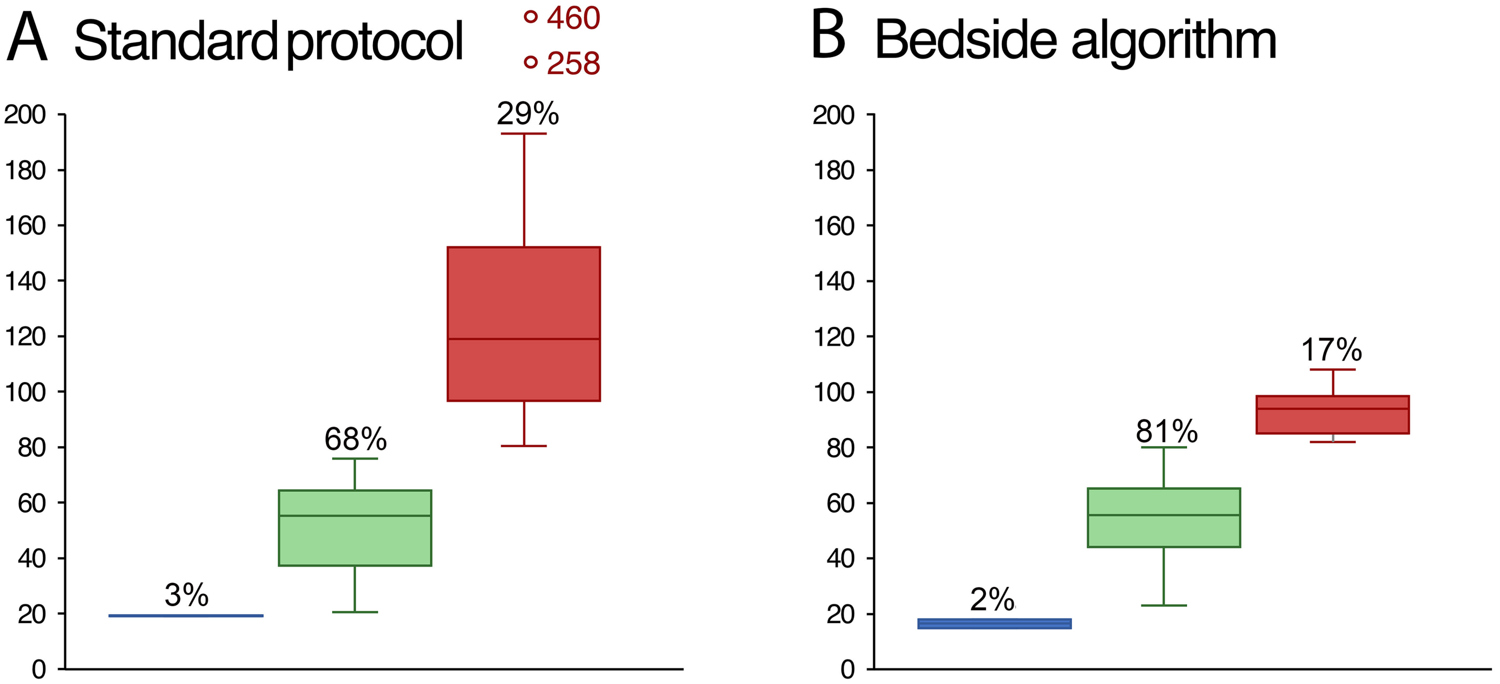
[#] Excluding one patient in whom the dose revision algorithm was not adhered to: algorithm recommended 50% reduction of infusion rate due to >25% increase in S-Crea at 6h.
[*]Chi-square test
[§]one-tailed t-test

Figure legends

Figure 1 **Schematic diagram of the dosing algoritm.**
The diagram shows the dosing algorithm for high-dose methotrexate (HD-MTX) in adult acute lymphoblastic leukemia.
*If both S-MTX >100 µM and S-creatinine increase ≥ 25%, infusion could be stopped prematurely at the physician´s discretion.
The algorithm was used under the condition that the urine production was >800mL/4h and urine-pH was ≥ 7

Figure 2: **Box plots comparing target attainment in treatment cycles with and without the bedside algorithm.**
The box plots show (A) the standard and (B) the bedside algorithm groups. The box plots represent treatment cycles with steady-state concentrations of methotrexate below (C_{23h} < 20 µM, blue), within (C_{23h} 20-80 µM, green) and above target (C_{23h} >80 µM, red). There is a non-significant trend towards improved target attainment (81% vs 68%) and fewer cycles above target (17% vs 29%), (p=0.1, Fishers exact test). The standard group included two outliers with C_{23h} at 258 and 460 µM, respectively. Treatment cycles with C_{23h} < 20 µM (2 cycles per group) used a low dose (1.5 g/m^2) which was not further reduced by the algorithm.


Measure methotrexate (S-MTX) and creatinine (S-crea) 6h after infusion start.
S-MTX ≥ 75 µM or S-crea ≥ 25 % increase
Confirm results with new sample (if turnaround < 2h). (If S-crea increase > 25% stop infusion meanwhile)
S-MTX < 75 µM and S-crea increase < 25 %
Continue infusion as planned. Stop infusion at 24h.
S-MTX 75 µM – < 100 µM and S-crea increase < 25% or S-MTX < 75 µM but S-crea increase > 25%
S-MTX ≥ 100 µM or S-crea increase ≥ 25%*
Reduce infusion rate with 20%. Stop infusion at 24h.
Stop infusion for one hour. Restart with 50% reduced infusion rate. Stop infusion at 24h.


A Standard protocol
460
258
29%
68%
3%
200
180
160
140
120
100
80
60
40
20
0
B Bedside algorithm
17%
81%
2%
200
180
160
140
120
100
80
60
40
20
0

Supplementary Table and Figures to

Bedside treatment algorithm for safe administration of 24-hour high-dose methotrexate in adult acute lymphoblastic leukemia.

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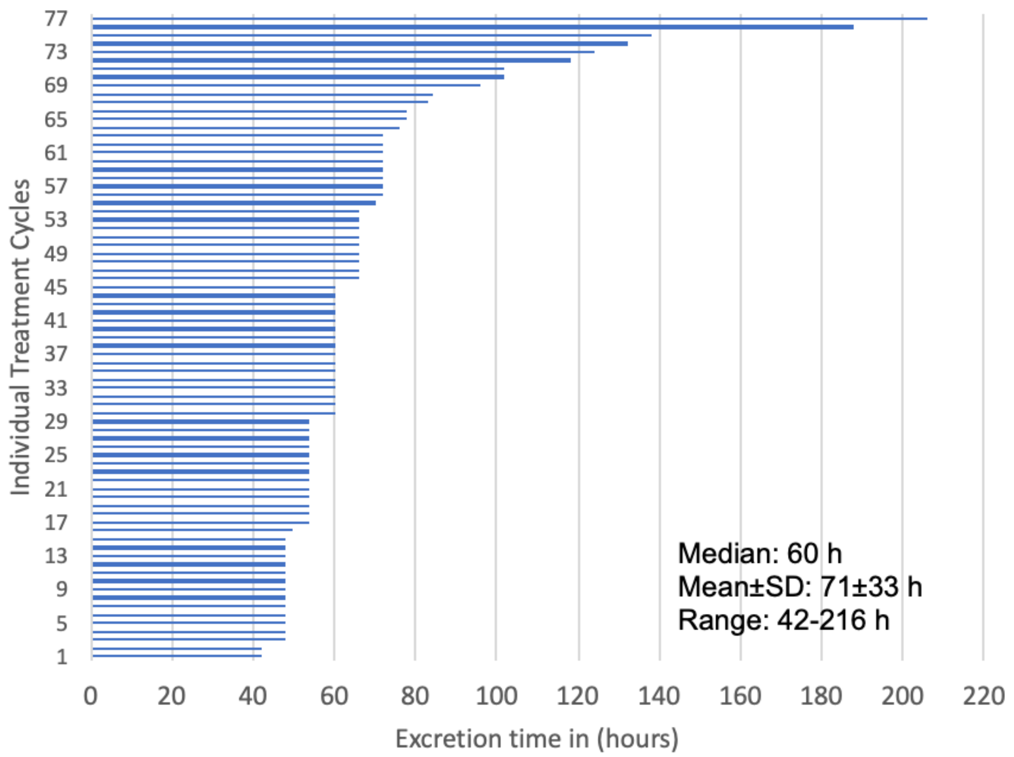
Table S1 Frequencies of dose reductions recommended by the algorithm based on all treatment cycles or divided based on age or planned dose

	No change of infusion rate	20% reduction of infusion rate	50% reduction of infusion rate
All treatment cycles n=106	69%	23%	8%
Per age group Patients < 46 years n=56	50%	38%	12%
Patients 46–55 years n=50	90%	6%	4%
Per dose group Dose ≥ 4 g/m^2 n=50	40%	46%	14%
Dose < 4 g/m^2 n=56	94%	4%	2%

Figure S1 Excretion time (time to MTX < 0.2 µM) for all patients comparing a) Standard protocol (78 cycles) versus b) Bedside algorithm (106 cycles)

a)



b)

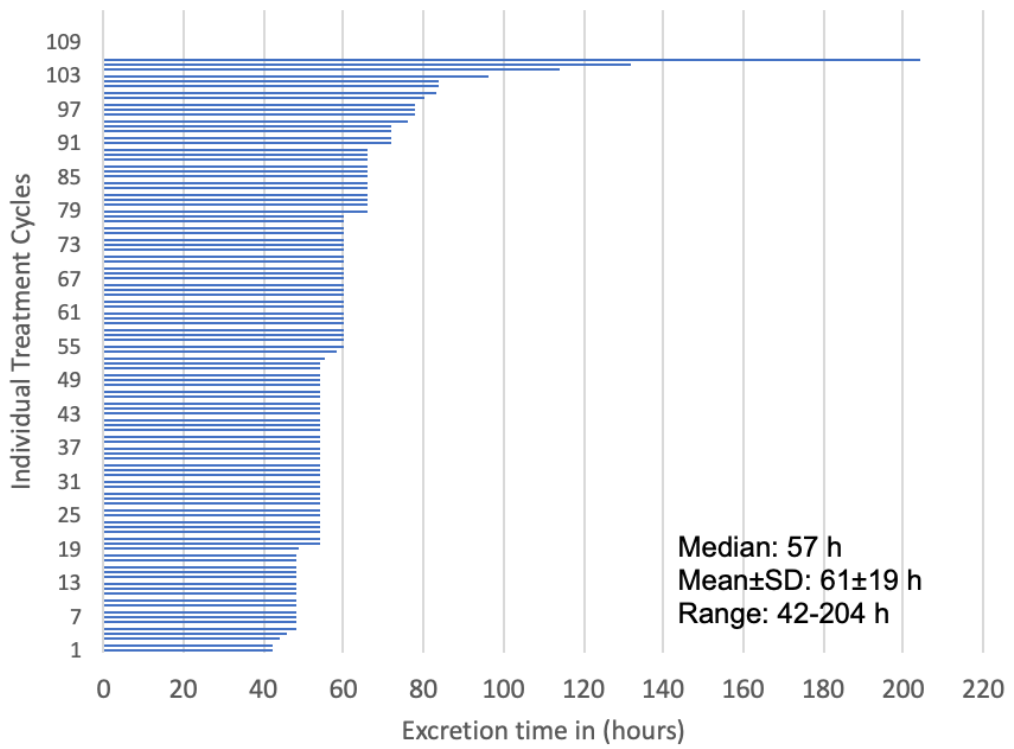
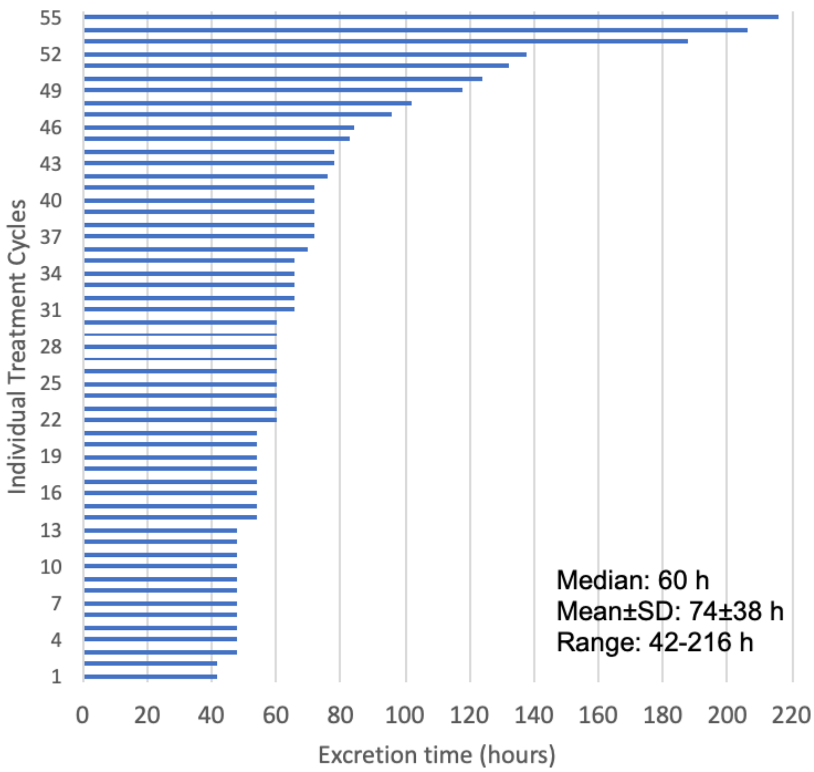


Figure S2 Excretion time (time to MTX < 0.2 µM) for patients < 46 years comparing a) Standard protocol (55 cycles) versus b) Bedside algorithm (56 cycles). If excluding one patient in the Bedside algorithm where the algorithm was not followed (50% reduction of infusion rate due to >25% increase in S-Crea at 6h), the mean±SD was reduced to 60±14 h and the range to 42–132 h.

a)



b)