

From the Children's Oncology Group: Evidence-Based Recommendations for PEG-Asparaginase Nurse Monitoring, Hypersensitivity Reaction Management, and Patient/Family Education

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Abstract

PEG-asparaginase is a backbone chemotherapy agent in pediatric acute lymphoblastic leukemia and in some non-Hodgkin lymphoma therapies. Nurses lack standardized guidelines for monitoring patients receiving PEG-asparaginase and for educating patients/families about hypersensitivity reaction risks. An electronic search of 6 databases using publication years 2000–2015 and multiple professional organizations and clinical resources was conducted. Evidence sources were reviewed for topic applicability. Each of the final 23 sources was appraised by 2 team members. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to assign a quality and strength rating for each recommendation. Multiple recommendations were developed: 4 relating to nurse monitoring of patients during and after drug administration, 8 guiding hypersensitivity reaction management, and 4 concerning patient/family educational content. These strong recommendations were based on moderate, low, or very-low-quality evidence. Several recommendations relied on generalized drug hypersensitivity guidelines. Additional research is needed to safely guide PEG-asparaginase monitoring, hypersensitivity reaction management, and patient/family education. Nurses administering PEG-asparaginase play a critical role in the early identification and management of hypersensitivity reactions.

Keywords

PEG-asparaginase, hypersensitivity, anaphylaxis, patient education, evidence-based practice

Introduction

Asparaginase is a key component of treatment for acute lymphoblastic leukemia (ALL) and some types of non-Hodgkin lymphoma, and its use has significantly improved outcomes and remission rates in children (Kawedia & Rytting, 2014). Unfortunately, hypersensitivity reactions are a known side effect that may interfere with its use (Hesselgrave, 2011; Vogel, 2010). To our knowledge, no standardized practices exist for nurses administering PEG-asparaginase and monitoring parameters during and postinfusion differ among institutions. Additionally, we were unable to identify standardized education recommendations for patients and families to facilitate early identification and management of hypersensitivity reactions. The purpose of this review is to examine the current evidence related to nurse monitoring,

hypersensitivity reaction management, and patient/family education in patients receiving PEG-asparaginase, and to develop recommendations to guide nursing practice for these patients.

Background

Asparaginase hydrolyzes the amino acid asparagine to aspartic acid and ammonia, and the asparagine supply

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depletion results in leukemic cell death (Muller & Boos, 1998). The tumor suppressor properties of what was later identified as the enzyme asparaginase were first discovered in the 1950s. Three forms of the drug have since been approved in the United States: native asparaginase (L-asparaginase, Elspar®) derived from *Escheria coli*; *Erwinia* asparaginase (Erwinase®) derived from *Erwinia chrysanthemi*; and PEG-asparaginase (pegaspargase, Oncaspar®), a version of L-asparaginase with polyethylene glycol covalently conjugated to it. L-asparaginase is no longer commercially available in the United States (Bechwith, Wheeler, & Jensen, 2013), and PEG-asparaginase is now used for frontline ALL therapy, given its prolonged half-life and intravenous administration option (Asselin & Fisher, 2014). Because the bacterial macromolecules of *E. coli* and *Erwinia chrysanthemi* are not native to humans, B-cell lymphocytes can produce anti-asparaginase antibodies which in turn trigger hypersensitivity reactions with the first or subsequent dose of the agent (Muller et al., 2001; Shinnick, Browning, & Koontz, 2013). The degree and clinical presentation of these reactions can vary from pruritus and urticarial rash to dyspnea and systemic anaphylaxis (Pidaparti & Bostrom, 2012; Ruggiero et al., 2013). A recent meta-analysis calculated pediatric hypersensitivity reaction rates to intravenous PEG-asparaginase (23.5%) as significantly greater than intramuscular rates (8.7%; Hasan, Shaikh, Rassekh, Howard, & Goddard, 2017). The same study also described high-risk patients, whose therapy exposes them to more doses of PEG-asparaginase, as having higher reaction rates than standard risk patients (Hasan et al., 2017).

Method

Evidence-Based Practice Team

The Children's Oncology Group (COG) Nursing Discipline supports teams of nurses and other health care professionals to develop systematic reviews and evidence-based guidelines pertinent to pediatric oncology nursing practice (Rodgers, Withycombe, & Hockenberry, 2014). The authors were selected to participate in a COG Nursing evidence-based practice project focused on the standardization of chemotherapy administration nursing practices. Two team members (D. W. and K. W.) served as team leaders, and a doctorally prepared nurse (E. B.) was assigned as their mentor. All team members participated in the question development, literature search, evidence appraisal and synthesis, and manuscript writing.

Question Development

Two PICOT (Patient, Intervention/Issue, Comparison, Outcome, and Timeframe) questions were developed to

guide the literature review and vetted with COG Nursing Discipline leadership:

1. For pediatric oncology nurses, what monitoring guidelines are needed during and after PEG-asparaginase administration to facilitate the early identification and management of hypersensitivity reactions?
2. For pediatric oncology patients and their families, what education is needed regarding PEG-asparaginase administration to facilitate the early identification and management of hypersensitivity reactions?

Literature Search

An extensive literature search was conducted in February 2015 and confirmed by a medical librarian. Six databases, including MEDLINE, Cumulative Index of Nursing and Allied Health Literature (CINAHL) Plus, EMBASE, the Cochrane Database of Systematic Reviews, National Guideline Clearinghouse, and Turning Research Into Practice (Trip), were searched using a combination of the terms hypersensitivity, monitoring, anaphylaxis, chemotherapy hypersensitivity, PEG-asparaginase, asparaginase, allergic reaction, pediatric, treatment, and education. Limits included English language and human subjects, and there was no initial publication date restriction. Professional organizations and clinical resources were also searched, including the Oncology Nursing Society, Association of Pediatric Hematology/Oncology Nurses, COG, American Academy of Pediatrics, World Allergy Organization, Academy of Allergy and Immunology, and Up to Date®. Additionally, 4 COG leukemia protocols (AALL1131, AALL0932, AALL0232, and AALL0331) were reviewed for PEG-asparaginase monitoring and hypersensitivity reaction management recommendations.

During the evidence appraisal process, the team was alerted to the potential overlap in symptom type and time to onset between asparaginase hypersensitivity reactions and symptomatic hyperammonemia (S. C. Howard, personal communication, December 15, 2015). The database search was repeated in December 2015 to include the search term *hyperammonemia* and discover any new publications. A total of 1 150 sources of evidence were identified from the 2 searches (see Figure 1). Articles were initially reviewed by title and abstract, and the majority of articles were eliminated because they were not relevant to the PICOT questions. During full-text review of the remaining 54 articles, additional sources were excluded as they contained only background information or were not specifically related to the PICOT questions. A decision was then made to exclude articles published prior to the year 2000 as they were no longer consistent

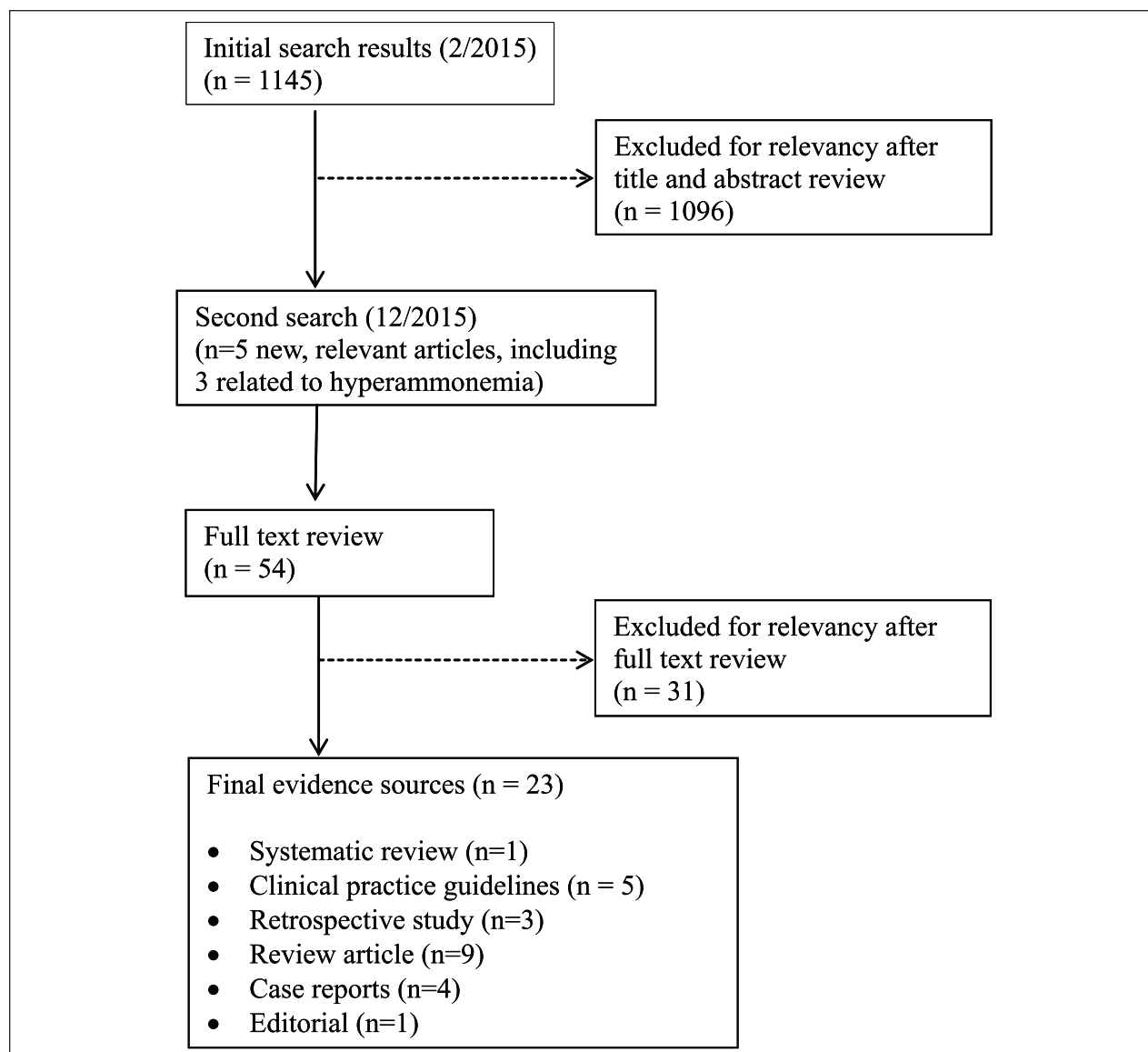


Figure 1. Evidence search results.

with current therapy. Articles exclusively related to food allergies or nonasparaginase chemotherapy agents were also excluded, reducing the total number of evidence sources to 23.

Data Evaluation

Articles were appraised by pairs of team members and presented to the entire team for discussion. Details and limitations of each article were recorded in an evidence table. Clinical practice guidelines (CPG) were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. The team then utilized the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system to

assign a quality of evidence (high, moderate, low, or very low) and strength (strong or weak) rating to each recommendation (Neumann et al., 2016).

Review of the Literature

Monitoring

Vital Signs and Observation During Administration. Four review articles addressed the importance of measuring vital signs and observing for hypersensitivity reaction signs and symptoms during PEG-asparaginase administration (Asselin & Fisher, 2014; Ruggiero et al., 2013; Shinnick et al., 2013; Zanotti & Markman, 2001). Asparaginase hypersensitivity may present as a local (intramuscular

injection site) or more generalized reaction, and either can be life threatening if not identified in a timely manner (Asselin & Fisher, 2014; Zanutti & Markman, 2001). Most hypersensitivity reactions occur within minutes of starting the infusion and symptoms may be general (lethargy, malaise, headache), dermatologic (pruritus, urticarial rash, flushing, angioedema), respiratory (dyspnea, wheezing, bronchospasm, stridor), gastrointestinal (abdominal pain, nausea/vomiting, diarrhea), or cardiovascular (hypotension, bradycardia; Kirkbright & Brown, 2012; Lieberman et al., 2015; Ruggiero et al., 2013). The Joint Task Force on Practice Parameters for the American Academy of Allergy, Asthma, and Immunology describes the continued debate within its group and among other organizations regarding the lack of a standardized definition of anaphylaxis (Lieberman et al., 2015). Anaphylaxis is generally recognized as a severe hypersensitivity reaction, which typically includes a rapid onset and multisystem symptomatology (Kirkbright & Brown, 2012; Lieberman et al., 2015). Symptoms may include respiratory compromise (eg, wheezing, dyspnea, upper airway angioedema), hypotension and circulatory collapse, and urticaria (Kirkbright & Brown, 2012). Fever and chills may also be present (Shinnick et al., 2013). Due to the frequency and severity of reactions, nurses should monitor vital signs, and observe for reaction signs and symptoms during PEG-asparaginase administration (Shinnick et al., 2013). None of the articles recommended specific time intervals for measuring vital signs; however, general monitoring parameters for drugs with infusion reaction potential include measuring vital signs preinfusion, then every 15 minutes during the infusion (Vogel, 2010).

Postadministration Observation Duration. A total of 5 review articles and 1 retrospective study discussed the need for continued vital sign monitoring and nurse observation after the completion of asparaginase infusions. Four of the articles report the typical occurrence of hypersensitivity symptoms within 1 hour of administration, making this a crucial period for observation (Ruggiero et al., 2013; Shepherd, 2003; Zanutti & Markman, 2001). However, these recommendations were based on older clinical data and a variety of asparaginase forms and administration routes. COG protocols (Shinnick et al., 2013) and the review by Asselin and Fisher (2014) advise that monitoring patients for 1 hour postadministration is sufficient, though the possibility of delayed reactions should not be ignored. A recent retrospective study of 615 children with ALL found 79 documented cases of PEG-asparaginase allergy, and noted that while no anaphylactic reactions occurred after 2 hours of administration, signs of hypersensitivity reactions occurred in 29% of patients between 2 and 6 hours following intramuscular PEG-asparaginase injection (Henriksen et al., 2015).

Emergency Medications and Anaphylaxis Action Plans. A total of 5 review articles and 1 CPG recommended that emergency medications (epinephrine, oxygen, normal saline, and albuterol) and equipment (bag valve mask, oropharyngeal airway, oxygen tubing, and intravenous access and infusion supplies) be readily available during and after administration of medications with a high risk of hypersensitivity reactions (Asselin & Fisher, 2014; Kirkbright & Brown, 2012; Lieberman et al., 2015; Shinnick et al., 2013; Wallace, 2013; Zanutti & Markman, 2001).

Nurses and clinical staff should receive ongoing education and training based on a written anaphylaxis action plan (Lieberman et al., 2015). This evidence-based plan should identify pertinent symptoms, necessary tasks, timing and location of each task, and the role of each staff member. Emphasis should be placed on the signs, symptoms, and triggers of anaphylaxis (Lieberman et al., 2015; Wallace, 2013). A copy of this evidence-based plan should be available in all areas of the clinic or office and attached to the emergency cart (Kirkbright & Brown, 2012; Wallace, 2013). Management algorithms and a list of emergency cart supplies and medications are outlined in the anaphylaxis practice parameter update (Lieberman et al., 2015).

Postreaction Observation Period. Most drug hypersensitivity reactions are monophasic, occurring as an isolated event within 30 minutes of stimulus exposure and resolving within 1 to 2 hours (Lieberman, 2014). However, up to 20% are biphasic reactions, defined by a second surge of symptoms after resolution of the first reaction. These symptoms typically occur within 8 hours of initial symptom onset (Kirkbright & Brown, 2012; Lieberman, 2014). Due to biphasic reaction potential, experts recommend postreaction observation in a medical setting with monitoring and resuscitation capabilities. A total of 2 review articles and 2 CPGs recommend that patients be observed for a minimum of 4 hours postanaphylaxis and hospital admission be considered for patients with severe reactions, other comorbidities, or age younger than 16 years (Kirkbright & Brown, 2012; Lieberman, 2014; Lieberman et al., 2015; National Institute for Health and Clinical Excellence, 2011). Unfortunately, there are no studies comparing postanaphylaxis observation times and clinical outcomes nor are there studies regarding ideal observation times following nonanaphylactic hypersensitivity reactions.

Management of Hypersensitivity Reactions

Epinephrine as First-Line Treatment. It is beyond the scope of this review to detail every step and supply needed in the management of hypersensitivity reactions. However,

our evidence review suggests great inconsistency in the selection of first-line treatment medications, and thus, this topic is addressed here. Evidence from 1 systematic review, 3 CPGs, and 2 review articles recommend that epinephrine be used as first-line treatment for suspected hypersensitivity reactions (Choo, Simons, & Sheikh, 2012; Kirkbright & Brown, 2012; Lieberman, 2014; Lieberman et al., 2015; National Institute for Health and Clinical Excellence, 2011; Simons et al., 2015). Epinephrine is the ideal first-line treatment, as it affects multiple receptors involved in anaphylaxis and has an optimal pharmacodynamic effect within 10 minutes of intramuscular administration (Lieberman, 2014; Lieberman et al., 2015). Lieberman (2014) notes that epinephrine should be given to anyone at risk for progressing to anaphylactic shock, as the clinical course of anaphylaxis can be unpredictable. Thus, all patients experiencing any hypersensitivity signs or symptoms should receive epinephrine. Delays in epinephrine administration place patients at increased risk for biphasic reactions or even fatality (Choo et al., 2012; Lieberman, 2014; Lieberman et al., 2015). Glucocorticoids and antihistamines are frequently administered as initial treatment for hypersensitivity reactions and anaphylaxis; however, there is a lack of high-level evidence to support their use (Choo et al., 2012; Lieberman et al., 2015).

Laboratory Tests. Following reactions to chemotherapeutic drugs such as PEG-asparaginase, the clinician must weigh the risks of the patient developing a fatal reaction on reexposure to the drug with the risks of switching drug formulations or even discontinuing potentially life-saving asparaginase treatment. Several laboratory tests can aid in the decision-making process.

Asparaginase antibodies. The immunogenicity of asparaginase products can lead to anti-asparaginase antibody development and subsequent hypersensitivity reaction on reexposure (August, Miller, Dalton, & Shinnick, 2013; Shinnick et al., 2013). High levels of anti-asparaginase antibodies may also result in decreased asparaginase serum activity, which several studies have correlated with poor outcomes for children with leukemia (August et al., 2013; Shinnick et al., 2013; Walenciak, Mlynarski, & Zalewska-Szewczyk, 2014). Antibodies can produce both clinical and subclinical hypersensitivity, and both forms may contribute to reduced asparaginase activity (Asselin & Fisher, 2014). Six articles of low level of evidence (2 retrospective studies, 2 reviews, 1 case series, and 1 editorial) supported measurement of asparaginase antibody levels following a hypersensitivity reaction.

Ammonia levels. Ammonia is a by-product of asparaginase activity, and its production begins immediately

after asparaginase administration is initiated (Jorck et al., 2011; Nussbaum, Lubcke, & Findlay, 2016). Production may peak in 2 to 5 days, and remain in the system for 10 days. Patients experiencing elevated levels of ammonia (hyperammonemia) postasparaginase may not exhibit any symptoms, may experience only mild symptoms, or may develop neurological symptoms that can progress to encephalopathy, coma, or death (Jorck et al., 2011; Nussbaum et al., 2016; Paulides et al., 2013). Some symptoms of hyperammonemia such as anxiety, malaise, weakness, nausea, vomiting, and abdominal cramping may appear similar to and be mistaken for PEG-asparaginase hypersensitivity reactions.

Therefore, it is important to differentiate hypersensitivity reactions from ammonia toxicity in order to treat the condition appropriately. Several case series suggest an advantage to measuring ammonia levels in symptomatic patients, as results may assist in differentiating the clinical presentation of hypersensitivity versus hyperammonemia and guide the appropriate treatment (Jorck et al., 2011; Nussbaum et al., 2016; Paulides et al., 2013). Due to the half-life of PEG-asparaginase, the potential for ammonia accumulation between doses exists. The clinical significance of this is unclear, and further research is needed to explore the utility of routine ammonia measurements in asymptomatic patients (Jorck et al., 2011; Nussbaum et al., 2016; Paulides et al., 2013).

Tryptase levels. Tryptase is an indicator of mast cell activation, and elevated tryptase levels may help confirm a drug-related hypersensitivity reaction or point toward an alternate etiology (Kirkbright & Brown, 2012; Lee, Gianos, & Klaustermeyer, 2009; Lieberman et al., 2015; Simons et al., 2015). Six sources of evidence (4 CPGs and 2 reviews) recommended obtaining tryptase levels in patients with suspected anaphylaxis (Kirkbright & Brown, 2012; Lee et al., 2009; Lieberman et al., 2015; National Institute for Health and Care Excellence, 2014; National Institute for Health and Clinical Excellence, 2011; Simons et al., 2015). One sample should be taken immediately after initiation of emergency treatment, and a second sample should be taken within 1 to 2 hours of symptom onset, when peak levels of tryptase occur (National Institute for Health and Care Excellence, 2014; National Institute for Health and Clinical Excellence, 2011).

Documentation. Following a suspected drug hypersensitivity reaction, 4 CPGs and 1 review article specifically recommend documenting detailed information in the patient's medical record about drug dosing, symptom onset and severity, interventions and response, and event follow-up (Joint Task Force on Practice Parameters, American Academy of Allergy Asthma & Immunology,

American College of Allergy Asthma & Immunology, & Joint Council of Allergy Asthma & Immunology, 2010; Lieberman et al., 2015; National Institute for Health and Care Excellence, 2014; National Institute for Health and Clinical Excellence, 2011; Shinnick et al., 2013). This information can assist in differentiating and confirming a hypersensitivity reaction. The guidelines also note a need to distribute this information to the patient's other health care providers (Joint Task Force on Practice Parameters et al., 2010; Lieberman et al., 2015; National Institute for Health and Care Excellence, 2014; National Institute for Health and Clinical Excellence, 2011; Shinnick et al., 2013). Thorough and accurate documentation may prevent further exposure and potential reaction to an offending medication, and may also prevent erroneous cessation of PEG-asparaginase when a hypersensitivity reaction did not truly occur.

Reaction Grading Tool. Three review articles recommend utilizing a validated tool to systematically classify hypersensitivity reactions (Asselin & Fisher, 2014; Shinnick et al., 2013; Wallace, 2013). The tool may be determined by institutional standards or be specific to the medication in question. For example, the CTCAE (Common Terminology Criteria for Adverse Events), developed by the National Cancer Institute, National Institutes of Health, and U.S. Department of Health & Human Services, is widely used in pediatric oncology (Asselin & Fisher, 2014; Wallace, 2013). While thorough documentation should support the assigned grade, it is also important to grade the reaction severity at the time of the event (Shinnick et al., 2013). Reaction grading is vital to making individual patient treatment decisions and for conducting research. In Pidaparti and Bostrom's (2012) study of asparaginase reactions, medical record documentation was used to retrospectively grade severity. Study outcomes were limited by the inability to grade some reactions due to poor documentation.

Reaction Prevention. Asparaginase therapy is a cornerstone of ALL treatment, and careful decision making is required when considering an asparaginase formulation change or discontinuation due to hypersensitivity reactions (Asselin & Fisher, 2014; Shinnick et al., 2013; Zanotti & Markman, 2001). Successful desensitization protocols of asparaginase dose escalation and/or slowed infusion rates have been reported, but this practice has not been rigorously studied (Zanotti & Markman, 2001). Several reviews mention intradermal skin testing as a method of predicting patients who will have an asparaginase reaction; however, both false positives and negatives have been documented, and skin testing has not become standard practice (Lee et al., 2009; Shepherd, 2003; Zanotti & Markman, 2001).

The most common method, and likely the most controversial, is premedication with corticosteroids and/or antihistamines (Ruggiero et al., 2013; Shinnick et al., 2013). Steroid and antihistamine pretreatment may decrease immune responsiveness and the likelihood of developing anti-asparaginase antibodies, thereby reducing the risk of a hypersensitivity reaction. However, recent reports indicate that premedication may mask the occurrence of hypersensitivity reactions, leading to unidentified enzyme activity reduction and decreased asparaginase benefit. There is a possibility that pretreatment with antihistamines and steroids may contribute to silent inactivation that may alter efficacy of therapy and event free survival (Asselin & Fisher, 2014; Fernandez et al., 2014; Henriksen et al., 2015; Shinnick et al., 2013; Walenciak et al., 2014). There are also case reports of anaphylaxis due to PEG-asparaginase despite premedication and desensitization (Sahiner et al., 2013).

Epinephrine Autoinjector. Patients with a prior history of anaphylaxis have a higher risk of both anaphylaxis on repeat drug exposure and death in the event of a subsequent anaphylactic episode (Kirkbright & Brown, 2012; Lieberman et al., 2015). Three CPGs on drug-induced anaphylaxis recommend that these patients be prescribed an epinephrine autoinjector (EAI) prior to subsequent drug exposure (Lieberman et al., 2015; National Institute for Health and Clinical Excellence, 2011; Simons et al., 2015).

Patient/Family Education

Providing education to patients and families is a key component of the oncology nurse's role (Hesselgrave, 2011). The scope of this review was to identify the content (ie, symptom identification and management instructions) that should be taught, rather than specific educational strategies. There were no studies specific to PEG-asparaginase education or chemotherapy hypersensitivity education, and therefore, no results regarding education efficacy. No studies were identified that describe the proportion of patients who experienced onset of asparaginase hypersensitivity reaction in the home setting, the population that would benefit most from education.

Signs, Symptoms, and Timing. COG recommends that due to the long half-life of PEG-asparaginase, patients and families should be educated regarding the signs and symptoms of hypersensitivity reactions that may appear hours to days after administration (Shinnick et al., 2013). Nurses should also reinforce that potential reactions may occur with any PEG-asparaginase dose, and that previous tolerance of an offending agent does not preclude it from subsequently triggering an immune response (Lieberman, 2014).

As discussed previously, symptoms of ammonia toxicity may mimic hypersensitivity and may develop immediately or within hours following asparaginase administration (Nussbaum et al., 2016; Paulides et al., 2013). These general symptoms should be included in patient/family education to initiate prompt evaluation and management (Nussbaum et al., 2016).

Reaction History and Action Plan. Patients who experience anaphylaxis to PEG-asparaginase should be prescribed an EAI for home administration, if they will receive any form of asparaginase in the future. These patients/families should receive an EAI demonstration and written instructions. Five CPGs and several review articles recommend that patients/families receive an individualized anaphylaxis action plan in both verbal and written form. The plan should include instructions to observe for specific hypersensitivity symptoms, to immediately administer an EAI and call 911, and to avoid accidental drug exposure by communicating the allergy history with all health care providers and ensuring the allergy is accurately recorded in the medical record (Joint Task Force on Practice Parameters et al., 2010; Kirkbright & Brown, 2012; Lieberman, 2014; Lieberman et al., 2015; National Institute for Health and Care Excellence, 2014; National Institute for Health and Clinical Excellence, 2011; Simons et al., 2015).

Summary of Recommendations

Table 1 summarizes the key PEG-asparaginase monitoring, hypersensitivity reaction management, and patient education recommendations. The Monitoring Recommendations and Hypersensitivity Reaction Management Recommendations sections address our first PICOT question regarding nurse monitoring guidelines and the facilitation of early identification and management of hypersensitivity reactions. The patient education recommendations reflect the second PICOT question about patient/family education content for early identification and management of hypersensitivity reaction.

Discussion

The inclusion of asparaginase in the treatment of ALL has dramatically improved outcomes and is therefore one of the mainstays of therapy; however, due to its bacterial derivation, hypersensitivity reactions continue to be a barrier to effective treatment. Despite the frequency of these reactions, a standardized approach for nurse monitoring, management, and patient/family education is lacking.

A systematic evaluation of the literature revealed that patient monitoring by nurses and emergent intervention

Table 1. Summary of PEG-Asparaginase Monitoring, Hypersensitivity Reaction Management, and Patient Education Recommendations.^a

Monitoring Recommendations

1. Measure vital signs (heart and respiratory rate, blood pressure, temperature) and observe patients for hypersensitivity signs and symptoms during and for 1 hour postadministration (S, L).
2. Have emergency medications and resuscitation equipment readily available during and postadministration (S, L).
3. Monitor patients for a minimum of 4 hours postanaphylactic reaction; consider hospital admission (S, L).
4. Educate clinical staff regarding the institution's anaphylaxis action plan (pertinent symptoms, steps to be taken, when, and by whom) (S, L).

Hypersensitivity Reaction Management Recommendations

1. Administer epinephrine as first-line treatment for suspected hypersensitivity reactions (S, M).
2. Obtain an asparaginase antibody (S, M) and ammonia level (S, VL) following a hypersensitivity reaction. Obtain tryptase following a suspected anaphylactic reaction (S, M).
3. Prescribe an epinephrine autoinjector to patients with a history of anaphylaxis who will receive future asparaginase doses (S, M).
4. Following a suspected hypersensitivity reaction, perform a thorough history and physical exam and document the following (S, L):
 - Description, time of onset, and severity of symptoms and clinical findings
 - Dose, route, and administration time of treatment medications
 - Results of any diagnostic evaluations
 - Update the allergy section of medical record
5. Grade reaction severity using a validated tool (S, L).
6. Following a hypersensitivity reaction, avoid desensitization or premedication with H₁ or H₂ antihistamines or corticosteroids prior to the next dose of asparaginase (S, VL).

Patient Education Recommendations

1. With each dose of asparaginase, educate the patient/family about the signs and symptoms of a hypersensitivity reaction and the duration of time that the reaction is possible (S, L).
2. For patients with a history of hypersensitivity reaction, provide written information to the patient/family about the reaction and advise them to share this information with other health care professionals (S, L).
3. For patients with a history of asparaginase anaphylaxis, provide education about proper epinephrine autoinjector use prior to the next asparaginase dose (S, L).
4. Include general signs and symptoms of ammonia toxicity in patient/family education (S, L).

^aRecommendation Strength: S = Strong, W = Weak; Evidence Quality: H = High, M = Moderate, L = Low, VL = Very Low.

for PEG-asparaginase reactions should align with generalized guidelines for drugs with hypersensitivity potential. Current standard of care suggests assessing vital signs immediately prior to PEG-asparaginase infusion,

during the infusion, and for 1 hour postadministration, but the optimal assessment frequency during and postinfusion is not known. A single retrospective study indicated a 2-hour postinfusion monitoring time period may be beneficial (Henriksen et al., 2015), but additional research is needed to confirm this finding. Nursing staff should be educated regarding hypersensitivity signs and symptoms and be aware that symptoms of malaise, headache, emesis, altered consciousness, may be related to ammonia toxicity. Emergency medications are recommended to be readily available at bedside. Since antihistamines and corticosteroids are often given as initial therapy for hypersensitivity reactions, nurses should review their institutional anaphylaxis action plans to confirm that epinephrine is recommended and available as the first-line medication (Lieberman et al., 2015).

Content for patient/family education should align with generalized drug hypersensitivity guidelines and focus on identifying hypersensitivity signs and symptoms as well as procedures for identifying and managing a reaction outside of a medical setting. Information specific to PEG-asparaginase should include typical time to reaction onset. Details of a PEG-asparaginase reaction should be conveyed to the patient and family.

It is important to correctly distinguish PEG-asparaginase hypersensitivity reactions from other diagnoses as erroneous classification could result in a change in asparaginase formulation or drug cessation, both of which could have prognostic implications for the patient. There is no single test to confirm a hypersensitivity reaction, and therefore, decisions should be based on a combination of specific laboratory tests and thorough clinical documentation.

Limitations

There is a lack of high-quality evidence to support our recommendations. Only 1 research study was identified that specifically addressed either of the 2 PICOT questions, and it was retrospective in design (Henriksen et al., 2015). All of the other recommendations were based on CPGs, review articles, or case series. Indirectness of evidence existed, because data were often based on trials of native asparaginase, *Erwinia*, or intramuscular PEG-asparaginase, rather than the currently utilized intravenous route. Several recommendations were applicable to all types of drug hypersensitivity reactions or anaphylaxis, and not specific to PEG-asparaginase. The potential for bias was introduced, as the search was limited to the English language and 3 review articles (Asselin & Fisher, 2014; Lieberman, 2014; Shinnick et al., 2013) disclosed funding and writing support from pharmaceutical companies. The quality of evidence regarding the clinical implications of measuring ammonia levels was downgraded due to imprecision, as

very few case reports exist. Several of the guidelines lacked implementation strategies (Joint Task Force on Practice Parameters et al., 2010; Lieberman et al., 2015) or did not indicate patient/family members as guideline development group participants (Joint Task Force on Practice Parameters et al., 2010; Lieberman et al., 2015; Simons et al., 2015). The World Allergy Organization's guideline update (Simons et al., 2015) lacked a systematic description of the evidence search and appraisal process, however, these processes were clearly described in the original guideline document (Simons et al., 2011). Content for family education and anaphylaxis actions plans were suggested. However, there was not strong evidence to support the efficacy of this education in successful home management of hypersensitivity reactions.

Conclusion

This review of the evidence outlines opportunities for both pediatric and adult oncology nurses to examine current practices specific to PEG-asparaginase and other chemotherapy drugs that commonly cause hypersensitivity reactions. The development of standardized clinical monitoring guidelines for nursing staff and patient/family education can promote early identification and treatment of hypersensitivity. This review also demonstrates opportunities for future nursing research regarding best education practices, the incidence and clinical implications of ammonia toxicity, and the time to hypersensitivity reaction onset following PEG-asparaginase administration.

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Declaration of Conflicting Interests

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