JOURNAL OF ONCOLOGY PHARMACY PRACTICE

Original article

J Oncol Pharm Practice
1–12

DOI: 10.1177/10781552261445610
journals.sagepub.com/home/opp
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High-Dose methotrexate in pediatric acute lymphoblastic leukemia: Variability across Mexican centers from a national survey

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Abstract

Introduction: High-dose methotrexate (HD-MTX) is a cornerstone of pediatric acute lymphoblastic leukemia (ALL) therapy. It's safe administration requires timely pharmacokinetic monitoring and comprehensive supportive care, which are frequently limited in low- and middle-income countries (LMICs). In Mexico, variability in HD-MTX practices may compromise treatment safety and efficacy. This study aimed to characterize national practice patterns and identify context-specific adaptations in the delivery of HD-MTX in resource constrained settings.

Methods: A nationwide, cross-sectional electronic survey was conducted between May and November 2023 among pediatric hematologists and oncologists treating patients younger than 18 years with ALL. The questionnaire assessed institutional guidelines, availability of pharmacokinetic monitoring, and supportive care practices, including hydration, urinary alkalinization, and folinic acid rescue. Data were analyzed descriptively.

Results: A total of 111 specialists from 27 Mexican states participated. Only 56% reported having institutional HD-MTX guidelines. While 97% administered HD-MTX to high-risk ALL patients, only 61% used full protocol-recommended doses, and nearly one-third reported dose reductions. Methotrexate plasma level monitoring was only available in 56% of centers. Most centers (86%) administered HD-MTX exclusively in the inpatient setting. Supportive care practices varied substantially across institutions and risk groups. Reported barriers included limited laboratory capacity (61%), lack of standardized protocols (44%), and delays related to bed availability (39%).

Conclusions: Optimizing HD-MTX delivery in Mexico requires integrating standardized clinical practices with targeted system-level interventions to ensure timely access to pharmacokinetic monitoring. The development and implementation of context-adapted national guidelines may improve safety, reduce variability in care, and mitigate outcome disparities in children with ALL.

Keywords

High-dose methotrexate, acute lymphoblastic leukemia, lower- and middle-income countries

Received: 25 February 2026; revised: 7 April 2026; accepted: 12 April 2026

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Introduction

Methotrexate (MTX) is a synthetic folate antagonist and one of the most versatile and essential anticancer agents, recognized by the World Health Organization (WHO) as an essential medicine since 1977.[1] High-dose methotrexate (HD-MTX), defined as a dose exceeding 500 mg/m^2, became a cornerstone of pediatric acute lymphoblastic leukemia (ALL) regimens in the 1970s, demonstrating both feasibility and efficacy, particularly for central nervous system (CNS) and testicular disease control. Its incorporation into multi-agent chemotherapy contributed significantly to the achievement of survival rates approaching 85–90% in high-income countries.[2,3]

Despite its proven efficacy, HD-MTX is associated with a well-recognized risk of toxicity, including myelosuppression, mucositis, and hepatic, renal, and neurologic adverse effects. Consequently, its safe administration depends on the integration of supportive care measures aimed at optimizing drug clearance and minimizing toxicity.[4] Contemporary pediatric ALL treatment protocols generally incorporate recommendations for hydration, urinary alkalinization, and folinic acid (leucovorin) rescue, together with pharmacokinetic monitoring to guide clinical decision-making. However, the specific approaches to HD-MTX administration and monitoring vary across protocols and treatment settings.

Pharmacokinetic monitoring of methotrexate is commonly used to inform supportive care adjustments and toxicity prevention strategies. Nevertheless, the feasibility of implementing standardized monitoring algorithms depends on the availability of laboratory infrastructure, trained personnel, and timely result reporting. In many health systems, particularly outside high-income settings, access to these resources is variable, which may limit adherence to protocol-based recommendations and necessitate alternative approaches to HD-MTX management.[5]

Globally, most children with ALL are treated in low- and middle-income countries (LMICs) where access to standard preventive and supportive measures is often restricted.[5] In these settings, treatment protocols are frequently adapted to local resource availability. Alternative strategies—such as extended hydration, prolonged folinic acid rescue, or MTX dose reduction—are commonly implemented to minimize toxicity but may inadvertently compromise treatment intensity and clinical outcomes.[6–8] These adaptations, however, are often empirical rather than protocol-driven, reflecting limitations in laboratory capacity, staffing, and hospital logistics. As a result, HD-MTX administration practices vary widely between institutions, with potential implications for both safety and efficacy.

This study aimed to describe the variability in HD-MTX administration practices across pediatric oncology centers in Mexico and to identify local adaptations implemented to optimize safety and feasibility in resource-limited settings.

Methods

We conducted a nationwide, cross-sectional survey to characterize current practices in the administration of high-dose methotrexate (HD-MTX) in Mexico. Hematologists and oncologists across the country who managed patients younger than 18 years with acute leukemia were invited to participate.

An anonymous electronic questionnaire was developed using Google Forms and distributed via email, WhatsApp professional groups, and the official electronic platforms of the Mexican Association of Hematology (AMEH) and the Mexican Association of Pediatric Oncology and Hematology (AMOHP).

The questionnaire covered three domains: (1) demographic and institutional characteristics (profession, experience, case volume, and funding model); (2) institutional definitions and infrastructure, including MTX dosing thresholds, outpatient feasibility, and access to serum MTX level monitoring; and (3) supportive care practices, addressing hydration, alkalinization, monitoring schedules, and leucovorin rescue protocols by risk group.

The study was approved by the local Institutional Review Board. Ethical approval details are provided in the Title Page. Participation was voluntary and anonymous.

A subgroup analysis was conducted to compare public and private institutions, evaluating differences in HD-MTX administration practices, monitoring strategies, dosing patterns, and reported barriers. Categorical variables were summarized descriptively and compared using the chi-square test, with a p-value <0.05 considered statistically significant.

Results

Demographic and institutional characteristics

A total of 111 respondents completed the survey, including 49 pediatric oncologists (44%), 34 pediatric hematologists (30%), and 28 clinical hematologists (25%) who reported treating patients under 18 years in their institutions. Most participants had between 6 and 10 years of professional experience (38%).

Of the 111 respondents, 96 (86%) worked in public health institutions—47 affiliated with IMSS Bienestar/Secretaria de Salud and 35 with the Mexican Institute of Social Security (IMSS)—while 15 participants (13%) practiced exclusively in the private sector.

Definitions of HD-MTX in ALL protocols were heterogeneous. Thirty-six respondents (32%) defined as >500 mg/m^2, 30 (27%) as >1000 mg/m^2, 22 (20%) as >2000 mg/m^2, and 20 (18%) as >5000 mg/m^2. Only 56% of respondents reported having formal institutional guidelines for HD-MTX administration (Table 1).

Table 1. Characteristics of survey respondents and institutional practices regarding high-dose methotrexate (HD-MTX).

Variable	Frequency n = 111 Percentage (100%)
Profession	
- Pediatric oncologists	49 (44%)
- Pediatric hematologists	34 (30%)
- Clinical hematologists	28 (25%)
Institutional setting	
- Public health institutions	96 (86%)
• IMSS Bienestar/Secretaria de Salud	• 47 (43%)
• IMSS	• 35 (32%)
• ISSSTE	• 14 (13%)
- Private sector only	15 (13%)
Definition of HD-MTX in ALL	
->500 mg/m^2	36 (32%)
->1000 mg/m^2	30 (27%)
->2000 mg/m^2	22 (20%)
->5000 mg/m^2	20 (18%)
Institutional guideline available	
-Yes	62 (56%)
-No	49 (44%)
Supportive Care and Monitoring Practices	
Pre-treatment evaluation *	
-Yes	108 (97%)
-No	3 (3%)
Post-treatment evaluation*	
• Daily	70 (63%)
• Every 48 h	20 (18%)
• Until discharge	14 (13%)
Hyperhydration administration	
• 6 h pre-infusion	14 (12.6%)
• 8 h pre-infusion	6 (5.4%)
• 12 h pre-infusion	38 (34%)
• 24 h pre-infusion	48 (43%)
Prescribed Fluid Volumes	
• ≥3000 mL/m^2/day	78 (70%)
• 2000–3000 mL/m^2/day	17 (15%)
• 1500–2000 mL/m^2/day	16 (14%)
• <1500 mL/m^2/day	8 (7.2%)
Hydration solutions	
• 1:1 mix of 5% glucose and saline	36 (32%)
• Normal saline alone	26 (23%)
• 2:1 mixture	16 (14%)
Alkalinization with sodium bicarbonate	
-Yes	111 (100%)
Urinary pH monitoring	
-No	5 (4.5%)
-Yes	105 (94.5%)
• Per shift	• 69 (62%)
• Every void	• 27 (24%)
• Only at the start of infusion	• 10 (9%)
Hyperhydration and alkalinization discontinuation	
• After completion of folinic acid rescue	• 36 (32%)
• Once MTX levels dropped below 0.2 µmol/L	• 33 (30%)
• At patient discharge	• 28 (25%)
• At the end of MTX infusion	• 9 (8%)
Institutional access to MTX level monitoring	
-Yes	42 (37%)
-No	69 (62%)
• Outsourced MTX levels	• 20 (18%)
+MTX level results report time	
<12 h	31 (27%)
12–24 h	6 (5.4%)
24–48 h	6 (5.4%)
> 48 h	13 (12%)
Adjustment of folinic acid based on MTX levels (nomogram-guided)	
Yes	40 (36%)
No	71 (64%)
Outpatient administration of HD-MTX	
-Yes	15 (14%)
-No	96 (86%)
Concomitant Practices	
• Avoided interaction drugs	(49%)
• Special diet	(39%)
Reported barriers	
- Treatment delays due to bed unavailability	44 (39%)
-Lack of methotrexate level monitoring	67 (60%)
- Delay in methotrexate level reporting	37 (33%)
- Shortage of chemotherapy drugs	18 (16%)

ALL, Acute Lymphoblastic Leukemia; HD-MTX, High-Dose Methotrexate; IMSS, Mexican Institute of Social Security; ISSSTE, Institute for Social Security and Services for State Workers; MTX, Methotrexate. * Evaluation included: electrolytes, renal and hepatic function tests and CBC.+ Methotrexate reporting times were calculated only among centers with consistent access to MTX level monitoring (n = 56).

Supportive care and monitoring practices

Pre-treatment evaluation was highly consistent: nearly all centers (97%) reported performing electrolytes, renal and hepatic function tests, and CBC before infusion. Post-infusion monitoring, however, varied: 63% monitored patients daily, 18% every 48 h, and 13% only until discharge.

Hydration and alkalinization

Most respondents reported initiating hyperhydration between 12 and 24 h before methotrexate infusion. Specifically, 43% of centers administered hyperhydration 24 h prior, while 34% began 12 h before infusion. A smaller proportion started at 6 h (12.6%) or 8 h (5.4%) pre-infusion. Most respondents prescribed fluid volumes ≥3000 mL/m^2/

Table 2. Practices for high-dose methotrexate (HD-MTX) administration by risk group in pediatric acute lymphoblastic leukemia.

	ALL low risk n(%)	ALL intermediate risk n(%)	ALL high risk n(%)
HD-MTX Protocol			
Yes	98 (88.3)	98 (88.3)	108 (97.2)
No	13 (11.7)	13 (11.7)	3 (2.7)
Dose			
500 mg/m^2	2 (1.8)	0	0
1000 mg/m^2	20 (18)	9 (8.1)	5 (4.5)
1500 mg/m^2	8 (7.2)	9 (8.1)	3 (2.7)
2000 mg/m^2	33 (29.7)	29 (26.1)	26 (23.4)
2500 mg/m^2	33 (29.7)	17 (15.3)	6 (5.4)
5000 mg/m^2	2 (1.8)	34 (30.6)	68 (61.3)
Infusion duration (hours)			
4 h	9 (8.1)	3 (2.7)	1 (0.9)
6 h	2 (1.8)	3 (2.7)	3 (2.7)
8 h	2 (1.8)	1 (0.9)	0
12 h	13 (11.7)	14 (12.9)	15 (13.5)
24 h	70 (63.1)	76 (68.5)	88 (79.3)
36 h	2 (1.8)	1 (0.9)	1 (0.9)
Timing of folinic acid rescue calculated from the start of MTX infusion			
12 h	13 (11.7)	12 (10.8)	13 (11.7)
24 h	19 (17.1)	21 (18.9)	22 (19.8)
36 h	30 (27)	32 (28.8)	37 (33.3)
42 h	36 (32.4)	33 (29.7)	36 (32.4)
Dose of folinic acid rescue			
5 mg/m^2	5 (4.5)	4 (3.6)	2 (1.8)
10 mg/m^2	38 (34.2)	21 (18.9)	18 (16.2)
12 mg/m^2	4 (3.6)	5 (4.5)	7 (6.3)
15 mg/m^2	43 (38.7)	61 (55)	70 (63.1)
Other	8 (7.2)	7 (6.3)	11 (9.9)
Frequency of folinic acid rescue			
Every 4 h	13 (11.7)	14 (12.6)	15 (13.5)
Every 6 h	89 (80.2)	91(81.9)	93 (83.8)
Every 8 h	6 (5.4)	6 (5.4)	3 (2.7)
Every 12 h	3 (2.7)	0 (0)	0 (0)
Number of folinic acid rescue			
2	2 (1.8)	2 (1.8)	2 (1.8)
3	6 (5.4)	2 (1.8)	0
4	11 (9.9)	7 (6.3)	6 (5.4)
5	23 (20.7)	27 (24.3)	28 (25.2)
6	43 (38.7)	45 (40.5)	54 (48.6)
Other	13 (11.7)	15 (13.5)	18 (16.2)

day (70%), compared with 17% using 1500–2500 mL/m^2/day and 13% prescribing <1500 mL/m^2/day. The most common hydration solutions were a 1:1 mix of 5% glucose and normal saline (32%), normal saline alone (22%), and a 2:1 mixture (12%).

Alkalinization with sodium bicarbonate was universally reported, most frequently at 50–100 mEq/m^2/day (42%). Urine pH was monitored in 95% of centers, with frequency varying: per shift (62%), every void (24%), or only at the start of infusion (9%).

Hyperhydration and alkalinization were discontinued at different points: 32% after completion of folinic acid rescue, 30% once MTX levels dropped below 0.2 μmol/L, 15% at patient discharge and 8% at the end of MTX infusion.

Administration

In most centers, HD-MTX was exclusively administered in the inpatient setting. Outpatient administration of HD-MTX was reported by 15 respondents (14%).

The methotrexate dose and infusion duration varied according to patient risk group. The most frequently reported dose in low risk (LR) was 2500 mg/m^2/day (59.4%) and 5000 mg/m^2/day in intermediate (IR) (30.6%) and high risk (HR) (61.8%).

A loading bolus of MTX was reported by 92 respondents (83%), while 19 (17%) did not use it. Among bolus users, 59 administered 10% of the total dose, 25 administered 20%, and 6 administered 25%.

Intrathecal chemotherapy at the start of MTX infusion was reported by 69% of respondents.

HD-MTX level monitoring

Capacity for MTX monitoring was limited. Sixty-two respondents (55.8%) could measure MTX levels and perform folinic acid rescue according to results, forty-two responders (37.8%) measured levels onsite, while 20 outsourced testing (18%). Only 31 responders (28%) reported receiving results within 12 h. Among centers with access, 46% measured MTX levels at 24, 48, and 72 h post-infusion.

Concomitant practices

Avoidance of concomitant drugs such as NSAIDs, trimethoprim-sulfamethoxazole, vancomycin, and omeprazole were reported by 49% of respondents, while only 39% reported special diet during HD-MTX (advising against carbonated beverages).

Folinic acid rescue

Folinic rescue was universally reported. However, the timing of initiation (24, 36, or 42 h post-MTX) and the number of doses differed according to patient risk group.

Folinic acid rescue practices varied regarding adjustment based on MTX levels. Only 36% of respondents reported adjusting folinic acid according to established MTX-based

nomograms, whereas 64% initiated rescue without MTX-guided adjustment.

HD-MTX use by risk group

Low risk (LR): Among respondents, 88.3% reported using HD-MTX for LR- ALL. The most common dose was 2000–2500 mg/m^2/day (59.4%), followed by 1000–1500 mg/m^2/day (25.2%), while higher or lower doses were rarely used (1.8%). Most centers (63.2%) administered MTX over 24 h. Folinic acid rescue was typically initiated at 36 h (27%) or 42 h (32.4%) after infusion, every 6 h in 80.2% or 4 h in 11.7%, with 5–6 total doses used in 59.4% of cases. The most frequent folinic acid dose was 15 mg/m^2 (38.4%), followed by 10 mg/m^2 (34.2%) (Table 2).

Intermediate risk (IR): the use of HD-MTX was reported in 98 respondents (88.3%). The most frequently documented dose was 5000 mg/m^2/day (30.6%), followed by 2000 mg/m^2/day (26.1%) and 2500 mg/m^2/day (15.3%). The most administered folinic acid dose was 15 mg/m^2 (55%), every 6 h in 81.9% or 4 h in 12.6%, with 5 to 6 doses (24.3% and 40.5%, respectively).

High risk (HR): A total of 97.2% (n = 108) reported using HD-MTX in this classification, at doses of 5000 mg/m^2/day (61.3%), 2500 mg/m^2/day (5.4%), 2000 mg/m^2/day (23.4%), and <2000 mg/m^2/day (7.2%). The infusion time was 36 h (0.9%), 24 h (77.5%), 12 h (13.5%), and <12 h (3.6%). The initiation of folinic acid rescue occurred at 42 h (32.4%), 36 h (32.4%), 24 h (19.8%), and 12 h (11.7%). The most frequently used dose was 15 mg/m^2 (63.1%) and 10 mg/m^2 (16.2%), every 6 h in 83.8% or 4 h in 13.5%, with 6 doses in 48.6%, 5 doses in 25.2%, and <5 doses in 7.2%.

Toxicity

Physicians reported that postponement—often with dose reduction—was the most common adjustment to HD-MTX across clinical scenarios. In cases of seizures or grade 3 mucositis, treatment was typically delayed with or without dose reduction (about one-third each), while permanent discontinuation occurred in roughly 20% of cases. Hematologic toxicities were mainly managed by postponement at the same dose (48%). Hepatic and renal impairments led to more frequent dose reductions (37% and 46%) Overall, clinicians favored postponement strategies over discontinuation, reserving treatment cessation for severe hepatic or renal toxicity (Figure 1).

Barriers

Finally, participants noted common logistical barriers, including delays due to limited bed availability (39%), lack of methotrexate level monitoring (61%), and reliance on outsourced testing (18%), with turnaround times ranging from 24 to 72 h.

Comparison of HD-MTX practices between public and private institutions

A comparative analysis between public and private institutions showed no statistically significant differences across most HD-MTX administration practices. The availability of institutional guidelines was limited in both settings (42.7% in public vs 26.7% in private institutions, $p = 0.23$). Similarly, hyperhydration timing, prescribed fluid volumes, and urinary pH monitoring practices were comparable between groups ($p > 0.05$).

Access to methotrexate (MTX) level monitoring was higher in private institutions (84% vs 51%), largely due to the availability of outsourced laboratory services; however, this difference did not reach statistical significance. Notably, private institutions reported significantly shorter turnaround times, with 53.3% receiving MTX results within 12 h compared to 24% in public centers ($p = 0.04$). Additionally, there was a trend toward earlier discontinuation of hyperhydration and alkalinization based on MTX levels in private institutions ($p = 0.05$).

No statistically significant differences were observed in MTX dosing across low-, intermediate-, and high-risk groups ($p > 0.05$), and infusion duration patterns were similar, with most centers administering MTX over 24 h regardless of institution type.

In contrast, significant differences were identified in reported barriers. Treatment delays due to bed unavailability and chemotherapy shortages were reported exclusively in public institutions (45% and 18%, respectively; $p = 0.001$), while these barriers were not reported in private settings (Table 3).

Discussion

The variability observed in pediatric ALL treatment protocols across Mexican centers reflects patterns reported in LMICs globally. A systematic review by Duffy et al.[9] found that 64% of pediatric ALL regimens in LMICs undergo protocol modifications, underscoring the challenges of implementing resource-intensive therapies in constrained settings.[5] In this context, HD-MTX appears particularly vulnerable to modification, accounting for 28.8% of regimen changes and representing the most frequently altered drug. These adjustments are largely driven by supportive care requirements, limited access to therapeutic drug monitoring, inconsistent drug availability, and infrastructure constraints. The variability in HD-MTX administration observed in our survey likely reflects these systemic barriers rather than isolated deviations from standard care.

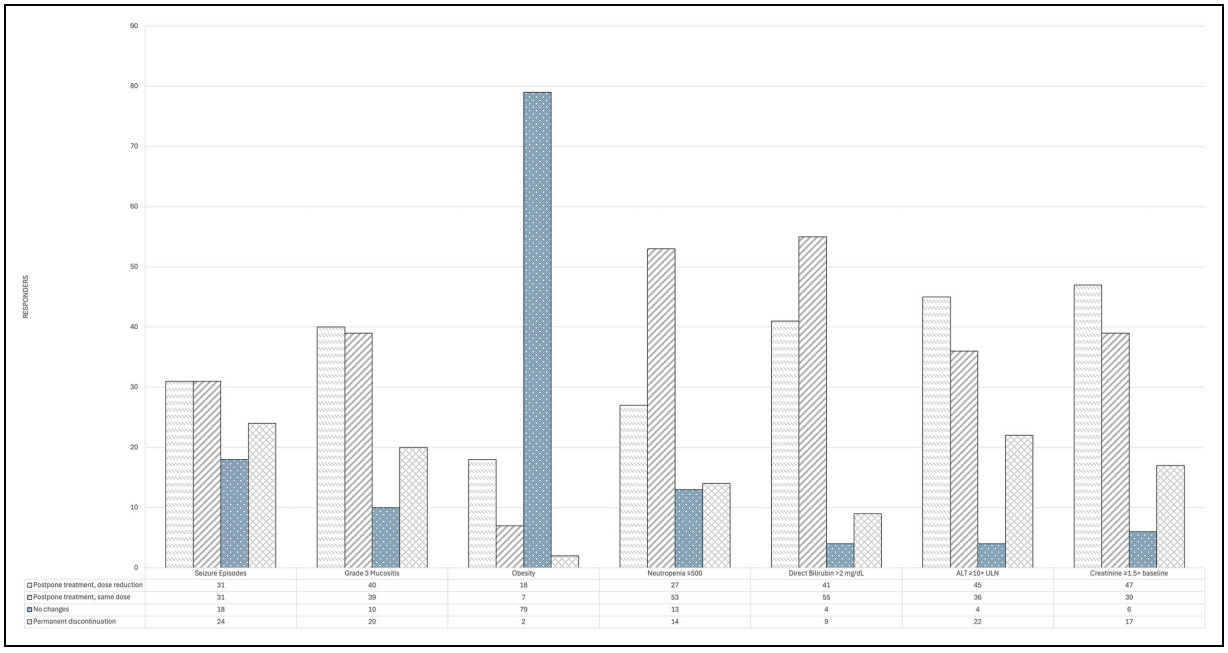

Figure 1. Reported treatment adjustments after toxicity during HD-MTX therapy reported clinical management strategies in response to selected adverse events occurring during or after high-dose methotrexate (HD-MTX) administration in pediatric acute lymphoblastic leukemia (ALL). Management options included treatment postponement with dose reduction, postponement at the same dose, no modification, and permanent discontinuation. Percentages represent the proportion of respondents selecting each strategy for the corresponding toxicity scenario. Data are based on self-reported institutional practice patterns. Abbreviations: HD-MTX, high-dose methotrexate; ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase.

HD-MTX is conventionally defined as a methotrexate dose $\geq$500 mg/m^2 administered intravenously. However, in most international ALL protocols, the actual doses used are considerably higher—typically $\geq$2000 mg/m^2—which may create confusion when comparing definitions across studies.[4] In our survey, only one-third of participating centers in Mexico adhered to this conventional threshold, reflecting both variability in interpretation and adaptation to local resource constraints. When compared with established international protocols (Table 4), which recommend 5000 mg/m^2 for HR patients and 2000–2500 mg/m^2 for IR patients, our results show considerable variability in local practice. Although 97% of respondents administered HD-MTX to HR patients (the group for whom optimal methotrexate intensity is most critical for central nervous system prophylaxis and relapse prevention) only 61% used the full recommended dose, while nearly one-third used reduced doses. This pattern likely reflects concerns about toxicity and limited monitoring capacity. In contrast, dosing for lower-risk groups was more consistent with protocol standards.

Most participating centers administered HD-MTX exclusively in inpatient settings, with only 14% offering outpatient infusions, highlighting a key opportunity for innovation. Outpatient HD-MTX has been shown to be safe and effective while substantially reducing costs, with hospitalization expenses up to tenfold higher than outpatient delivery ($10,921–$44,533 vs. $1981–$3197).[10] However, successful outpatient implementation requires adequate supportive infrastructure, access to MTX level monitoring, and structured caregiver education for early toxicity recognition. Strengthening these components could enable broader adoption of outpatient HD-MTX programs in LMICs without compromising treatment quality.

Renal toxicity remains one of the most clinically significant complications of HD-MTX.[11] Prevention relies primarily on adequate hydration and urine alkalinization. For doses commonly used in acute leukemia, hydration calculated at 3000 mL/m^2 of body surface area—typically using a 1:1 mixture of glucose-containing solutions and normal saline—is generally recommended.[12] Maintaining urinary pH $\geq$ 7 is critical to prevent MTX crystal precipitation and tubular injury,[4] with no proven benefit from targeting higher pH levels, however, this specific practice was not directly assessed in our survey..[13] While bicarbonate-containing fluids were used by all respondents to maintain urine alkalinization, their incompatibility with many supportive medications may increase nursing workload and disrupt adequate hydration.

While traditional protocols recommend prolonged prehydration, randomized data indicate that reducing prehydration from 12 to 6 h does not increase nephrotoxicity

Table 3. Comparison of institutional practices for high-dose methotrexate (HD-MTX) administration between public and private health institutions.

Variable	Public health institutions Frequency n = 96 Percentage (100%)	Private health institutions Frequency n = 15 Percentage (100%)	p
Institutional guideline available			0.23
-Yes	41 (42.7%)	4 (26.7%)	
-No	55 (57.3%)	11 (73.3)	
Hyperhydration administration			0.15
• 6 h pre-infusion	12 (12.5%)	3 (20%)	
• 8 h pre-infusion	5 (5.2%)	1 (6.7%)	
• 12 h pre-infusion	37 (38.5%)	1 (6.7%)	
• 24 h pre-infusion	40 (41.7%)	9 (60%)	
• 36 h pre-infusion	2 (2.1%)	1 (6.7%)	
Prescribed Fluid Volumes			0.17
• ≥ 3000 mL/m^2/day	67 (69.8%)	11 (73.3%)	
• 2000–3000 mL/m^2/day	16 (16.7%)	1 (6.7%)	
• 1500–2000 mL/m^2/day	8 (8.3%)	0 (0%)	
• < 1500 mL/m^2/day	5 (5.2%)	3 (20%)	
Urinary pH monitoring			0.43
-No	4 (4.2%)	1 (6.7%)	
-Yes	92 (95.8%)	14 (93.3%)	
• Per shift	• 62 (%)	• 7 (50%)	
• Every void	• 21 (%)	• 6 (40%)	
• Only at the start of infusion	• 9 (%)	• 1(6.7%)	
Hyperhydration and alkalinization discontinuation			0.05
• After completion of folinic acid rescue	• 34 (35.4%)	2 (13.3%)	
• Once MTX levels dropped below 0.2 µmol/L	• 30 (31.3%)	8 (53.3%)	
• At patient discharge	• 26 (27.1%)	2 (13.3%)	
• At the end of MTX infusion	• 6 (6.3%)	3 (20%)	
Institutional access to MTX level monitoring			0.21
-Yes	35 (36.5%)	7 (46.7%)	
-No	61 (63.5%)	8 (53.3%)	
• Outsourced MTX levels	• 14 (14.6%)	• 6 (40%)	
MTX level results report time			0.04
<12 h	23 (24%)	8 (53.3%)	
12–24 h	6 (6.3%)	4 (26.7%)	
24–48 h	7 (7.3%)	1 (6.7%)	
> 48 h	13 (13.5%)	0 (0%)	
Outpatient administration of HD-MTX			0.67
-Yes	13 (13.5%)	2 (13.3%)	
-No	83 (86.5%)	13 (86.7%)	
Concomitant Practices			0.28
• Avoided interaction drugs			
• Yes	44 (45.8%)	7 (46.7%)	
• No	52 (54.2%)	8 (53.3%)	
• Special diet			
• Yes	35 (36.5%)	5 (33.3%)	
• No	61(63.5%)	10 (66.7%)	
ALL Low Risk Dose			0.20
500 mg/m^2	2 (2.1%)	0 (0%)	
1000 mg/m^2	16 (16.7%)	4 (26.7%)	
1500 mg/m^2	7 (7.3%)	1 (6.7%)	
2000 mg/m^2	26 (27.1%)	7 (46.7%)	
2500 mg/m^2	32 (33.3%)	1 (6.7%)	
5000 mg/m^2	1 (1%)	1 (6.7%)	
NA	12 (12.5%)	1 (6.7%)	
ALL Intermediate Risk Dose			0.10
500 mg/m^2	0 (0%)	0 (0%)	
1000 mg/m^2	7 (7.3%)	2 (13.3%)	

(*continued*)

Table 3. Continued.

Variable	Public health institutions Frequency n = 96 Percentage (100%)	Private health institutions Frequency n = 15 Percentage (100%)	p
1500 mg/m^2	8 (8.3%)	1 (6.7%)	
2000 mg/m^2	21 (21.9%)	8 (53.3%)	
2500 mg/m^2	16 (16.7%)	1 (6.7%)	
5000 mg/m^2	31 (32.3%)	3 (20%)	
NA	13 (13.5%)	1 (6.7%)	
ALL High Risk Dose			0.61
500 mg/m^2	0 (0%)	0 (0%)	
1000 mg/m^2	5 (5.2%)	0 (0%)	
1500 mg/m^2	2 (2.1%)	1 (6.7%)	
2000 mg/m^2	21 (21.9%)	5 (33.3%)	
2500 mg/m^2	5 (5.2%)	1 (6.7%)	
5000 mg/m^2	60 (62.5%)	8 (53.3%)	
NA	3 (3.1%)	0 (0%)	
Low Risk Infusion duration (hours)			0.58
4 h	10 (10.4%)	1 (6.7%)	
6 h	1 (1.0%)	1 (6.7%)	
8 h	2 (2.1%)	0 (0%)	
12 h	11 (11.5%)	3 (20%)	
24 h	58 (60.4%)	9 (60%)	
36 h	2 (2.1%)	0 (0%)	
NA	12 (12.5%)	1 (6.7%)	
Intermediate Risk Infusion duration (hours)			0.71
4 h	2 (2.1%)	1 (6.7%)	
6 h	2 (2.1%)	1 (6.7%)	
8 h	1 (1%)	0 (0%)	
12 h	11 (11.5%)	2 (13.3%)	
24 h	66 (68.8%)	10 (66.7%)	
36 h	1 (1%)	0 (0%)	
NA	13 (13.5%)	1(6.7%)	
High Risk Infusion duration (hours)			0.14
4 h	2 (2.1%)	0 (0%)	
6 h	1 (1%)	2 (13.3%)	
8 h	3 (3.1%)	0 (0%)	
12 h	13 (13.5%)	2 (13.3%)	
24 h	76 (89.2%)	11 (73.3%)	
36 h	1 (1%)	0 (0%)	
Reported barriers			0.001
- Treatment delays due to bed unavailability	44 (45%)	0(0%)	
-Lack of methotrexate level monitoring	65 (67%)	2(13%)	
- Delay in methotrexate level reporting	35 (36%)	2(13%)	
- Shortage of chemotherapy drugs	18 (18%)	0 (0%)	

HD-MTX: High-dose methotrexate; MTX: Methotrexate; ALL: Acute lymphoblastic leukemia; NA: Not available; h: Hours; mL/m^2/day: Milliliters per square meter per day; µmol/L: Micromoles per liter.

or impair MTX clearance, offering flexibility for high-occupancy or resource-limited centers.[14] Low-cost surrogate markers, such as urine specific gravity, may also help guide adequate hydration prior to MTX initiation. Continued hydration for 24–48 h post-infusion remains consistently recommended.[4] Additional risk factors, including concomitant nephrotoxic medications and hypoalbuminemia, further increase the risk of renal injury and require systematic assessment.[15]

A major safety concern identified in our survey was the limited availability of MTX plasma level monitoring. Nearly half of centers lacked access to MTX assays, either onsite or via referral laboratories. This represents a substantial patient-safety gap, as pharmacokinetic monitoring is central to HD-MTX management and is explicitly recommended by international protocols.[5] These guidelines uniformly advocate serial MTX measurements until serum levels fall below 0.01 µmol/L, accompanied by renal

Table 4. Summary of supportive care parameters and monitoring schedules for high-dose methotrexate (HD-MTX) administration according to international pediatric ALL protocols.

Protocol (Reference)	MTX dose	MTX doses bolus	Pre-TX labs	During-TX labs	Hyperhydration	Hydration (volume and solution)	Bicarbonate dose & target pH	When start folinic & dose	When to monitor MTX level
ALL IC-BFM 2009 (1)	SR, IR: 2 g/m2 HR: 5 g/m^2	10% for 30 min	Cr, ALT, urine pH	24 h, 48 h	Begin ≥12 h before MTX, continue 48–72 h after	125 mL/m^2/h (0.45% NaCl + 5% dextrose + 20 mmol KCl)	50 mmol/L; urine pH ≥7	15 mg/m^2 at 42, 48, 54 h	24, 48 h (MTX and creatinine)
IciCLe (2)	HR: 3 g/m^2	10% for 30 min	Cr urine pH	0, 24, 48 h	Begin 12 h prior to MTX, continue 72 h after	125 mL/m^2/h (0.45% NaCl + 5% dextrose + KCl 20 mmol/L)	50 mmol/L; urine pH ≥7	15 mg/m^2 at 42, 48, 54, 60, 66, 72 h	42–48 h
TOTAL XV (3)	LR: 2.5 g/m^2 SR, HR: 5 g/m^2	10% over 1h	CBC, Cr, ALT, AST, uric acid, urine pH	24 h, 48 h	Start ≥2 h before, continue 48–72 h post-infusion	200 mL/m^2/h with 40 mEq $NaHCO_3$/L	Maintain pH ≥6.5; bolus $NaHCO_3$ 12mEq/m^2 if <6.5	15 mg/m^2 at 42, 48, 54 h	24, 42h
COG (Children's Oncology Group) (4)	5 g/m^2	10% over 30 min	CBC, Cr, BUN, Bili, ALT, urine pH	24 h, 48 h	Begin 6–12 h before MTX; continue until levels <0.1 µmol/L	≥125 mL/m^2/h (5% dextrose + 0.25–0.45% NaCl + 30 mEq $NaHCO_3$/L)	Maintain urine pH 7–8	15 mg/m^2 at 42, 48, 54 h	24, 42, 48h
UKALL 2011 (5)	5 g/m^2	10% over 30 min	CBC, Cr, LFTs, urine pH	24 h, 48 h	Begin 6 h prior, continue ≥24 h after	125–150 mL/m^2/h (0.45% NaCl + KCl + $NaHCO_3$)	Maintain urine pH 7–8	15 mg/m^2 at 42, 48, 54 h	24, 42, 48 h

MTX; methotrexate; SR; standard risk; IR; intermediate risk; HR; high risk; CBC: complete blood count; Cr: creatinine; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LFTs: liver function tests; BUN: blood urea nitrogen; Bili: bilirubin; NaCl: sodium chloride; $NaHCO_3$: sodium bicarbonate; KCl: potassium chloride; pH: potential of hydrogen; TX: treatment; HD-MTX: high-dose methotrexate; µmol/L: micromoles per liter; mmol/L: millimoles per liter; mEq, milliequivalents.

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function monitoring, to guide folinic rescue and supportive care adjustments. Structural barriers such as high assay costs, limited sample throughput, and challenges in laboratory validation largely explain this deficiency. From a geographic perspective, regional reference centers could potentially be coordinated (e.g., Northern region—Monterrey; Central Southern region—Mexico City; Western—Guadalajara Southern region— Mérida). Additionally, sample transport and processing between centers may introduce delays in result turnaround times. In our setting this is further constrained by the fragmentation of the public healthcare system, where funding and laboratory services are restricted within each institutional network (e.g., IMSS, ISSSTE, IMSS-Bienestar), limiting cross-institutional coordination.

In response, simplified monitoring strategies have been proposed. Reduced-sampling approaches, including two-point measurements at 48 and 72 h using Bayesian modeling[16] or single-time-point monitoring at 36 h[17] have demonstrated safety and efficacy comparable to conventional serial sampling.[18]

Importantly, renal function has emerged as a clinically meaningful surrogate marker for delayed MTX clearance. Large cohort analyses have shown that a > 50% increase in serum creatinine from baseline is a stronger predictor of delayed elimination than MTX levels at infusion completion.[19] Consistent findings across multiple studies support the routine use of serum creatinine at 24 and 48 h as a low-cost, widely accessible tool to guide toxicity risk assessment and rescue escalation in resource-limited environments.[20] However, universal recommendations still favor direct MTX level measurement, and the use of renal function as a surrogate should be reserved for settings where pharmacokinetic monitoring is unavailable.

Strict adherence to standardized folinic acid rescue protocols constitutes the cornerstone of HD-MTX safety. This is especially relevant in Mexico, where access to glucarpidase is severely limited by high costs and importation barriers. HD-MTX toxicity is primarily determined by the duration of exposure rather than peak plasma concentration; thus, timely initiation and appropriate continuation of folinic acid rescue—usually beginning 36–48 h after infusion start—can substantially mitigate toxicity, even in the presence of elevated MTX levels.[4]

Empirical folinic acid dosing strategies, including nomogram-based and clinically guided escalation, lack universal validation. Furthermore, excessive folinic acid rescue may compromise antileukemic efficacy, underscoring the delicate therapeutic balance between preventing toxicity and preserving treatment effectiveness[19] In our cohort, only 36% of centers reported nomogram-guided adjustment of folinic acid, while the majority initiated rescue without MTX level guidance, likely reflecting limited access to timely MTX monitoring. Simplified MTX monitoring strategies and national efforts to strengthen laboratory capacity therefore represent complementary pathways to improve the safety, feasibility, and equity of HD-MTX delivery in resource-limited environments.

For centers where standard HD-MTX administration is logistically unfeasible, Capizzi-style methotrexate regimens offer a pragmatic alternative, although they do not replace HD-MTX in HR disease. This outpatient-based approach requires less intensive monitoring and omits MTX level measurement and LV rescue, while maintaining favorable outcomes—particularly in T-cell ALL—as demonstrated in both ICiCLe and COG AALL0434 studies.[21,22] Selective adoption of such regimens may reduce hospitalization burden without compromising efficacy in appropriately selected patients.

Notably, only 56% of surveyed centers reported having formal institutional guidelines for HD-MTX administration. The absence of standardized protocols, combined with limited monitoring capacity, places critical decisions regarding hydration, alkalinization, and rescue management at the level of individual clinicians, increasing the risk of delayed toxicity recognition and inconsistent care. While international protocols provide comprehensive supportive care recommendations, our findings reveal substantial divergence in local practice, to address these gaps. Institutions should prioritize the development of locally adapted, evidence-based HD-MTX protocols.

Despite structural differences between healthcare sectors, HD-MTX practices were largely comparable between public and private institutions, with no significant differences observed in guideline availability, supportive care measures, dosing, or infusion strategies. While private institutions demonstrated greater overall access to MTX level monitoring and significantly shorter turnaround times, these advantages did not translate into meaningful differences in clinical practice. In contrast, systemic barriers such as treatment delays and chemotherapy shortages were exclusively reported in public centers, underscoring persistent resource inequities. These findings suggest that variability in HD-MTX delivery is driven more by a lack of standardization than by institutional type, while highlighting infrastructure gaps that may impact timely and safe treatment delivery. The imbalance in group distribution reflects the real-world context of pediatric oncology care in Mexico and has been acknowledged as a study limitation.

This study has some limitations. Data were self-reported, which may introduce bias and limit verification of actual clinical practices. The sample size was modest, and on-site confirmation of reported practices was not feasible. The true response rate could not be calculated since the number of eligible participants reached was unknown. Additionally, differences between public and private institutions were not analyzed, which may be relevant given resource

disparities. Despite these limitations, the study provides valuable real-world insight into HD-MTX administration in Mexico.

Collectively, this national survey provides the first comprehensive characterization of HD-MTX implementation practices across pediatric oncology centers in Mexico, demonstrating substantial variability and identifying critical system-level gaps with direct implications for patient safety. Efforts to reduce disparities in childhood cancer outcomes require not only the identification of these barriers, but also the application of feasible, context-adapted interventions informed by available evidence.

Based on these findings, several measures can be consistently implemented across centers to improve the safety and standardization of HD-MTX delivery. These include discontinuation of nephrotoxic or interacting medications prior to infusion; standardized pre-treatment assessment of renal function and third-space effusions; maintenance of adequate hydration ($\geq$125 mL/m^2/h) with urine alkalinization (pH $\geq$7); and protocolized folinic acid rescue with predefined criteria for dose escalation.

In settings where MTX plasma level monitoring is not available, daily assessment of renal function (BUN and creatinine) may provide a pragmatic approach to support clinical decision-making, although it does not substitute for pharmacokinetic monitoring. Evidence of delayed methotrexate clearance should prompt intensification of supportive care measures. Despite the feasibility of these interventions, the limited availability and delayed turnaround times of MTX plasma level monitoring remain significant constraints. Improving access to timely MTX level assessment represents a key priority for optimizing HD-MTX safety at a national level.

Potential system-level strategies include the establishment of regional laboratory networks to facilitate sample processing and reduce turnaround times, as well as the development of a nationally adapted, evidence-based guideline to support standardized clinical practice and reduce inter-institutional variability. These approaches are consistent with the need to strengthen care delivery frameworks in resource-constrained settings.

Conclusion

In conclusion, optimizing HD-MTX delivery in LMICs requires the integration of standardized clinical practices with targeted health system interventions, particularly those aimed at improving access to timely pharmacokinetic monitoring.

Acknowledgments

The authors thank the participating pediatric oncology and hematology centers and clinicians for their contributions to this national survey, as well as the Mexican Association of Pediatric Hematology (AMEH) and the Mexican Association of Pediatric Oncology and Hematology (AMOHP) for facilitating participation through their electronic platforms.

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Ethical approval and informed consent

The study was reviewed and approved by the Ethics Committee of the School of Medicine of the Autonomous University of Nuevo León (PI23-00024). Given the survey-based design and the use of anonymized institutional data, informed consent was not required in accordance with local regulations.

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Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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