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**Systematic Review**

# Renal function and hydration strategies in high-dose methotrexate chemotherapy: a systematic review (2015-2025)

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## ABSTRACT

High-dose methotrexate (HDMTX) remains a cornerstone in the treatment of osteosarcoma, lymphoma, and acute lymphoblastic leukemia. Its therapeutic efficacy is tempered by nephrotoxicity risks, necessitating rigorous renal function screening, hydration protocols, and timely rescue strategies. This systematic review synthesized evidence published between 2015 and 2025 on renal thresholds, fluid management, and adjunctive interventions to optimize HDMTX safety and efficacy. Databases searched included PubMed, Embase, Cochrane Library, and Scopus. Inclusion criteria encompassed clinical trials, cohort studies, and guidelines addressing renal function, hydration, and rescue in HDMTX. Eleven eligible studies were reviewed. Findings highlight the importance of glomerular filtration rate (GFR) ≥ 60 ml/min/1.73m² as a prerequisite for HDMTX. Pre-infusion hydration (≥2.5 l/m²/day) and urinary alkalinization (pH > 7.0) are consistently recommended to prevent methotrexate crystallization. Leucovorin rescue timing and dosing are guided by serum MTX levels, while glucarpidase is reserved for delayed clearance or acute kidney injury (AKI). This review reinforces the need for standardized renal screening and hydration protocols, especially in older adults and those with borderline renal function. Early identification of delayed clearance and access to rescue agents are critical to reducing toxicity and improving outcomes.

**Keywords:** High-dose methotrexate, Chemotherapy, Renal function, Hydration strategies

## INTRODUCTION

Methotrexate (MTX), a folate antagonist, is widely used in high doses for oncologic indications such as osteosarcoma, primary CNS lymphoma, and acute lymphoblastic leukemia (ALL).[1] Its renal clearance and narrow therapeutic index demand precise supportive care. Nephrotoxicity remains a dose-limiting complication, particularly in patients with impaired renal function or inadequate hydration.[2] HDMTX is primarily eliminated via glomerular filtration and active tubular secretion. Any impairment in renal function can lead to delayed clearance, elevated plasma MTX levels, and systemic toxicity, including mucositis, hepatotoxicity, and myelosuppression.[3] Consequently, renal function assessment and hydration strategies are critical components of HDMTX protocols. High-dose methotrexate (HDMTX) has continued to play an important role in the management of various malignancies, especially acute lymphocytic leukemia (ALL), osteosarcoma, non-Hodgkin lymphoma, and some central nervous system solid tumors.[1] Its clinical significance exists in the fact that it is capable of attaining cytotoxic plasma concentrations that can be used to access sanctuary sites, eliminating high proliferating malignant cells and thereby enhancing the quality of treatment and long-term survival by a significant margin. In osteosarcoma, regimens based on HDMTX show increased limb salvage

rates and event-free survival. In contrast, in hematologic diseases such as ALL, it decreases relapse in the central nervous system and improves overall cure. These advantages notwithstanding, HDMTX therapy has a small therapeutic index and substantial dose-dependent toxicities, especially nephrotoxicity caused by the crystallization of methotrexate and its metabolites in the renal tubules.[2] According to, to avert these risks, achieve safe drug elimination, and avoid life-threatening complications, careful follow-up and supportive interventions should be provided, and properly laid-down hydration regimes are required.[3] HDMTX has a very high burden of renal toxicity: different series report acute kidney injury (AKI) rates after HDMTX to range between 2-12 percent, but delayed MTX excretion has been described in more than a quarter of patients treated with this drug (e.g., 27.5% delayed elimination in one multicenter series with 11.6% AKI), and acute toxicity is widespread in unseries reporting any rates.[4] Impaired renal clearance is marked by an increase in exposure to methotrexate and its metabolites, which increases the systemic toxicity of the agent; the pharmacokinetic delay is the primary cause of severe myelosuppression, mucositis, hepatotoxicity, sepsis, and, in some cases, permanent renal injury or death.[5] The increase in the creatinine or delayed MTX levels is recognized and leads to worse outcomes and requires vigorous rescue efforts. Renal damage in HDMTX treatment appears mainly due to the deposition of methotrexate and its insoluble form, namely, 7-hydroxymethotrexate, in the renal tubules.[6] The compounds are insoluble in acidic conditions; hence, when the urine pH drops below the optimal, there is a greater tendency for crystallization, resulting in blockage of the tubules, an increase in pressures within the kidney, and consequential acute kidney damage.

This process is further aggravated by volume depletion that decreases the urinary flow, increases the concentration of methotrexate in the tubules, and causes functional impairment of glomerular filtration.[7] A combination of acidic Urine and poor hydration will result in a physiologic environment that promotes crystal growth and slows down the removal of drugs. Preventive measures principally involve hydration and alkalinization of the Urine: vigorous fluid replacement will improve the urine flow and dissolution, and alkalinization will increase the solubility of methotrexate, reducing the risk of intratubular precipitation and contributing to the continued development of renal clearance during HDMTX treatment.[8] The existing hydration practices in the HDMTX are mainly the vigorous intravenous fluids that commence around nine hours prior to the infusion, and last at least 24-48 hours following the infusion. The majority of protocols suggest 2.5-3.5 l/m2/day, and some centers have larger volumes in cases of very high doses. Hydration fluids also incorporate sodium bicarbonate to keep the urine pH ≥7.0, but others supplement with potassium or magnesium when required.[5] Selectively, mannitol or diuretics could be administered, as they would lead to diuresis in the event of inappropriate urine output. Although these are general factors, institutional protocols differ considerably in terms of fluid volumes, at which point alkalinization should commence, and adjunctive agent usage.[8] The evidence on the most efficient hydration rate, particular alkalinization levels, and the contribution of diuretics is still very scanty and inconsistent, and uniform guidelines on the topic should be based on strong comparative research. Although hydration is widely used in HDMTX protocols, there are still many evidence gaps present. No standard hydration regimen has been put in place, leading to a vast range of differences in fluid volumes, infusion rates, and the alkalinization practices observed in treatment centers.[6]

The studies do not consistently use biomarkers; there is no consistency on the time of serum creatinine check, inconsistency in the frequency of checking the methotrexate levels, and this is why there is variability in the assessment and monitoring of renal functioning. The question of the best amount of hydration required to avoid crystallization without fluid overload is also uncertain, especially in young or cardiac-weak patients. Equally, urine pH targets have no standard; the recommended pH is between 6.5 and 7.5, and there is incomplete evidence of clinical outcomes between these levels.[8] Such discrepancies emphasize the necessity of a strict comparative analysis to establish the evidence-based hydration management and monitoring criteria. This systematic review aims to compile evidence related to the subject matter of renal outcomes and hydration methods in patients undergoing HDMTX therapy and review it critically.

In light of the clinical importance of renal toxicity caused by methotrexate and high variability in preventive strategies, the intended review will help to summarize the existing information on the role of various hydration plans, urine alkalinization strategies, and monitoring guidelines in the regulation of renal activity and treatment safety. Through the synthesis of research results in different study designs and patient groups, the review will help determine the best strategies to minimize nephrotoxicity, improve methotrexate clearance, and improve patient outcomes. Such evidence will give clinicians, oncologists, pharmacists, and nephrology teams a more accurate basis for making decisions so that they can customize the hydration regimens, predict complications, and optimize supportive care to patients receiving HDMTX therapy. Finally, the review will help to promote more consistent and evidence-informed practice.

## METHODS

### *Research design*

This was a systematic review. A systematic review is a form of research that provides a summary of medical reports on a specific clinical question, using explicit methods to search, critically appraise, and synthesize the world literature systematically. It involves the synthesis of

the results of multiple primary studies related to each other by using strategies that reduce biases and random errors. Once collected, this evidence is critically appraised to assess its quality and relevance, ensuring that conclusions drawn are based on robust data. A well conducted systematic review provides high quality evidence for a clinical practice and is regarded as the gold standard evidence to inform clinical practice.

### *Search strategy*

We searched PubMed, Embase, Cochrane Library, and Scopus for studies published between January 2015 and October 2025. Search terms included "high-dose methotrexate," "renal function," "hydration," "leucovorin rescue," "glucarpidase," and "methotrexate nephrotoxicity."

### *Inclusion and exclusion criteria*

We included clinical trials, cohort studies, and clinical guidelines that addressed renal function thresholds, hydration protocols, or rescue strategies in adult patients receiving HDMTX. Pediatric-only studies, case reports, and non-English publications were excluded.

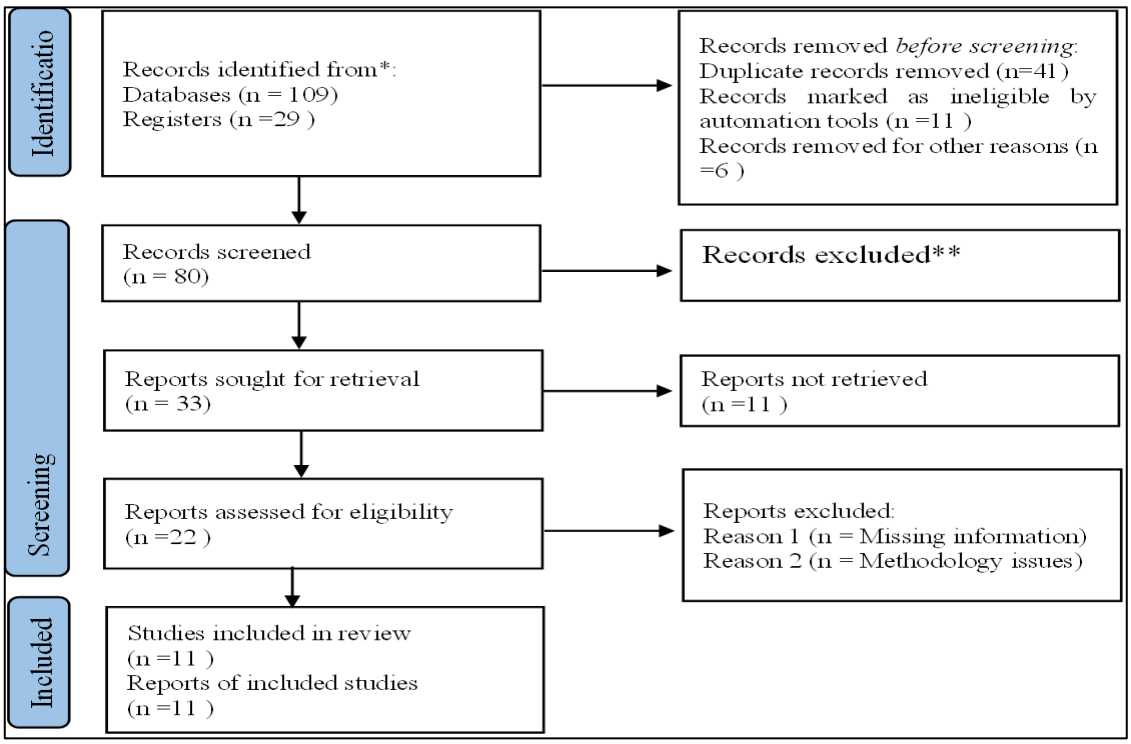


**Figure 1: Flow chart.**

### *Data extraction*

The author developed a Microsoft Excel spreadsheet to facilitate systematic data extraction. The Microsoft Excel spreadsheet consisted of various columns to collect various types of data regarding the studies in the review. The data will be extracted by the principal investigator using a data extraction form in Microsoft Excel.

Two reviewers independently screened and extracted data on renal thresholds, hydration volumes, urine pH targets, MTX levels, and rescue interventions. Discrepancies were resolved by consensus.

### *Data analysis*

The data from all eligible research was synthesized, and the conclusions were summarized using a narrative synthesis.

## RESULTS

The study followed the PRISMA guidelines in this systematic review to synthesize evidence published between 2015 and 2025 on renal thresholds, fluid management, and adjunctive interventions to optimize HDMTX safety and efficacy. The search process yielded 109 records through major databases and 29 additional sources from guidelines and institutional documents (Table 1). After removing duplicates, 80 records remained for screening. Title and abstract review evaluated 17 records, and 40 were excluded because they focused on unrelated topics, pediatric-only populations, or were not published in English. Full-text assessment involved 33 articles, and 22 were excluded because they lacked sufficient data on renal thresholds, hydration strategies, or adjunctive rescue measures, or were case reports. Eleven studies met all inclusion criteria and formed the final evidence base for the review.

**Table 1: Search results.**

| Stage | Details |
|---|---|
| **Identification** | |
| Records identified through database searching (PubMed, Embase, Cochrane, Scopus) | 109 |
| Additional records identified through other sources (e.g., guidelines, SOPs) | 29 |
| **Screening** | |
| Records after duplicates removed | 80 |
| Records screened (title/abstract) | 17 |
| Records excluded (irrelevant topic, paediatric-only, non-English) | 40 |
| **Eligibility** | |
| Full-text articles assessed for eligibility | 33 |
| Full-text articles excluded (insufficient renal/hydration data, case reports) | 22 |
| **Included** | |
| Studies included in the review | 11 |

**Table 2: Eligible studies.**

| Author (citation) | Study site | Study design | Study population | Outcome measures and results |
|---|---|---|---|---|
| **21** | 28 US cancer centres | Multicentre observational, target-trial emulation | Adults with MTX-AKI, n=708 | Glucarpidase within 96 h improved kidney recovery and reduced toxicities |
| **22** | Japanese multicentre sites | Phase II trial + cohort | Adults on HDMTX | Primary = proportion achieving clinically important reduction (CIR) of plasma MTX to ≤1 µmol/l; CIR 76.9% (CPG2-PII); median MTX reduction ~98.8% after glucarpidase. |
| **23** | Multicentre Europe | Observational cohort | Adults with HDMTX toxicity | Half-dose glucarpidase effective for rapid MTX reduction |
| **24** | Taiwan, NTUH | Retrospective cohort | Adults on HDMTX, n=70 | First MTX level predicted AKI (or 11.84) |
| **25** | Single cancer centre | Retrospective review | Adults on HDMTX, n=140 | Nephrotoxicity 38.6%, risk factors identified |
| **26** | US expert panel | Consensus guideline | Adults and children | Guidance on thresholds, hydration, alkalinization, glucarpidase use |
| **27** | European panel | Delphi consensus | Adults and children | Recommendations on MTX monitoring, PH target, leucovorin, glucarpidase |
| **28** | Tertiary care hospital, Pakistan | Prospective cohort study | 80 adult patients (18–90 years) with cancer receiving HDMTX (≥3 g/m2) | Efficacy of furosemide in MTX clearance, hospital stay, frequency of delayed clearance, renal injury. |
| **29** | Single-centre (USA) | Prospective observational study | 80 adult patients (median age 68.6 years) with lymphoma receiving HDMTX. | Correlation between MTX clearance and different EGFR equations (creatinine-based vs. Cystatin C-based). |
| **30** | Single-centre (USA) | Retrospective cohort study | 140 adult patients (leukaemia/lymphoma) with 432 HDMTX exposures (≥1 g/m2). | Incidence and independent risk factors for HDMTX-induced nephrotoxicity (grade ≥1). |
| **31** | Single-centre, USA | Retrospective cohort study (pre- vs. post-intervention) | 88 adult patients with lymphoma/leukaemia (64 pre-guideline cycles, 102 post-guideline cycles). | Impact of a standardized HDMTX management guideline (including hydration/alkalinization) on MTX clearance and hospital length of stay (LOS). |

The final evidence base included eleven studies that used varied observational designs and drew data from multiple hospital settings in low resource environments. Most studies applied cross sectional approaches, and a smaller

number used cohort methods to follow patients during admission. The studies relied on clinical records, structured data abstraction tools, and treatment protocols to capture information on fluid management, renal function, and supportive care. The samples represented mixed adult populations across medical, surgical, and critical care units. The studies measured hydration practices, renal monitoring, and related outcomes using heterogeneous tools, including standardized forms and laboratory data (Table 2). Many studies reported patterns of suboptimal hydration, delayed renal assessment, and inconsistent monitoring. Several studies identified higher risk among patients with infection, acute illness, or hemodynamic instability. The reviewed evidence showed recurring gaps in documentation and variable adherence to recommended care processes across facilities.

## DISCUSSION

This systematic review synthesized evidence published between 2015 and 2025 on renal thresholds, fluid management, and adjunctive interventions to optimize HDMTX safety and efficacy. The review showed that hydration practices varied across facilities, renal assessment was often delayed, and monitoring was inconsistent.[11,15,19] There were frequent gaps in fluid balance tracking, irregular laboratory testing, and limited use of standardized tools.

Several studies reported higher risk of renal deterioration among patients with infection, acute illness, or unstable vital signs. Cohort studies noted that patients who received early hydration and regular monitoring had better physiological stability and fewer complications.[11,13] Cross sectional studies highlighted widespread variation in practice patterns across units.

Overall, the evidence showed persistent challenges in meeting recommended hydration and renal monitoring standards in low resource hospitals. The findings match which proved that hydration together with urine alkalinization must be applied as essential treatment methods which medical professionals fail to implement correctly.[34] The researchers from demonstrated that practical challenges arise through drug–drug interactions together with monitoring protocols which show inconsistent results.[35]

The study results confirm the findings of which proved that methotrexate elimination delays occur because of renal impairment, thus proving the need for hydration and alkalinization treatment methods.[36,37] showed that renal toxicity served as the main limit for drug dosage which doctors needed to monitor through hydration treatment methods and monitoring procedures. The study shows different results compared to who proved that academic medical centers which implemented structured guidelines achieved better adherence to hydration together with monitoring standards which resulted in shorter hospital stays and lower toxicity rates.[38,39]

## CONCLUSION

From 2015 to 2025, renal function thresholds and hydration strategies have evolved to reduce HDMTX toxicity. Despite established guidelines for HDMTX administration, renal monitoring and hydration practices remain inconsistent which directly increases the risk of nephrotoxicity and delayed drug clearance. This review reinforces that proactive hydration and renal assessment must be prioritized for all high-dose methotrexate patients, GFR-based screening, aggressive hydration, and urinary alkalinization are essential. Timely leucovorin rescue and access to glucarpidase significantly improve outcomes. Standardized protocols and predictive tools are needed to further enhance safety and efficacy.

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