

Evidence-Based Practice Recommendations for Hydration in Children and Adolescents With Cancer Receiving Intravenous Cyclophosphamide

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Deborah Robinson, DNP, APRN, BC, PNP, CPON¹,
Ginny Schulz, MSN, RN, CPNP¹, Rachel Langley, PharmD¹,
Kevin Donze, BSN, RN¹, Kari Winchester, BSN, RN²,
and Cheryl Rodgers, PhD, RN, CPNP, CPON³

Abstract

Hemorrhagic cystitis is a known complication of cyclophosphamide, an antineoplastic agent used to treat a variety of oncologic diseases in children. Hydration can prevent hemorrhagic cystitis; however, use varies in clinical practice. A team was assembled to develop evidence-based practice recommendations to address the following question: in a population of children with cancer, what is the appropriate pre- and posthydration for the administration of different dose levels of intravenous cyclophosphamide to prevent bladder toxicity? The purpose was to identify the appropriate rate, duration, and route of hydration to prevent bladder toxicity with low, intermediate, and high dose cyclophosphamide. After a systematic search of the literature, 15 pieces of evidence were evaluated and used. There is a moderate level of quality evidence related to hydration for high dose cyclophosphamide and very low quality evidence related to intermediate or low dose cyclophosphamide. Three general recommendations were made for hydration associated with cyclophosphamide. There is a need for further research related to the prevention of bladder toxicity in children with cancer receiving cyclophosphamide.

Keywords

cyclophosphamide, hemorrhagic cystitis, bladder toxicity, pediatric, cancer

Cyclophosphamide (CTX) is an antineoplastic alkylating agent used to treat a wide variety of malignant and non-malignant disorders (Fraiser, Kanekal, & Kehrer, 1991). It is used in pediatric oncology as part of the standard treatment for leukemia, solid tumors, and brain tumors. Cyclophosphamide is commonly administered intravenously but it is also available as an oral agent, although this is rarely used in children with cancer. The dosing for CTX ranges from low to intermediate to high dose and is based on the diagnosis and specific treatment regimen. Cyclophosphamide is the most commonly used agent in stem cell transplant (SCT) preparative regimens and is prescribed in high doses in this population (Hadjibabaie et al., 2008). One of the known side effects of CTX is hemorrhagic cystitis (West, 1997). Hydration is commonly administered in patients receiving CTX to prevent hemorrhagic cystitis; however, the hydration rate, timing, and duration vary significantly in clinical practice. The purpose of this review is to identify appropriate

recommendations for hydration before and after low, intermediate, and high doses of CTX to prevent bladder toxicity in children and adolescents with cancer.

Background

Cyclophosphamide was first used for the treatment of cancer in 1958, and it was found to be associated with bladder injury, causing symptoms such as frequency, urgency, dysuria, and hematuria (deVries & Freiha, 1990). Acrolein, a metabolite of CTX, has been identified

¹Saint Louis Children's Hospital, St Louis, MO, USA

²Washington University School of Medicine, St Louis, MO, USA

³Duke University School of Nursing, Durham, NC, USA

Corresponding Author:

Cheryl Rodgers, PhD, RN, CPNP, CPON, Duke University School of Nursing, 307 Trent Drive, Durham, NC 27710, USA.

Email: cheryl.rodgers@duke.edu

as the causative agent responsible for damage to the bladder (Ramu, Fraiser, Mamiya, Ahmed, & Kehrer, 1995). The acrolein metabolite can accumulate in the urine, causing sloughing, thinning, and inflammation of the bladder wall. This irritation causes bleeding of the endothelial lining in the bladder, known as hemorrhagic cystitis, that may be initially microscopic but can progress to gross hematuria and severe bleeding (West, 1997). The original grading scale for hemorrhagic cystitis developed by Droller, Saral, and Santos (1982) defined 4 grades of severity ranging from microscopic hematuria (grade 1) to gross hematuria, clot formation, and urinary tract obstruction (grade 4).

The definitions used for cyclophosphamide dosing levels for consistency in this evidence review and based on the literature (Ballen et al., 1999; Children's Oncology Group, 2010; Droller et al., 1982; Hows et al., 1984; Khojasteh, Zakerinia, Ramzi, & Haghshenas, 2000; Marshall et al., 2011; Meisenberg et al., 1994; Monach, Arnold, & Merkel, 2010; Shepherd et al., 1991; Vose et al., 1993) are as follows:

High dose CTX ≥ 1500 mg/m²/dose

Intermediate dose CTX ≥ 750 mg to < 1500 mg/m²/dose

Low dose CTX < 750 mg/m²/dose

Significance

Hemorrhagic cystitis (HC) is a known complication of CTX that can cause distressing and painful symptoms for the child or adolescent. Hemorrhagic cystitis can cause significant morbidities such as severe bladder disease and damage to the renal system (McCarville, Hoffer, Gingrich, & Jenkins, 2000). There are reported fatalities related to severe HC and bleeding complications (Droller et al., 1982). Medical intervention can be invasive, aggressive, and costly. Hemorrhagic cystitis can prolong hospitalization, significantly affect quality of life, and adversely affect patient outcomes including overall survival (Decker, Karam, & Wilcox, 2009; West, 1997).

The incidence of CTX-induced HC without preventive measures is estimated to be 25% to 60% (Stillwell, Benson, & Burgert, 1988; West, 1997). Lawrence, Simone, and Aur (1975) reported HC in children with leukemia after repeated and prolonged exposure to both intravenous and oral CTX. Risk factors for pediatric HC in children with cancer include CTX or busulfan chemotherapy, age > 5 years, male sex, bone marrow or peripheral stem cell transplant recipients, and bladder irradiation (Riachy et al., in press; Stillwell et al., 1988). Although some risk factors have been identified, any patient who receives CTX at any dose level has the potential to

develop bladder toxicity at any time (early or late in their treatment course).

Standard practice to prevent HC (unless medically contraindicated) has included adequate hydration with or without diuretics to keep the urine dilute and urine flow adequate (Haselberger & Schwinghammer, 1995). Hydration has the potential to reduce or prevent bladder toxicity associated with CTX (Walker, 1999). There are wide variations in hydration recommendations and practices for children and adolescents with cancer receiving intravenous CTX. One publication reported significant variations of hydration recommendations across multiple pediatric oncology treatment protocols (Sievers, Lagan, Bartel, Rasco, & Blanding, 2001). Consistency in hydration practice recommendations for children and adolescents with cancer receiving CTX based on evidence could standardize practice and improve patient outcomes.

Evidence Guideline Development Methods

EBP Review Team

Evidence-based practice (EBP) topics were developed in alignment with the Children's Oncology Group (COG) Nursing Discipline's blueprint and organizing framework (Kelly, Hooke, Ruccione, Landier, & Haase, in press; Landier, Leonard, & Ruccione, 2013). These topics were vetted with COG leadership and other key stakeholders (ie, COG committees such as Leukemia Committee), and then a call for the EBP projects was disseminated through the COG Nursing Discipline membership. Multidisciplinary pediatric oncology health care providers from Saint Louis Children's Hospital assembled an EBP team and submitted an application. The EBP team consisted of 2 advanced practice pediatric oncology nurses, 1 pediatric oncology nurse coordinator, 1 pediatric oncology staff nurse, and 1 specialized oncology doctor of pharmacy (PharmD), all from a major academic pediatric children's hospital. After a competitive selection application process, the proposal was selected for development. A mentor was assigned to the group who was a doctoral prepared advanced practice pediatric oncology nurse with experience in evidence-based reviews. All team members volunteered for the project and participated in review of the evidence, determination of findings, and completion of the manuscript.

Question Development

Clinical questions can be phrased in a PICOT format to provide essential elements for the EBP review. PICOT stands for Patient, Intervention or Issue of Interest, Comparison,

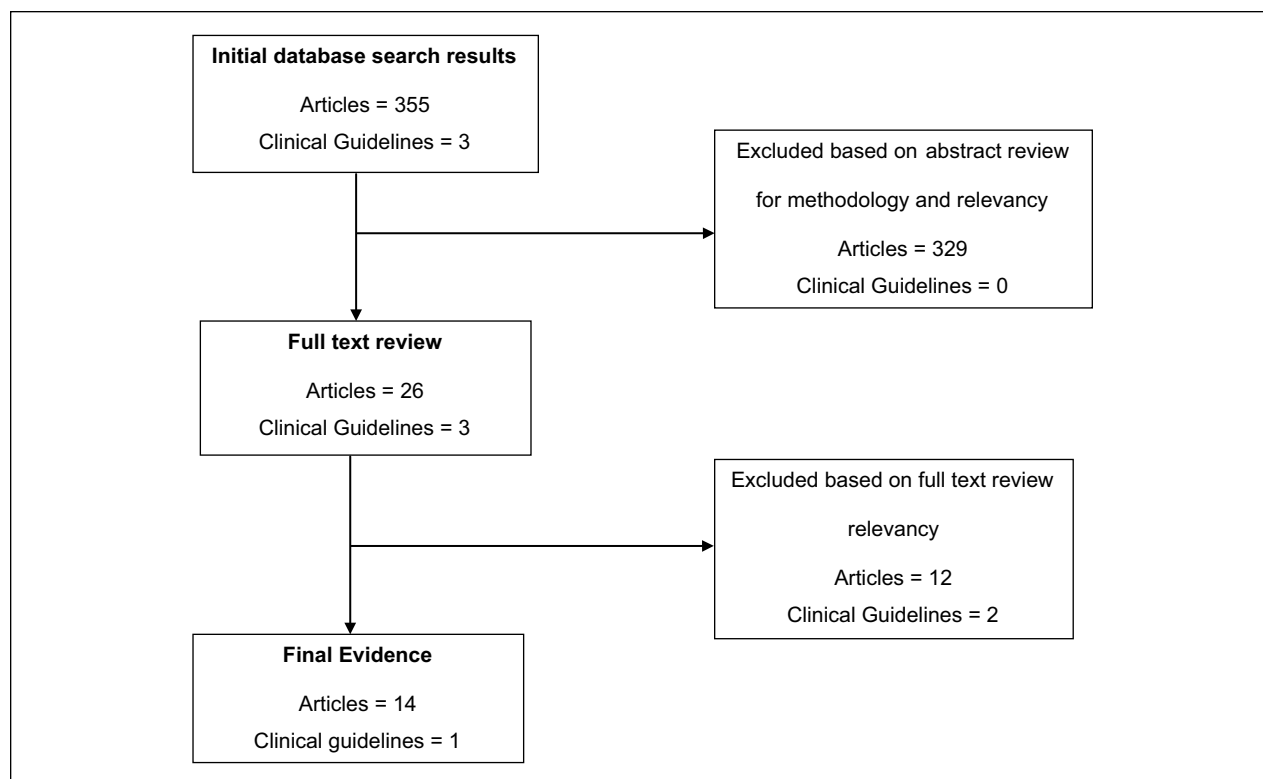


Figure 1. Search results.

Outcome, and Time (Melnik & Fineout-Overholt, 2011). The specific PICOT question that this guideline addressed was, *In a population of children with cancer, what is the appropriate pre- and posthydration for the administration of different dose levels of intravenous cyclophosphamide to prevent bladder toxicity?* The question was developed to determine differences in hydration for low, intermediate, and high dose cyclophosphamide. The goal of the project was to establish a standard practice recommendation for both rate and duration of hydration.

Literature Search Strategies

The literature search included an extensive search of major databases including PubMed, CINAHL, Embase, OVID, Cochrane, BestBETS, PedsCCM, and Up to Date. Key terms and MeSH terms used included *cyclophosphamide*, *intravenous hydration*, *hemorrhagic cystitis*, *bladder*, and *MESNA* (sodium-2-mercaptoethanesulfonate). The limits were set for English and human subjects. Due to the limited published evidence in the past 10 years, the search was not restricted by time frame or patient age. Hand searching was also used. A medical librarian assisted with all literature searches. The initial search yielded 355 articles. Articles focused on cyclophosphamide-based

regimens for efficacy or disease response were eliminated. Search results are illustrated in Figure 1.

In addition, the EBP team searched for chemotherapy guidelines and chemotherapy administration recommendations. The search included professional organizations linked to the topic: Oncology Nursing Society (ONS), Association of Pediatric Hematology/Oncology Nurses (APHON), Children's Oncology Group, and the American Society of Clinical Oncology (ASCO). Additional exploration on the topic included searches within Google Scholar and 2 National Guideline databases.

Inclusion/Exclusion Criteria

The inclusion criteria consisted of research articles that described the administration of hydration and supportive care with CTX. Systematic reviews, meta-analysis, research studies, and clinical guidelines were used. Due to the paucity of literature in pediatric oncology on this topic, all ages without restriction to disease and all oncologic diagnoses were included in the review.

Exclusion criteria included general background articles, basic review articles, disease-based review articles regarding the efficacy of CTX, and medical or surgical intervention for HC.

Table 1. Hydration Evidence.

First Author, Year, Study Design	Patients	Findings	GRADE Quality Level
Droller, 1982, prospective, descriptive	198 adult patients with oncology or aplastic anemia diagnosis	Significant HC prevalence difference between no hydration and IV fluids at 4-5 liters per day during CTX infusion ($P < .01$)	High
Haselberger, 1995, literature review	Published evidence: high dose CTX in SCT patients	Hydration/adequate urine flow should be mandatory with high dose CTX	Moderate
Ballen, 1999, prospective, descriptive	100 SCT adult patients	Hydration with IV fluids at 250 mL/h for 4 hours before through 24 hours after CTX effective in reducing HC	Moderate
Takamoto, 2004, case study	19 pediatric patients with solid tumor or hematological disease	Acrolein concentrations increased as urine volume decreased; peak times were 1-12 hours after CTX	Low

Abbreviations: CTX, Cytoxan; HC, hemorrhagic cystitis; IV, intravenous; SCT, stem cell transplant.

Review Approach

Each article was thoroughly reviewed by an EBP review team member and key information was extracted into a matrix evidence table. The articles and tables were then reviewed by the EB practice team leader and team mentor. Each study was analyzed and the following information was summarized: purpose, design, variables, population, interventions, instruments, measurements, results, implications, and confounding factors.

Analysis Techniques

The evidence was analyzed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Guyatt et al., 2011). Each article was given a grade of high, moderate, low, or very low depending on the quality of evidence. If there was any question about the GRADE rating, the evidence was discussed among team members and a team consensus was reached. The team leader and team mentor synthesized all of the evidence and provided 1 overall GRADE rating for the quality of the evidence. Recommendation statements were developed from this synthesized evidence and labeled as strong or weak, as described in the introduction article of this journal issue. The strength of each recommendation was determined by the desirable and undesirable effects of the evidence and made independently of the quality level of the evidence (Andrews et al., 2013).

A total of 3 guidelines, all from ASCO, were found. Two guidelines were updated versions of the same original guideline published in 1999 by Hensley et al. The EBP team used the 2002 guideline for this evidence review (Schuchter, Hensley, Meropol, & Winer, 2002) since the revised guideline in 2009 (Hensley et al., 2009) had no new evidence related to hydration with cyclophosphamide. The clinical guideline was reviewed and scored

independently by the team leader and mentor using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool. Scores were averaged between the 2 raters and an overall mean score was obtained for each of the 6 domains (Cluzeau et al., 2003). These scores were discussed with the team leader and mentor for consensus and a decision was made about the inclusion of the guideline in the body of evidence.

Evidence Review

Fifteen pieces of evidence met the criteria for final inclusion in this review, including 3 systematic reviews, 3 randomized controlled trials, 1 nonrandomized clinical trial, 2 descriptive studies, 2 retrospective studies, 3 case study series, and 1 clinical guideline. The evidence included patient populations of adults, adolescents, children, and combined age groups. Although the PICOT question focused on hydration with CTX, other interventions were reported in the hydration literature including the use of diuretics, MESNA, and continuous bladder irrigation (CBI).

Hydration Evidence

Four studies evaluated hydration and HC (Table 1). Droller et al. (1982) evaluated hyperhydration as a preventive method for HC among 198 adult patients receiving high dose CTX and found a significant reduction in HC. The hydration was given 24 hours prior to CTX and every day of the regimen with hourly voiding. This study appeared to set the standard for hydration with high dose CTX. From a literature review performed in 1995, Haselberger and Schwinghammer concluded that hydration should be the key component of all prophylactic regimens with high dose intravenous cyclophosphamide. A study by Ballen and colleagues (1999) showed that

Table 2. MESNA With Hydration Evidence.

First Author, Year, Study Design	Patients	Findings	GRADE Quality Level
Hows, 1984, RCT	61 SCT adult patients	MESNA plus 3 liters of IV hydration daily during CTX is more effective for HC than 6 liters of IV hydration plus diuresis ($P < .05$)	Moderate
Shepherd, 1991, RCT	100 adult patients with cancer	No difference between MESNA plus 1.5 L/m ² /d of IV fluids compared to 3 L/m ² /d of IV fluids plus Lasix for severe HC ($P = .71$)	High
Khojasteh, 2000, case study	18 pediatric and young adults with leukemia or hematological disease	Adding MESNA with IV fluids at 3 L/m ² /d is effective in preventing HC	Low
Murphy, 1993, retrospective	217 adult patients with cancer	No HC prevalence difference between IV hydration at 3.6 L/m ² /d compared to same IV hydration plus MESNA	Moderate
Marshall, 2011, case study	1 adult patient with breast cancer	CTX without hydration caused HC but MESNA plus IV hydration given with subsequent CTX with no HC	Very low
Monach, 2010, systematic review	38 articles	No HC prevalence difference between IV hydration at 3 L/m ² /d compared to IV hydration of 1.5-3 L/d plus MESNA	Moderate
Schuchter, 2002, clinical guideline		Update of the 1999 chemotherapy and radiotherapy protectants clinical guideline by ASCO; MESNA plus saline diuresis or forced saline diuresis is recommended for high dose CTX	Not applicable
Damron, 2009, systematic review	54 articles	MESNA plus saline diuresis or forced diuresis with high dose CTX	High

Abbreviations: ASCO, American Society of Clinical Oncology; CTX, Cytoxan; HC, hemorrhagic cystitis; IV, intravenous; MESNA, sodium-2-mercaptoethanesulfonate; RCT, randomized controlled trial; SCT, stem cell transplant.

hyperhydration alone was effective in preventing HC in 100 patients who received high dose CTX for SCT regimens.

Takamoto and colleagues (2004) established the risk period for HC by measuring the acrolein concentrations of the urine in 36 occurrences of 19 patients receiving intermediate or high dose CTX (1000-2100 mg/m²/dose). This article demonstrated that high urine volume was important for reducing urinary acroleins. The urinary acrolein concentration is an index of hydration and is the key to the prevention of bladder toxicity. No clinical symptoms of HC occurred in this study, although 3 patients had hematuria. The highest risk for high acrolein concentrations occurred within the first several hours after CTX. The authors concluded that this is the most significant time to maintain urine flow to prevent HC.

MESNA With Hydration Evidence

The use and efficacy of MESNA with high dose CTX was a common theme in the literature review of hydration requirements with CTX and included 8 pieces of evidence (Table 2). This made it difficult to separate the definitive intervention that was successful. One of the

first articles to compare the use of MESNA versus forced diuresis was a randomized trial among 61 adult patients receiving high dose CTX (Hows et al., 1984). This trial showed that MESNA was more effective in the prevention of HC; however, both groups received hydration including 3 liters/day in the MESNA group and 6 liters/day in the hydration group. Conversely, a study by Shepherd et al. (1991) found MESNA to be equally effective as hyperhydration for the prevention of CTX-induced HC among 100 patients with cancer.

In 2000, Khojasteh and colleagues reported a case study with 18 patients who received high dose CTX and showed that MESNA was effective in preventing HC, however, all of these patients also received 3 L/m²/d of hydration. A retrospective analysis of 217 patients who received high dose CTX showed no significant difference in the incidence of HC among patients receiving MESNA plus hyperhydration versus hyperhydration alone (Murphy et al., 1993).

There is limited evidence regarding the use of MESNA with intermediate or low dose CTX. A single case study described the occurrence of HC in a patient with the first administration of low dose CTX (600 mg/m²/dose) (Marshall et al., 2011). Subsequent cycles were given

Table 3. Continuous Bladder Irrigation With Hydration Evidence.

First Author, Year, Study Design	Patients	Findings	GRADE Quality Level
Hadjibabaie, 2008, nonrandomized trial with historical controls	80 adult SCT patients	No HC prevalence difference between IV hydration versus IV hydration with CBI ($P = .11$)	Moderate
Vose, 1993, RCT	200 adult SCT patients	No HC prevalence difference between IV hydration plus MESNA versus IV hydration plus CBI but more bladder spasm, discomfort, and urinary tract infections in CBI group	High
Meisenberg, 1994, retrospective	303 adult SCT patients	CBI plus IV hydration at 200 mL/m ² /h is effective in preventing HC	Moderate

Abbreviations: CBI, continuous bladder irrigation; CTX, Cytoxan; HC, hemorrhagic cystitis; IV, intravenous; MESNA, sodium-2-mercaptoethanesulfonate; RCT, randomized controlled trial; SCT, stem cell transplant.

with hydration and MESNA with no recurrence of the HC. A systematic review of 38 studies evaluated the evidence on bladder toxicity secondary to intermediate or high dose CTX in rheumatology patients (Monach et al., 2010). The reviewers found that bladder toxicity was more likely to occur with daily long-term oral CTX as compared to periodic intravenous use. Although there are no contraindications for use of MESNA among the rheumatology population, the routine use of MESNA could not be fully supported. Hydration with IV fluids prior to and for several hours after IV administration of cyclophosphamide is typically recommended in this population, as well as 72 hours of oral hydration after the dose.

In 1999, ASCO published evidence-based guidelines regarding the use of chemotherapy protectant agents (Hensley et al., 1999), which were updated in 2002 (Schuchter et al., 2002) and again in 2009 (Hensley et al., 2009). The guidelines recommended MESNA plus saline diuresis or forced saline diuresis for patients receiving high dose cyclophosphamide in the setting of SCT. Recommendations for surveillance from the ASCO guideline are based on the opinion of the expert panel and include baseline urinalysis, monitoring for hematuria, and monitoring of urine output. There were no recommendations for hydration with low or intermediate dose CTX. In 2009, ONS published an evidence-based literature review regarding the prevention of bleeding in patients with cancer (Damron et al., 2009). The ONS review is similar to the ASCO guidelines with forced saline diuresis or MESNA with saline diuresis being recommended for high dose CTX in the SCT setting.

Continuous Bladder Irrigation With Hydration Evidence

Three studies evaluated the effect of hydration along with CBI for the prevention of HC in patients receiving CTX (Table 3). Through a nonrandomized clinical trial, Hadjibabaie et al. (2008) demonstrated that hydration with MESNA and CBI was effective in reducing the rate

and duration of HC in 80 patients who received high dose CTX for a SCT preparative regimen. Vose et al. (1993) compared MESNA with CBI in a randomized clinical trial of 200 SCT patients receiving high dose CTX. Both arms of the study received hyperhydration, and the results showed no significant difference between CBI or MESNA in preventing HC. Meisenberg and colleagues (1994) evaluated CBI and hyperhydration together (both interventions in all patients) and found it to be labor intensive but highly effective in the prevention of HC-associated high dose CTX.

Best Practices

The EBP team, who are active members of COG, reviewed 44 COG protocols that contained CTX infusions to assess hydration evidence. The recommended hydration ranged from 2 to 24 hours after low/intermediate dose CTX, and 24 hours after high dose CTX in these protocols. Almost all COG protocols for low, intermediate, and high dose CTX suggest achieving a dilute specific gravity less than or equal to 1.010 prior to any CTX administration (Children's Oncology Group, 2013). An effort is currently under way within COG to standardize chemotherapy administration practices, including associated hydration, across COG protocols (R. Womer, personal communication, January 3, 2014).

Rapid prehydration protocols have been implemented in some institutions to reduce the duration of hydration required prior to the administration of some chemotherapy agents, including CTX. A rapid prehydration protocol for CTX, ifosfamide, cisplatin, and methotrexate was evaluated in 1 children's hospital and demonstrated a significant reduction in prehydration time (6.75 to 1.57 hours) without any adverse side effects (Tracy, DiTaranto, & Womer, 2004; Womer et al., 2002). Fratino, Daniel, Cohen, and Chen (2008) also implemented an aggressive prehydration protocol, which resulted in a reduction of the time to achieve adequate hydration status (4.9 to 1.4 hours) prior to the initiation of chemotherapy.

Confounding Factors

There are numerous confounding factors for HC in the literature that include low platelet count, which increases the risk of bleeding; viral causes of HC such as BK or adenovirus; previous radiation to the bladder; repeated doses of CTX; and other chemotherapy agents that cause HC such as busulfan. Some of the literature accounts for these confounding factors but many articles did not address these issues. The overall evidence can be difficult to interpret due to numerous variables and combined interventions to prevent HC. These factors make definitive conclusions about a single intervention more challenging.

Overall Summary of Recommendations

Based on the effects of the synthesized evidence, the following recommendations are made.

Recommendation No. 1

The EBP team makes a strong recommendation with an overall moderate quality of evidence that administering at least 3 L/m²/d of intravenous fluids is the standard pre- and posthydration rate for patients receiving high dose CTX. The evidence recommends achieving a dilute specific gravity prior to high dose CTX and 24 hours of hydration post high dose CTX.

Recommendation No. 2

The EBP team makes a strong recommendation with an overall low quality of evidence that pre- and posthydration be administered to patients who are receiving low or intermediate doses of intravenous CTX. There is insufficient evidence to recommend intravenous versus oral hydration, intravenous fluid infusion rate, or duration of hydration in patients receiving low or intermediate CTX.

Recommendation No. 3

The EBP team makes a strong recommendation with an overall moderate quality of evidence that forced saline diuresis or MESNA with forced saline diuresis in patients receiving high dose intravenous CTX is effective in reducing the incidence of hemorrhagic cystitis.

Considerations

Patients enrolled in clinical trials should follow protocol guidelines for the use of pre- and posthydration with CTX, and protocol recommendations for MESNA dosing

and administration. Consistency in the care of patients enrolled in clinical trials is crucial to accurately report grades of toxicity and study outcomes.

Individual patient factors need to be considered in all patients receiving CTX. There may be specific comorbidities present that affect a patient's ability to tolerate recommended hydration. These factors include but are not limited to age, disease status, mobility, renal function, and cardiac status. Nausea and fatigue induced by chemotherapy may further decrease the likelihood of sufficient oral hydration.

Conclusion and Discussion

Hydration is a crucial component of supportive care for the patient receiving intravenous CTX. Overall, the evidence in pediatric oncology patients related to HC from high dose CTX is very limited. In addition, there is limited or no research-based evidence regarding hydration with low or intermediate dose CTX. There was limited information about duration of pre- and posthydration for different dose levels of CTX. There were no recommendations related to oral versus intravenous hydration for CTX. In addition, the administration of hydration in the outpatient clinic for CTX was not addressed in the literature. Although the quality of evidence is low (no. 2), the EBP team elected to make a strong recommendation with a low quality of evidence because hydration with CTX has become part of the clinical standard of care and the benefits of hydration greatly outweigh any associated risks.

There is a need for research-based recommendations in the pediatric population that include the following:

1. pre- and posthydration with low or intermediate dose cyclophosphamide;
2. outpatient administration of hydration with cyclophosphamide;
3. comparisons of intravenous versus oral hydration; and
4. supportive care measures that may prevent or reduce HC (such as timing of administration, frequent voiding, use of diuretics).

Best current practices for CTX hydration are currently used at most pediatric oncology centers that include following protocol recommendations or adhering to individual institutional policies. A consistent approach for pre- and posthydration with CTX could simplify prescribing and administration of this agent, provide important outcome measures, improve patient safety, reduce costs, and decrease the incidence of bladder toxicity.

Declaration of Conflicting Interests

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Author Biographies

Deborah Robinson, DNP, APRN, BC, PNP, CPON, is an advanced practice nurse at Saint Louis Children's Hospital.

Ginny Schulz, MSN, RN, CPNP, is an advanced practice nurse at Saint Louis Children's Hospital.

Rachel Langley, PharmD, is a clinical pharmacist at Saint Louis Children's Hospital.

Kevin Donze, BSN, RN, is a nurse clinician at Saint Louis Children's Hospital.

Kari Winchester, BSN, RN, is a staff nurse at Washington University School of Medicine.

Cheryl Rodgers, PhD, RN, CPNP, CPON, is an assistant professor at Duke University School of Nursing.