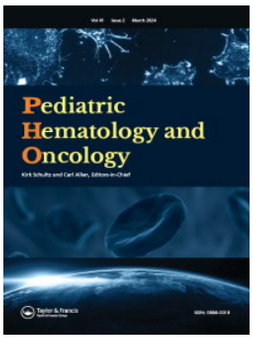

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Access to Methotrexate Monitoring in Latin America: A Multicountry Survey of Supportive Care Capacity

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ABSTRACT

High-dose methotrexate (HDMTX) is used to treat a broad spectrum of cancers. Methotrexate (MTX) monitoring and adequate supportive care are critical for safe drug administration; however, MTX level timing is not always possible in low- and middle-income countries. The aim of this study was to evaluate HDMTX supportive care capacity and MTX monitoring practices in Latin America (LATAM) to identify gaps and opportunities for improvement. A multicenter survey was conducted among LATAM pediatric oncologists. Twenty healthcare providers from 20 institutions answered the online questionnaire. HDMTX was used to treat acute lymphoblastic leukemia (ALL; 100%), non-Hodgkin lymphoma (84.2%), diffuse large B-cell lymphoma (47.4%), osteosarcoma (78.9%), and medulloblastoma (31.6%). Delays in starting HDMTX infusion were related to bed shortages (47.4%) and MTX shortages (21.1%). MTX monitoring was performed at an in-hospital laboratory in 52%, at an external/nearby laboratory in 31.6%, and was not available in 10.5%. Median interval between sampling and obtaining MTX levels was ≤ 2 h in 45% and ≥ 6 h in 30%, related to laboratory location. Sites without access to MTX monitoring reduced the MTX dose for patients with high-risk ALL or did not include MTX in the treatment of patients with osteosarcoma. Respondents reported that implementation of point-of-care testing of MTX levels is feasible. In LATAM, highly variable supportive care capacity may affect the safe administration of MTX doses. Improving accessibility of MTX monitoring and the speed of obtaining results should be prioritized to allow delivery of full doses of MTX required by the current protocols.

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Introduction

Methotrexate (MTX) has been classified as an essential medicine by the World Health Organization (WHO)[1] and it is broadly used worldwide to treat various pediatric and adult cancers, including acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), osteosarcoma, and medulloblastoma, among others.[2]

High-dose MTX (HDMTX) can cause multiple toxic side effects including acute kidney injury, mucositis, neurotoxicity, hepatotoxicity, and myelosuppression. Supportive care interventions to ensure the safety and efficacy of HDMTX administration have been reported in the literature[2–4] and MTX has been delivered without or with limited MTX monitoring in a variety of contexts using additional fluids, leucovorin, and hospitalization days.[2,5–8] Nevertheless, therapeutic MTX monitoring is crucial to better guide supportive care measures and prevent MTX-related serious adverse events and sub-optimal uses.

The lack of supportive care resources and the difficulties of managing patients with a higher risk for HDMTX-induced toxicities (e.g. elderly patients, patients with renal dysfunction) result in sub-optimal use of HDMTX, even in conditions and age groups for which it is routinely included in the treatment plan.[9] Furthermore, the occurrence of toxicities may lead to the omission of future doses or dose reduction in subsequent cycles, thereby increasing the risk of relapse.[10] In addition, extra supportive care measures such as the addition of extra days of intravenous fluids and leucovorin rescue to compensate for the lack of MTX levels might lead to longer hospital stay, a relevant metric in middle-income countries where chronic bed shortages frequently delay chemotherapy for other patients.

In recent decades, point-of-care testing has been implemented in many areas of medicine as a strategy to make diagnostic results easily available and allow for timely clinical decision-making.[11] Such technologies have led to improvements in care of a wide range of diseases including diabetes (blood glucose meter),[12] the diagnosis and monitoring of multiple infectious diseases,[13,14] such as coronavirus disease (COVID-19),[15] and therapeutic drug monitoring[16–18] with an ongoing effort to develop a point-of-care testing device to measure MTX levels.[19] Point-of-care testing strategies to monitor MTX levels would be particularly beneficial to institutions with limited or no access to MTX levels and with a relatively small volume of patients requiring MTX monitoring.

Supportive care capacity has been reported from low- and middle-income countries around the world; however, it has not been systematically evaluated in Latin America. Therefore, this research aimed to evaluate supportive care capacity in Latin America to identify gaps and opportunities for improvement within this region.

Methods

A multicenter cross-sectional survey study was designed to capture information about supportive care strategies used for HDMTX infusion and the feasibility of implementing point-of-care testing to measure MTX levels in Latin America. The survey was conducted using a questionnaire consisting of 79 questions in five domains, including on-site demographics, patient population, HDMTX supportive care practices (e.g. hydration practices, supportive care medications, MTX levels, and other toxicity measurements), HDMTX disease-specific questions (e.g. regarding methotrexate dosing and supportive care practices by cancer type), as well as questions on point-of-care testing implementation. The survey was available in

English and Spanish (Supplementary data – Questionnaire). Pretesting of the questionnaire was done in both English and Spanish by seven pediatric hematologists and oncologists (key opinion leaders) from four countries within the target region and members of the High-Dose Methotrexate Supportive Care Committee of the Resonance Research Network. They provided feedback on each of the questions, the survey methodology, questionnaire completion time, and interface. Pretesting resulted in modifications to refine question phrasing and to improve Spanish translations for clarity. They also recommended to allow respondents to enter data about Diffuse Large B Cell Lymphoma separately from non-Hodgkin lymphoma, as sometime the doses, time of infusions and number of cycles differ among the protocols used in the region. The questionnaire was then distributed *via* a proprietary system called Resonance Places[1].[20] All members of the Latin American High-Dose Methotrexate Supportive Care Committee of the Resonance Research Network, an open access research and medical education network, were contacted and invited to participate. The members of this network represent a broad spectrum of practitioners from centers that treat children, adolescents, and young adults with cancer in South and Central America, including public and private institutions, oncology referral hospitals, and community hospitals. Each member was contacted on behalf of the Latin America High-Dose Methotrexate Supportive Care Committee of the Resonance Research Network. Overall, 96 physicians in 17 countries received an invitation by email containing a custom link to complete the questionnaire for their hospital, followed by two reminder emails between the period of November 2021 and January 2022. The survey was also presented at the Grupo América Latina de Oncología Pediátrica (GALOP) meeting, which took place in the first week of November 2021, to improve response rates. The custom link ensured only the intended participant could complete the questionnaire and avoided duplicate participation. All responses were anonymous, and no patient level data were collected; therefore, institutional ethical review was not required.

The laboratory location was categorized as in-hospital or external/nearby. If a respondent reported having access to an in-hospital as well as a nearby or external laboratory, it was classified as in-hospital.

Responses were summarized using descriptive statistics. Quantitative variables are presented as mean and standard deviation or median and interquartile range as appropriate and categorical variables as proportions. All statistical analysis was performed using *R Statistical Software* (version 4.2.2).

Results

Twenty healthcare providers from 20 different centers in 12 countries responded to more than 70% of the questionnaire items and were subsequently included in the analysis. Because not all respondents completed all items of the questionnaire, the denominator differs throughout these results. The respondents were from the following countries: Argentina, Brazil, Chile, Colombia, Ecuador, Haiti, Honduras, Mexico, Paraguay, Peru, Uruguay, and Venezuela. The questionnaire was completed by pediatric oncologists, some of whom also treated adolescents and young adults. Each center was assigned a site number, which was used for analysis and presentation.

[1] Resonance Places is a web-based-application provided by Resonance Inc. (https://resonancehealth.org/) available free of cost to collect institution level data.

Site characteristics

Nine of the 19 responding centers (47.37%) that reported on site characteristics treated more than 100 patients per year, with a median number of newly diagnosed patients with cancer per year of 76 (IQR, 40 - 200). Eighteen respondents (94.7%) provided information about the number of patients they treat with HDMTX per year. Median number of newly diagnosed pediatric oncology patients treated with HDMTX each year was 30 (IQR, 16 – 50), with 14 out of 18 sites (88.9%) treating more than 25% of their newly diagnosed patients with HDMTX every month (Supplementary data Table S1).

Gaps identified in supportive care measurements

The identified gaps in supportive care practices are summarized in Table 1 described in detail below and in Supplementary data Table S2.

Table 1. Gaps identified in supportive care measurements.

	Problem	GAP in supportive care	Solution/Endorsement
Delayed start of HDMTX infusion	**Preparedness of the medical system**	47% reported not having a bed available as a cause of delays in starting a HDTMX infusion.21% reported MTX shortages.	The administration of HDMTX in the outpatient setting allows for decreased costs and more effective bed utilization. Even though this is a feasible strategy reported in different settings, it has not yet been broadly implemented in LATAM.[21–23]
	Admission / Effective bed utilization	Only 2 sites administered HDMTX in the outpatient setting (both sites see >400 patients/year).	MTX has been classified as an essential drug by the WHO, meaning that it should be available in functional health systems at all times.[1]
	Patient preparedness to safely receive HDMTX	66.7% reported delays in achieving the urine pH goal. 94% reported using bicarbonate boluses if urine pH <7 during pre-hydration. Pre-hydration: median time of 7 h (IQR, 3.75 – 12). 90% reported giving IV hydration only (starting at the clinic/ hospital).10% reported giving both oral and IV hydration.	Urinary pre-alkalinization with oral bicarbonate and outpatient oral hydration days prior to MTX infusion at home is a feasible and safe strategy.[23,24] Foods and beverages can acidify the urine despite treatment with large amounts of bicarbonate. Those types of food and beverages should be avoided during HDMTX treatment.[3,25]
Hydration-Diuresis	**Delay in reaching/ maintaining urine output goal**	68.4% of respondents reported that they use diuretics during HDMTX courses when urine output is below goal:10 (76.9%) used furosemide 2 (15.4%) used acetazolamide1 (7.7%) used chlorothiazide	Furosemide has been reported as a risk factor for severe MTX-related renal toxicity (OR 2.56, 95% CI 1.46-4.48, $p = 0.001$). Furosemide should be avoided when using HDMTX.[26]
Alkalinization (urine pH)	**Alkalinization (urine pH)**	93.3% of respondents measure urine pH before starting MTX infusion. 46.7% with each void. One respondent reported not measuring urine pH before, during, or after HDMTX infusion	Urine pH should be maintained above 7 prior to, during, and after MTX administration until plasma solubility levels drops below threshold. Urine pH should be part of the routine of care of patients receiving HDMTX to assure safety.[3]

(*Continued*)

Table 1. Continued.

	Problem	GAP in supportive care	Solution/Endorsement
HDMTX administration safety	**Leucovorin dose adjustment**	Median minimum number of doses of leucovorin rescue was 8 in sites with $a \geq 6$-h delay or no access to MTX levels (compared to a median of 4.75 doses in sites with $a < 6$-h delay in obtaining MTX levels). If MTX level increases above target: 65% of respondents increase the dose and 35% decrease the interval between doses of leucovorin.	It has been reported in the literature that institutions with delayed or no access to MTX level monitoring (≥ 2 h) or those with access to only a limited number of MTX levels usually intensify leucovorin rescue;[8,27] however, over-rescuing has the potential risk of decreasing HDMTX efficacy and has been related to a higher risk of relapse in patients with leukemia and a decrease in the anti-leukemia effect of MTX.[28–30]
	Access to MTX levels	**Laboratory Location** 2 sites have no access to MTX levels. 31.6% only have access through an external/nearby laboratory. 52.6% reported having access to an in-house laboratory. **MTX levels results timing** 88.2% have access on weekdays during working hours (8AM to 5PM).29.4% have access on weekdays after working hours (5PM to 8AM). 47.1% have access during weekends. 35.3% have access during holidays. The median time to MTX level results was 6 h (IQR: 4-24) for external/nearby laboratories and 2 h (IQR: 2-3.5) for in-hospital laboratories.	Access to timing MTX levels is essential for the safe administration of HDMTX and to prevent over-rescuing; however, in-house MTX level monitoring is costly to implement, especially in institutions with a relatively small number of patients. Point-of-care testing has been implemented in many areas of medicine as a strategy to make diagnostic results easily available and allow for timely clinical decisions.[11] Work is underway to apply this point-of-care testing strategy to HDMTX drug monitoring.[19] The implementation of a bedside/point-of-care testing device to measure MTX levels could overcome barriers in care and cost and speed-up the availability of MTX level results for institutions with delays in access and those with no access at all.
	Glucarpidase	None of the respondents currently has access to glucarpidase. None of the respondents used glucarpidase in a patient with severely delayed MTX clearance.	Glucarpidase is useful in the management of patients with delayed MTX elimination, which is a medical emergency as prolonged exposure to MTX can result in life-threating toxicities.[3]
Identification and management of acute kidney injury	**Standard of care practices for measuring creatinine level**	Serum creatinine levels are measured: - When the patient arrives at the hospital (94.1%). - At the end of HDMTX infusion (47.1%). - Only 23.5% reported measuring creatinine with every MTX level.	Management of HDMTX-induced nephrotoxicity calls for aggressive supportive care adjustments: increase of IV fluids, optimization of alkalinization, addition of acetazolamide when urine pH < 7 to maximize MTX elimination, and reduction of the risk of crystal formations in the kidney. High doses of leucovorin should be administrated until MTX is completely eliminated.[2]
	Adjustment of supportive care practices to an elevated creatinine level of >50% from baseline	56.2% reported increasing IV fluid infusion and optimizing urine alkalinization.37.5% increased the dose of leucovorin and decreased the interval between leucovorin doses.18.8% switched leucovorin from oral to IV administration.68.8% measured the MTX level. 12.5% responded not making changes based on creatinine levels.	

Abbreviations: IV: intravenous, MTX: methotrexate, HDMTX: high-dose methotrexate.

Delays in the initiation of MTX infusion

Preparedness of the medical system. Administrative delays to start an HDMTX infusion were reported by 60% of the respondents, and the main causes were not having a bed available at the time of admission (47.4%), problems with MTX shortages (21.1%), and temporarily not having nursing or other staff available (15%).

Six out of 18 sites (33.3%) administered more than 10 cycles of HDMTX per month with a median of 6 cycles (IQR, 3 - 15). Two of the 20 responding institutions (10%) frequently administer HDMTX in an outpatient setting, both of which with a high patient volume (700 and 450 new patients per year).

Patient preparedness to safely receive HDMTX. Of 20 respondents, 18 (90%) reported administering pre-hydration using intravenous fluids only, while the remaining two (10%) gave fluids both intravenously and orally. The minimum duration of pre-hydration varied widely among sites (median, 7 h; IQR, 3.75 – 12) (Supplementary data Table S3).

More than half of the respondents (66.7%) reported delays in achieving urine pH, which resulted in delays in the initiation of HDMTX infusion. All participants reported starting pre-alkalinization at the hospital/clinic with intravenous infusions of bicarbonate and most respondents (16 out of 17) reported giving bicarbonate boluses to patients with urine pH <7 before starting HDMTX infusion in order to achieve target urinary pH. Only one site reported not measuring urine pH routinely for patients treated with HDMTX.

Hydration-Diuresis

The median urine output goal before starting HDMTX infusion was 100 ml/m^2/hr (IQR, 85 - 115). The median hydration rate was 125 ml/m^2/hour (IQR, 125 – 150) and the median concentration of bicarbonate in the intravenous fluid was 40 mEq/L (IQR, 32.5 - 40). Diuretics were used when urine output was below goal by 13 out of 19 (68.4%) respondents, 10 (76.9%) of whom used furosemide, two (15.4%) acetazolamide, and one (7.7%) chlorothiazide.

Alkalinization

Fourteen out of 15 respondents (93.3%) reported that they measure urine pH before HDMTX infusion. Only one reported not measuring urine pH before, during, or after the infusion and seven (46.7%) routinely measured urine pH with each void. Most sites reported using intravenous bicarbonate boluses if urine pH was less than 7 during HDMTX infusion.

HDMTX administration safety

Leucovorin. Leucovorin was administered at all participating sites starting with a 6-h dosing interval. Sites with no access to or $a \geq 6$-h delay in obtaining MTX levels administered a median of 8 scheduled doses of leucovorin during a HDMTX course (IQR, 8 - 12), compared to a median of 4.75 doses (IQR, 3 – 5.75) at sites with $a < 6$-h delay in obtaining MTX levels. Details on leucovorin administration according to cancer type, including the timing of the first dose, dose intervals, and criteria to discontinue

leucovorin, are presented in Supplementary data Table S4. For patients with ALL, the median minimum plasma MTX level to discontinue leucovorin was 0.25 µmol/L (IQR, 0.20 – 0.28), whereas for patients with NHL, it was 0.2 µmol/L (IQR, 0.2 – 0.25), for patients with DLBCL 0.25 µmol/L (IQR, 0.24 – 0.25), and for patients with osteosarcoma 0.20 µmol/L (IQR, 0.10 – 0.28).

Upon detection of an elevated MTX level, seven out of 20 (35%) respondents decreased the interval of leucovorin doses, and 13 (65%) increased the current dose. In addition, nine (45%) optimized alkalinization and increased the rate of intravenous fluids and 10 (50%) monitored serum creatinine levels.

Access to MTX levels: laboratory location and time to methotrexate levels results. Ten out of 19 respondents (52.6%) reported MTX levels were measured at an in-hospital laboratory, six (31.6%) had access to an external-nearby laboratory, and two (10.5%) had no possibility to obtain MTX levels. During weekdays, 15 of 17 sites (88.2%) had access to MTX levels during working hours (8AM – 5 PM) and five (29.4%) after working hours (5PM to 8AM). Nine of 17 respondents (47.1%) had access to MTX levels during weekends and six (35.3%) during holidays. Median time to obtain MTX level results was 2 h (IQR, 2-3.5) for in-hospital laboratories and 6 h (IQR, 4 - 24) for external and nearby laboratories.

The median minimum dose for which sites measure MTX levels as part of their standard of care was 2 g/m^2 (IQR, 1 - 3), with only one site reporting measuring MTX levels for doses of 0.5 g/m^2 and three sites for patients treated with doses of 5 g/m^2.

A series of questions were asked about the respondents' present use of point-of-care testing devices as well as factors influencing adoption of a point-of-care testing for measuring MTX, should it become available to them. Nine of 19 (47.4%) respondents reported that they routinely use point-of-care testing in their hospitals for patient care and that it is performed mainly by nurses (53.3%), followed by doctors and residents (20%). The most important factors influencing adoption of a point-of-care testing device for measuring MTX levels appear to be time saving (ranked as very important or important by 95%), practicality (ranked as very important or important by 90%), and not compromising patient safety (ranked as very important or important by 90%). When asked about the barriers to adopting point-of-care testing to measure MTX levels, the greatest barriers reported were funding needed to acquire and implement the device in 13 of 19 (68.4%), followed by hospital administration approval in 10 of 19 (52.6%).

Glucarpidase

All respondents reported they currently did not have access to glucarpidase and that they had never used glucarpidase in patients with severely delayed MTX clearance.

Identification and management of acute toxicities

Respondents were asked about their standard of care practices for measuring creatinine levels). Sixteen out of 17 sites (94.1%) reported measuring baseline serum creatinine when the patient arrived at the hospital, eight sites (47.1%) reported measuring serum creatinine before starting the HDMTX infusion, and eight others (47.1%) at the end

of HDMTX infusion. Only four sites (23.5%) reported measuring creatinine simultaneously with every MTX level (Supplementary Table S5).

The adjustment of supportive care practices to an elevated creatinine level was also assessed (reported as a creatinine increase higher than 50% from baseline), 9 out of 16 sites (56.2%) reported increasing intravenous fluid infusion and optimizing urine alkalinization, six (37.5%) increased the dose of leucovorin and decreased the interval between leucovorin doses, three (18.8%) switched leucovorin from oral to intravenous administration, and 11 (68.8%) measured the MTX level. Two (12.5%) responded not making changes based on creatinine levels.

High-dose methotrexate dosing and dose reductions

Table 2 shows a summary of MTX dosing and administration based on disease type and risk category. All sites reported using HDMTX to treat ALL (100%), 16 sites (84.2%) to treat NHL, nine (47.4%) diffuse large B-cell lymphoma (DLBCL), 15 (78.9%) osteosarcoma, and six (31.6%) medulloblastoma. No other cancers were reported to be treated with HDMTX. ALL dosing varied based on risk stratification, with most intermediate/standard-risk ALL being treated with doses of 2-3 g/m^2 infused over 24 h and most high-risk ALL with 5 g/m^2 over 24 h. Dosing for osteosarcoma was uniformly 12 g/m^2 with most sites administering it over a 4-h period. Dosing for medulloblastoma ranged from 5 g/m^2 over a 24-h infusion to 12 g/m^2 over a 4-h infusion. Most variation in dosing and time of infusion was observed in the treatment of non-Hodgkin lymphoma.

Twelve out of 14 sites (85.7%) reported administering doses of ≥ 5 g/m^2 for patients with high-risk ALL (full dose). Of those sites, four reported that the time to MTX level results was ≥ 6 h (33.3%). The two sites that reported treating high-risk leukemia with a dose of 1 g/m^2 over 36 h (14.3%) had no access to MTX levels. Standard risk ALL was treated with doses of between 2 and 3 g/m^2 (full dose) in 14 out of 15 sites (93.3%), with three sites reporting the time to MTX level results to be ≥ 6 h. Only one site reported using lower doses (1 g/m^2 over 36 h) (6.7%) and that site had no access to MTX levels.

All sites that reported on the treatment of osteosarcoma with MTX (n:15) used full doses (12 g/m^2). Four sites reported not using MTX to treat osteosarcoma, with two of these sites having no access to MTX levels (Supplementary data Table S5).

Discussion

Methotrexate has been used to treat cancer since the 1950s and has become an integral part of multiple oncologic protocols; however, successful management of HDMTX relies on rigorous and standardized supportive care guided by MTX level timing to prevent severe toxicities. Delays in MTX clearance without prompt detection and treatment prolong the exposure to MTX, potentially increasing the risk of morbidity and mortality, and prolonging the length of stay and cost of hospitalization. In this survey, almost half of the respondents reported not having beds available as one of the most common causes of delays in HDMTX infusion initiation. Bed shortages are a common problem in all healthcare systems, and even though MTX administration

Table 2. Summary of methotrexate dose, infusion time, and courses by cancer type compared to methotrexate level availability.

Site ID	Cancer type	Risk stratification	MTX dose(g/m^2)	Time of infusion (hours)	Number of courses	Time to MTX levels results	Laboratory location
122	NHL	VHR	5	24	6	1	In-hospital laboratory
	DLBCL	VHR	5	24	6	1	
	NHL	HR	3	24	6	1	
	DLBCL	HR	3	24	6	1	
	NHL	SR	2	24	2	1	
	DLBCL	SR	2	24	3	1	
	NHL	LR	1	4	3	1	
	DLBCL	LR	1	4	3	1	
	ALL	All risk groups	2	4	4	1	
	Osteosarcoma	All risk groups	12	4	6	1	
	Medulloblastoma	--	5	24	4	1	
159	NHL	--	8	24	--	2	In-hospital laboratory
	ALL	--	5	24	4	2	
	ALL	--	2	24	4	2	
	Osteosarcoma	--	12	4	--	2	
160	Medulloblastoma	HR	8	4	5	2	In-hospital laboratory
	DLBCL	HR	5	24	4	2	
	ALL	HR	5	24	2	2	
	DLBCL	IR	5	24	4	2	
	ALL	IR	5	24	4	2	
	DLBCL	SR	1	4	4	2	
	ALL	SR	2	24	4	2	
	DLBCL	VLR	1	4	2	2	
	DLBCL	LR	2	24	4	2	
	NHL	All risk groups	3	4	6	2	
	Osteosarcoma	All risk groups	12	4	6	2	
225	ALL	HR	5	24	4	2	In-hospital laboratory
	ALL	Relapse/ salvage therapy	--	--	--	2	
	ALL	IR	2	24	4	2	
	ALL	SR	2	24	4	2	
	Osteosarcoma	All risk groups	12	4	6	2	
226	NHL	HR[a]	3	3	6	2	In-hospital laboratory
	NHL	HR[b]	5	24	4	2	
	ALL	HR[c]	5	24	4	2	
	ALL	IR	2	24	4	2	
	ALL	SR	2	24	4	2	
	NHL	VLR[d]	1	4	2	2	
	NHL	LR[d]	1	4	4	2	
	NHL	LR[e]	3	3	3	2	
	Osteosarcoma	All risk groups	12	4	12	2	
	NHL	All risk groups[f]	5	24	4	2	
231	Osteosarcoma	HR[g]	12	4	6	6	In-hospital laboratory
	ALL	HR	5	24	6	6	
	ALL	IR	2	--	--	6	
	NHL	HR	5	24	6	6	
	NHL	SR	2	24	4	6	
	DLBCL	SR	5	24	6	6	
332	Medulloblastoma	VHR	8	4	4	4	In-hospital laboratory
	Osteosarcoma	HR[g]	12	4	12	4	
	NHL	HR	5	24	3	4	
	ALL	HR	5	24	4	4	
	NHL	IR	2	24	3	4	
	Osteosarcoma	SR[h]	12	4	12	4	
	ALL	SR	2	24	4	4	
	Medulloblastoma	SR	5	24	6	4	
	NHL	VLR	1	4	2	4	
	NHL	LR	1	4	4	4	

(*Continued*)

Table 2. Continued.

Site ID	Cancer type	Risk stratification	MTX dose(g/m^2)	Time of infusion (hours)	Number of courses	Time to MTX levels results	Laboratory location
342	DLBCL	HR	5	24	4	2	In-hospital laboratory
	ALL	HR	5	24	4	2	
	ALL	IR[i]	5	24	4	2	
	ALL	IR[i]	2	24	4	2	
	ALL	SR	2	24	4	2	
	NHL	LR	1	24	4	2	
	Osteosarcoma	All risk groups	12	4	16	2	
386	NHL	HR	8	4	3	6	In-hospital laboratory
	ALL	HR	8	4	4	6	
	NHL	SR	3	24	5	6	
	ALL	SR	3	24	4	6	
	Osteosarcoma	All risk groups	12	4	--	6	
420	NHL	HR	5	24	4	1	In-hospital laboratory
	DLBCL	HR	5	24	4	1	
	ALL	HR	5	24	4	1	
	ALL	Relapse/ salvage therapy	1	36	4	1	
	ALL	IR	2	24	4	1	
	NHL	LR	1	4	4	1	
183	DLBCL	HR	1	4	4	--	External/nearby referral laboratory
	ALL	HR	5	24	4	--	
	ALL	SR	3	24	4	--	
	Osteosarcoma	All risk groups	12	4	12	--	
385	NHL	HR	8	4	6	24	External/nearby referral laboratory
	ALL	HR	5	24	6	24	
	NHL	IR	3	3	4	24	
	ALL	IR	5	24	4	24	
389	NHL	All risk groups[k]	8	24	4	4	External/nearby referral laboratory
	ALL	All risk groups	5	24	4	4	
	Osteosarcoma	All risk groups	12	8	6	4	
427	Osteosarcoma	--	12	4	12	6	External/nearby referral laboratory
	Medulloblastoma	--	12	4	5	6	
	NHL	--	5	24	4	6	
	DLBCL	--	5	24	4	6	
444	NHL	HR	5	24	5	1	External/nearby referral laboratory
	ALL	HR	5	24	4	1	
	ALL	IR	2	24	4	1	
	ALL	SR	2	24	4	1	
	Osteosarcoma	All risk groups	12	4	6	1	
	DLBCL	All risk groups	5	24	4	1	
470	ALL	HR	5	24	4	36	External/nearby referral laboratory
	ALL	IR	2	24	4	36	
	Osteosarcoma	--	12	4	12	36	
	Medulloblastoma	--	8	4	5	36	
62	NHL	HR[l]	3	4	7	0	No MTX levels available
	NHL	HR[m]	1	36	4	0	
	ALL	HR	1	36	4	0	
	ALL	Relapse/ salvage therapy	1	36	3	0	
	ALL	IR	1	36	4	0	
	ALL	SR	1	36	4	0	
	NHL	LR[n]	1	4	4	0	
75	ALL	HR	2	8	4	--	No MTX levels available
	NHL	--	2	8	4	--	
469	Osteosarcoma	--	12	4	12	--	No data available

(*Continued*)

Table 2. Continued.

Site ID	Cancer type	Risk stratification	MTX dose(g/m^2)	Time of infusion (hours)	Number of courses	Time to MTX levels results	Laboratory location

Abbreviations: VHR: very high risk, HR: high risk, SR: standard risk, IR: intermediate risk, LR: low risk, VLR: very low risk, NHL: non-Hodgkin lymphoma, ALL: acute lymphoblastic leukemia, DLBCL: diffuse large B-cell lymphoma, MTX: methotrexate.
[a]Anaplastic Large B Cell Lymphoma.
[b]B-NHL.
[c]T- ALL.
[d]B-NHL.
[e]Anaplastic Large B Cell Lymphoma.
[f]Lymphoblastic lymphoma.
[g]Metastatic osteosarcoma.
[h]non-metastatic osteosarcoma.
[i]T- ALL.
[j]B-ALL.
[k]B-NHL: 8 gr/m^2 and T-NHL: 5 gr/m^2.
[l]Stage III y IV.
[m]Lymphoblastic Lymphoma.
[n]Stage I and II.

is not the only contributing factor, the unique aspects associated with its administration and monitoring may significantly exacerbate this situation. The administration of HDMTX in the outpatient setting allows for a more efficient utilization of beds and a reduction in costs. Even though this is a feasible strategy,[21–23] it has not yet been broadly implemented in LATAM, with only 2 sites reporting routinely administering HDMTX in outpatients. Patients treated with HDMTX require strict urine pH and hydration monitoring in order to prevent toxicities. Difficulties in achieving such goals result in longer hospital admissions to ensure optimal pre-infusion diuresis and urine alkalinization. This data shows that 66.7% of sites have to delay HDMTX infusions because of difficulties in achieving optimal urine pH and diuresis. Urinary pre-alkalinization with oral bicarbonate and outpatient oral hydration at home days prior to MTX infusion has been shown to be a feasible and safe strategy.[23,24] In addition, it is important to mention other factors that are usually overlooked, such as certain foods and beverages that can acidify the urine despite treatment with large amounts of bicarbonate and should be avoided during HDMTX treatment.[3,25] Most of the respondents reported using furosemide as their diuretic of choice for patients treated with HDMTX, even when furosemide was reported to double the risk of MTX-related nephrotoxicity and should be avoided when using HDMTX.[26]

This data shows that even though all sites evaluate creatinine level before MTX infusion, only 4 sites routinely measure serum creatinine with every MTX level, which shows an important gap in care. Standardized supportive care guidelines might help assure the safe administration of high-dose methotrexate. Institutions that lack access to MTX level testing or that have delays in obtaining results, or those that have access to only a limited number of MTX levels face significant challenges in optimally and safely treating patients. Some strategies adopted to overcome these issues consist of decreasing the dose and/or decreasing the time of HDMTX infusion or limiting MTX monitoring to a single drug level while intensifying leucovorin rescue.[8,27,31,32] However, over-rescuing has the potential to decrease HDMTX efficacy and has been related to a higher risk of relapse in patients with leukemia and a decrease in the anti-leukemia effect of MTX.[28–30]

Supplementary data Figure S1 shows a roadmap to guide the provider with no or limited access to methotrexate levels, to weigh the risks and benefits of adjusting HDMTX therapy and options on how to optimize their practice. This survey shows that almost one third of respondents do not have access to timely MTX level results and need to wait for more than 6 h following sampling, resulting in inadequate management of possible MTX-related toxicities for long and vital periods of time. This delay in obtaining MTX level results appears to be associated with the location of the laboratory, with a median time of 6 h (IQR, 4 - 24 h) for an external or nearby laboratory and a median of 2 h (IQR, 2-3.5) for in-hospital laboratories. As a result, some sites decrease the dose or avoid using MTX due to restraints in MTX level monitoring. Lack of access to MTX depends on multiple variables (cost, number of patients, laboratory resources among others), and no single solution could address this problem. In this survey, respondents were asked about the feasibility of implementing a bedside/point-of-care testing device to measure MTX levels as an intervention that could overcome barriers in care This new strategy could speed up the availability of MTX level results not only for institutions with delays but also for those with no access to MTX testing at all. Our data demonstrate that most of the survey respondents are willing to implement a point-of-care testing device as a preemptive detection strategy if such intervention would save time, is easy to implement, and safe for their patients. In addition, with adequate and timely access to MTX levels, physicians would be able to input these results into free online platforms, such as MTXPK.org, to guide the management and monitoring of patients at risk for delayed MTX elimination, facilitating early interventions.[33]

Even with pristine supportive care, oncologists with limited or no access to MTX levels and without access to glucarpidase rely on other preventive strategies, including hydration, leucovorin rescue, and urine alkalinization, to manage patients with delayed MTX clearance and HDMTX toxicities. Having access to timely serum MTX levels could help rescue these patients, preventing delays in treatments and ultimately improving outcomes.

This study has several limitations. The data collected provides information on the general practices adopted at each institution but does not provide information at a patient level. Hence, specific information about grading and incidence of toxicities, length of hospital stay, delays in therapy and patient outcome could not be evaluated. Responses were included from those who completed at least 70% of the questionnaire items, which resulted in a smaller number of total responses for each domain and an overall response rate of the sites invited of 21% (20 of 96). In addition, not all respondents completed all the questions, hence the denominator differs throughout the results.

Conclusion

Supportive care for HDMTX is generally appropriate in LATAM sites; however, there are multiple gaps in the care of patients treated with HDMTX that resulted in an increased risk of toxicities and inefficient bed utilization. Access to timely methotrexate levels in addition to standardized care guidelines adapted to each country/facility's resources are a key element to assure the efficacy and safety of high-dose methotrexate administration. By reducing the turnaround time for MTX level testing,

it becomes safer to administer MTX at full doses in treatment sites that were previously dose-reducing. Furthermore, this faster testing process enables sites without access to MTX level testing to safely use HDMTX. point-of-care testing is a potential solution for sites with limited patient capacity that cannot afford in-house laboratory testing. This device can serve as a feasible preemptive detection strategy for MTX level monitoring.

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Data availability statement

Data available on request from the authors

References

1. World Health Organization. Model list of essential medicines. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02. Accessed June 20, 2023.
2. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. *Oncologist*. 2016;21(12):1471–1482. doi:10.1634/theoncologist.2015-0164.
3. Ramsey LB, Balis FM, O'Brien MM, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. *Oncologist*. 2018;23(1):52–61. doi:10.1634/theoncologist.2017-0243.
4. Wa B. Methotrexate: clinical pharmacology, current status and therapeutic guidelines. *Cancer Treatment Rev*. 1977;4(2):87–101. doi:10.1016/s0305-7372(77)80007-8.
5. Vaishnavi K, Bansal D, Trehan A, Jain R, Attri SV. Improving the safety of high-dose methotrexate for children with hematologic cancers in settings without access to MTX levels using extended hydration and additional leucovorin. *Pediatr Blood Cancer*. 2018;65(12):e27241. doi:10.1002/pbc.27241.
6. Totadri S, Srinivasan HN, Joseph LL, Boddu D, Mathew LG, John R. A single assessment of methotrexate levels at 42 hours permits safe administration and early discharge in children with lymphoblastic lymphoma and leukemia receiving high-dose methotrexate. *Pediatr Hematol Oncol*. 2021;38(5):434–443. doi:10.1080/08880018.2020.1863535.
7. Howard SC, Pedrosa M, Lins M, et al. Establishment of a pediatric oncology program and outcomes of childhood acute lymphoblastic leukemia in a resource-poor area. *JAMA*. 2004;291(20):2471–2475. doi:10.1001/jama.291.20.2471.
8. Dhingra H, Kalra M, Mahajan A. Safe administration of high-dose methotrexate with minimal drug level monitoring: Experience from a center in north India. *Pediatr Blood Cancer*. 2020;67(11):e28394. doi:10.1002/pbc.28394.
9. Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. *Oncologist*. 2006;11(6):694–703. doi:10.1634/theoncologist.11-6-694.

10. Jahnke K, Korfel A, Martus P, et al. High-dose methotrexate toxicity in elderly patients with primary central nervous system lymphoma. *Ann Oncol*. 2005;16(3):445–449. doi:10.1093/annonc/mdi075.
11. Florkowski C, Don-Wauchope A, Gimenez N, Rodriguez-Capote K, Wils J, Zemlin A. Point-of-care testing (POCT) and evidence-based laboratory medicine (EBLM) - does it leverage any advantage in clinical decision making? *Crit Rev Clin Lab Sci*. 2017;54(7–8):471–494. doi:10.1080/10408363.2017.1399336.
12. Yoo EH, Lee SY. Glucose biosensors: an overview of use in clinical practice. *Sensors (Basel)*. 2010;10(5):4558–4576. doi:10.3390/s100504558.
13. Chen H, Liu K, Li Z, Wang P. Point of care testing for infectious diseases. *Clin Chim Acta*. 2019;493:138–147. doi:10.1016/j.cca.2019.03.008.
14. Nicholas S, Poulet E, Wolters L, et al. Point-of-care viral load monitoring: outcomes from a decentralized HIV programme in Malawi. *J Int AIDS Soc*. 2019;22(8):e25387. doi:10.1002/jia2.25387.
15. Dinnes J, Deeks JJ, Adriano A, Cochrane COVID-19 Diagnostic Test Accuracy Group., et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. *Cochrane Database Syst Rev*. 2020;8(8):CD013705. doi:10.1002/14651858.CD013705.
16. Pearce CM, Resmini M. Towards point of care systems for the therapeutic drug monitoring of imatinib. *Anal Bioanal Chem*. 2020;412(24):5925–5933. doi:10.1007/s00216-020-02545-4.
17. Qu JH, Ordutowski H, Van Tricht C, et al. Point-of-care therapeutic drug monitoring of adalimumab by integrating a FO-SPR biosensor in a self-powered microfluidic cartridge. *Biosens Bioelectron*. 2022;206:114125. doi:10.1016/j.bios.2022.114125.
18. Zhang M, He J, Zheng Y, Shi G, Zhang M. Aptamer-engineered extended-gate field-effect transistor device for point-of-care therapeutic drug monitoring. *Analyst*. 2022;147(20):4413–4416. PMID: 36148514. doi:10.1039/d2an01393b.
19. Griss R, Schena A, Reymond L, et al. Bioluminescent sensor proteins for point-of-care therapeutic drug monitoring. *Nat Chem Biol*. 2014;10(7):598–603. doi:10.1038/nchembio.1554.
20. https://resonancehealth.org/. Resonance Places is a web-based-application provided by Resonance Inc. https://resonancehealth.org/. available free of cost to collect intuition level data.
21. Zelcer S, Kellick M, Wexler LH, Gorlick R, Meyers PA. The Memorial Sloan Kettering Cancer Center experience with outpatient administration of high dose methotrexate with leucovorin rescue. *Pediatr Blood Cancer*. 2008;50(6):1176–1180. PMID: 18266225. doi:10.1002/pbc.21419.
22. Mahadeo KM, Santizo R, Baker L, Curry JO, Gorlick R, Levy AS. Ambulatory high-dose methotrexate administration among pediatric osteosarcoma patients in an urban, underserved setting is feasible, safe, and cost-effective. *Pediatr Blood Cancer*. 2010;55(7):1296–1299. doi:10.1002/pbc.22772.
23. Villegas Rubio JA, Cacciavillano W, Rose A, Zubizarreta P, Scopinaro M. Ambulatory high-dose methotrexate administration in pediatric osteosarcoma patients at a single institution in Argentina. *J Pediatr Hematol Oncol*. 2017;39(7):e349–e352. doi:10.1097/MPH.0000000000000922.
24. Pampín R, Labeaga Y, Rodríguez B, Fernández B, Fernández R, Carbajales M. Experience with ambulatory high-dose methotrexate administration as CNS prophylaxis in patients with non-Hodgkin lymphoma. *J Oncol Pharm Pract*. 2020;26(3):549–555. doi:10.1177/1078155219852412.
25. Santucci R, Levêque D, Herbrecht R. Cola beverage and delayed elimination of methotrexate. *Br J Clin Pharmacol*. 2010;70(5):762–764. doi:10.1111/j.1365-2125.2010.03744.x.
26. Wiczer T, Dotson E, Tuten A, Phillips G, Maddocks K. Evaluation of incidence and risk factors for high-dose methotrexate-induced nephrotoxicity. *J Oncol Pharm Pract*. 2016;22(3):430–436. doi:10.1177/1078155215594417.
27. Navarrete M, Rossi E, Brivio E, et al. Treatment of childhood acute lymphoblastic leukemia in central America: A lower-middle income countries experience: Treatment of Childhood ALL in Central America. *Pediatr Blood Cancer*. 2014;61(5):803–809. doi:10.1002/pbc.24911.

28. Borsi JD, Wesenberg F, Stokland T, Moe PJ. How much is too much? Folinic acid rescue dose in children with acute lymphoblastic leukaemia. *Eur J Cancer*. 1991;27(8):1006–1009. doi:10.1016/0277-5379(91)90269-j.
29. Skärby TVC, Anderson H, Heldrup J, Kanerva JA, Seidel H, Schmiegelow K, Nordic Society of Paediatric Haematology and Oncology (NOPHO). High leucovorin doses during high-dose methotrexate treatment may reduce the cure rate in childhood acute lymphoblastic leukemia. *Leukemia*. 2006;20(11):1955–1962. doi:10.1038/sj.leu.2404404.
30. Mikkelsen TS, Sparreboom A, Cheng C, et al. Shortening infusion time for high-dose methotrexate alters antileukemic effects: a randomized prospective clinical trial. *J Clin Oncol*. 2011;29(13):1771–1778. doi:10.1200/JCO.2010.32.534.
31. von Stackelberg A, Hartmann R, Bührer C, et al. High-dose compared with intermediate-dose methotrexate in children with a first relapse of acute lymphoblastic leukemia. *Blood*. 2008;111(5):2573–2580. doi:10.1182/blood-2007-07-102525.
32. Khera S, Kapoor R, Pramanik SK. Solitary serum methotrexate level 36 hours post high-dose methotrexate: A safe, efficacious, and cost-effective strategy to monitor methotrexate toxicities in childhood leukemia in resource-limited centers. *Pediatr Blood Cancer*. 2020;67(7):e28387. doi:10.1002/pbc.28387.
33. Taylor ZL, Mizuno T, Punt NC, et al. MTXPK.org: A clinical decision support tool evaluating high-dose methotrexate pharmacokinetics to inform post-infusion care and use of glucarpidase. *Clin Pharmacol Ther*. 2020;108(3):635–643. doi:10.1002/cpt.1957.