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Abstract

Hypersensitivity reactions to chemotherapeutic drugs have been documented for numerous cancer therapies. Clinical hypersensitivity to *Escherichia coli* asparaginase has been reported to range from 0% to 75%. Throughout the United States, nurses assume frontline responsibility for the assessment of asparaginase-related hypersensitivity reactions. It is essential that nurses educate themselves on the signs and symptoms of asparaginase-related hypersensitivity reactions as well as current supportive care approaches. The purpose of this review is to summarize acute lymphoblastic leukemia and the role of asparaginase and the pathology of allergic reactions. We will also update nurses on the differences in asparaginase preparations including dosing, half-life, rates of hypersensitivity, and routes of administration. A summary of current management and supportive care strategies will be provided as will a discussion of the relationship between allergy, antibodies, and asparaginase activity.

Keywords

asparaginase, hypersensitivity, acute lymphoblastic leukemia, allergic reactions

Introduction: Acute Lymphoblastic Leukemia (ALL) Incidence, ALL Treatment Regimens, Role of Asparaginase

Acute lymphoblastic leukemia (ALL) is the most common type of cancer affecting children and adolescents. An estimated 6050 patients in the United States will be diagnosed with ALL in 2012, of which, approximately 70% will be patients younger than 34 years (U.S. Department of Health and Human Services, National Institute of Health [NIH], National Cancer Institute [NCI], 2012). Treatment for ALL has continually evolved over the past 50 years. Substantial improvement in event-free survival (EFS) has been realized, particularly for B-cell ALL, with current estimates of 5-year EFS ranging from 76% to 86% for children who are treated with protocol-based regimens (Pui, Carroll, Meshinchi, & Arceci, 2011). The primary factors leading to the improved survival of ALL include the use of multiagent chemotherapy regimens, inclusion of an intensification cycle of chemotherapy, central nervous system-directed therapy, and assignment of treatment regimens based on identified risk factors (Carroll & Raetz, 2012).

Treatment for most patients will involve multiple chemotherapy agents, administered in phases (remission

induction, consolidation or intensification, and continuation or maintenance) over a period of 2 to 3 years, depending on the patient's risk status (Pui & Evans, 2006). Pui and Evans (2006) note that the purpose of induction therapy is to eliminate more than 99% of the disease and restore normal hematopoiesis. Although the overwhelming majority of children are able to achieve a remission at the end of induction therapy, they will still require the intensification phase, which consists of noncross resistant drugs given in an alternating fashion, in order to eradicate residual disease. The continuation or maintenance phase then serves to sustain the remission.

Asparaginase is a crucial drug in ALL therapy, and for more than 30 years, has been incorporated into multiagent chemotherapy regimens (Steiner et al., 2012). Asparaginases are bacterial proteins that act by depleting plasma asparagine and glutamine, which are nonessential amino acids for normal cells but are essential to the survival of

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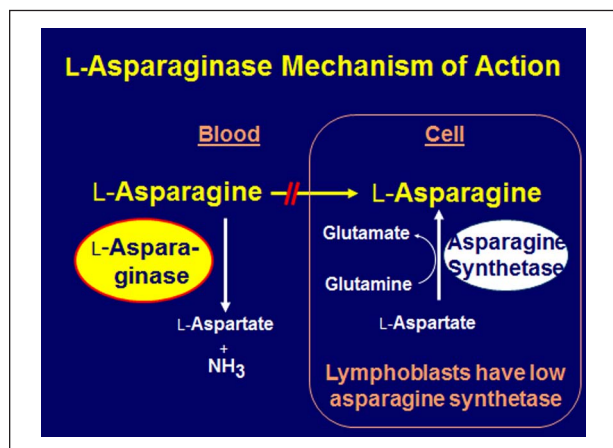


Figure 1. Mechanism of action of asparaginase on lymphoblast

SOURCE: Reprinted with permission from Douer and De Angelo (2008). NOTE: Asparaginase functions by depleting the serum of asparagine, thereby depriving cells of their exogenous source of asparagine. Most normal tissue is able to resynthesize its own asparagine through adequate stores of the enzyme asparagine synthetase. Lymphoblasts have low or undetectable levels of asparagine synthetase, and therefore asparagine becomes an essential amino acid for these cells. Depleting the lymphoblast of serum asparagine deprives the cell of an essential amino acid, causing lymphoblasts to undergo apoptosis, or programmed cell death.

leukemia cells (Avramis & Panosyan, 2005; Capizzi, 1993). For leukemia cells, which lack the ability to synthesize asparagine, the depletion of plasma asparagine leads to cell death by way of inhibition of protein synthesis and inhibition of RNA and DNA synthesis. Simply stated, the depletion of asparagine by an asparaginase product essentially starves the leukemia cell (Figure 1).

The sensitivity or resistance of leukemia cells to asparagine depletion has been shown to influence treatment outcome (Steiner et al., 2012). Capizzi (1993) noted that asparaginase products with very short half-lives are cleared rapidly from the plasma and have limited therapeutic duration. Pieters et al. (2011) later summarized the study results of the randomized trials by the European Organization for Research and Treatment of Cancer–Children’s Leukemia Group (EORTC-CLG 58881 trial) and by Dana-Farber Cancer Institute ALL Consortium (DFCI protocol 95-01) stating that asparaginase preparations with a shorter half-life resulted in an inferior EFS, although there was less toxicity, as compared with the asparaginase product with a longer half-life given at the same dose and frequency. Subsequent studies have shown that the dose intensity and duration of asparaginase therapy are more important than the type of asparaginase used in the treatment regimen (Pui & Evans, 2006; Woo et al., 2000). In the DFCI consortium study 91-01, outcomes were worse for pediatric patients who tolerated fewer than 26 weeks of asparaginase either native (asparaginase product with a short half-life of elimination) or pegylated (asparaginase with a long

half-life of elimination), as compared with those who were able to receive at least 26 weeks or more of the planned therapy (Silverman et al., 2001). In this study, a multivariate analysis showed that asparaginase intolerance was the only significant prognostic factor that predicted 5-year EFS. Silverman et al. (2001) indicated that one reason for intolerance to more than 25 weeks of asparaginase therapy was allergic reaction, which occurred in 19% of patients treated on their study.

This article will review the 3 types of commercially available asparaginase formulations in the United States with a focus on the management of hypersensitivity reactions associated with these products (Table 1).

Allergic Reaction or Hypersensitivity to Asparaginase Products: Pathology of Allergic Reactions

For a substance to elicit an allergic reaction, it must be of a high molecular weight (ie, greater than 100 000 dalton), have a regularly reoccurring structure, and possess molecular epitopes on its surface so that it can activate B-cell receptors (Müller & Boos, 1998; Sompayrac, 2008). Since commercially available asparaginases are derived from a bacterial source, either *Escherichia coli* or *Erwinia chrysanthemi*, and are nonnative in the human species, they are targets for the immune system to produce anti-asparaginase antibodies, which in turn lead to allergic reactions on reexposure of the drug (Pieters et al., 2011). In the immune system, the B-cell lymphocytes, in response to the presence of an antigen, or allergen such as an asparaginase product, will proliferate and produce antibodies against the antigen. In the case of asparaginase hypersensitivity, the antibody is thought to be of the IgG (immunoglobulin G) class, although others have reported detecting both IgM and IgE antibodies (Avramis, Avramis, Hunter, & Long, 2009; Körholz, Wahn, Jürgens, & Wahn, 1990; Zalewska-Szewczyk et al., 2007).

All antibodies are produced by B-cell lymphocytes. Class switching is an immune function that allows a B-cell to produce more than one class of antibody. In response to allergens, B-cells produce either IgG or IgE antibodies (Sompayrac, 2008). Antibodies are composed of a variable region with a fragment antigen binding (Fab) site, which is specific to an antigen or allergen, and a constant region (Fc), which interacts with other cells in the immune system. The Fc portion determines the class and function of the antibody (Abbas & Lichtman, 2003). The Fc portion of an antibody, once its Fab region is bound to an antigen, is able to stimulate immune cells and proteins, including complement, T-cell lymphocytes, macrophages, and mast cells, to migrate to the antibody-coated antigen to eliminate it. IgE antibodies have a strong affinity to

Table 1. Comparison of Commercially Available Asparaginase Products in the United States

Generic Name	L-Asparaginase ^a	Pegaspargase ^b	Asparaginase <i>Erwinia chrysanthemi</i> ^c
Brand name	Elspar	Oncaspar	Erwinaze
Manufacturer	Lundbeck, Inc.	Sigma-Tau Pharmaceuticals, Inc.	Jazz Pharmaceuticals, plc (product formerly owned by EUSA Pharma, Inc.)
Availability	Single-use vial—10 000 IU as lyophilized powder	Single-use vial—3750 IU/5 mL as solution	Single-use vial—10 000 IU as lyophilized powder
Initial FDA approval	1978	1994	2011
FDA-approved indication(s)	As a component of a multiagent chemotherapeutic regimen for the treatment of patients with ALL	As a component of a multiagent chemotherapeutic regimen for treatment of patients with (1) first-line (newly diagnosed) ALL and (2) ALL and hypersensitivity to native forms of L-asparaginase	As a component of a multiagent chemotherapeutic regimen for the treatment of patients with ALL who have developed hypersensitivity to <i>E. coli</i> -derived asparaginase
FDA-approved dose	6000 IU/m ² intramuscularly or intravenously 3 times weekly	2500 IU/m ² intramuscularly or intravenously no more frequently than every 14 days	To substitute for a dose of pegaspargase: The recommended dose is 25 000 IU/m ² administered intramuscularly 3 times a week (Monday/Wednesday/Friday) for six doses for each planned dose of pegaspargase To substitute for a dose of native <i>E. coli</i> asparaginase: The recommended dose is 25 000 IU/m ² administered intramuscularly for each scheduled dose of native <i>E. coli</i> asparaginase within a treatment
Description	Contains the enzyme L-asparaginase amidohydrolase, type EC-2	L-asparaginase that is covalently conjugated to monomethoxypolyethylene glycol	Contains the enzyme L-asparaginase
Bacteria source	<i>Escherichia coli</i>	<i>Escherichia coli</i>	<i>Erwinia chrysanthemi</i> (formerly <i>Erwinia carotovora</i>)
Half-life (days $\pm$ SD) ^d	1.28 $\pm$ 0.35	5.73 $\pm$ 3.24	0.65 $\pm$ 0.13

NOTE: ALL, acute lymphoblastic leukemia. FDA, Food and Drug Administration.

a. Lundbeck, Inc. (2010).

b. Sigma-Tau Pharmaceuticals, Inc. (2011).

c. EUSA Pharma, Inc. (2011).

d. Medac Hematology (2009).

mast cells and attach their Fc region to the mast cell, leaving the Fab region available to encounter an allergen, as seen with Type I immediate hypersensitivity reactions. On repeated exposure to an identified allergen, the Fab region binds in clusters, or crosslinks, to the antigen, leading to degranulation of the mast cell and release of histamine. Histamine, along with other chemicals in the mast cell, increase capillary permeability, which, if left uncontrolled, can subsequently reduce blood volume, leading to hypotension, and can cause smooth muscles to contract, leading to difficulty in breathing, and subsequent anaphylaxis (Sompayrac, 2008; Figure 2).

Avramis et al. (2009) found that IgG4 antibodies were likely the cause of asparaginase allergic reactions and that most of the antibodies were neutralizing, which suggests that they reduced the efficacy of asparaginase. Other researchers have found higher levels of IgG1,

IgG2, and IgM antibodies in patients experiencing an allergic reaction or having decreased plasma levels of asparaginase (Müller & Boos, 1998; Table 2). Körholz et al. (1990) reported in one small study of 27 children with ALL that IgE antibodies to asparaginase were formed and contributed to clinical allergy symptoms. In these patients, even prior to the asparaginase administration, higher IgE titers were detected more frequently as compared with those children who did not have clinical reactions. In some cases allergic reactions may be thought to have a genetic predisposition. Chen et al. (2010) reported that an increase in alterations on the long arm of chromosome 5 (5q33) has shown correlation with asparaginase allergic reactions.

Hypersensitivity reactions to chemotherapeutic drugs have been documented for numerous cancer chemotherapies and the actual incidence is possibly underestimated, as

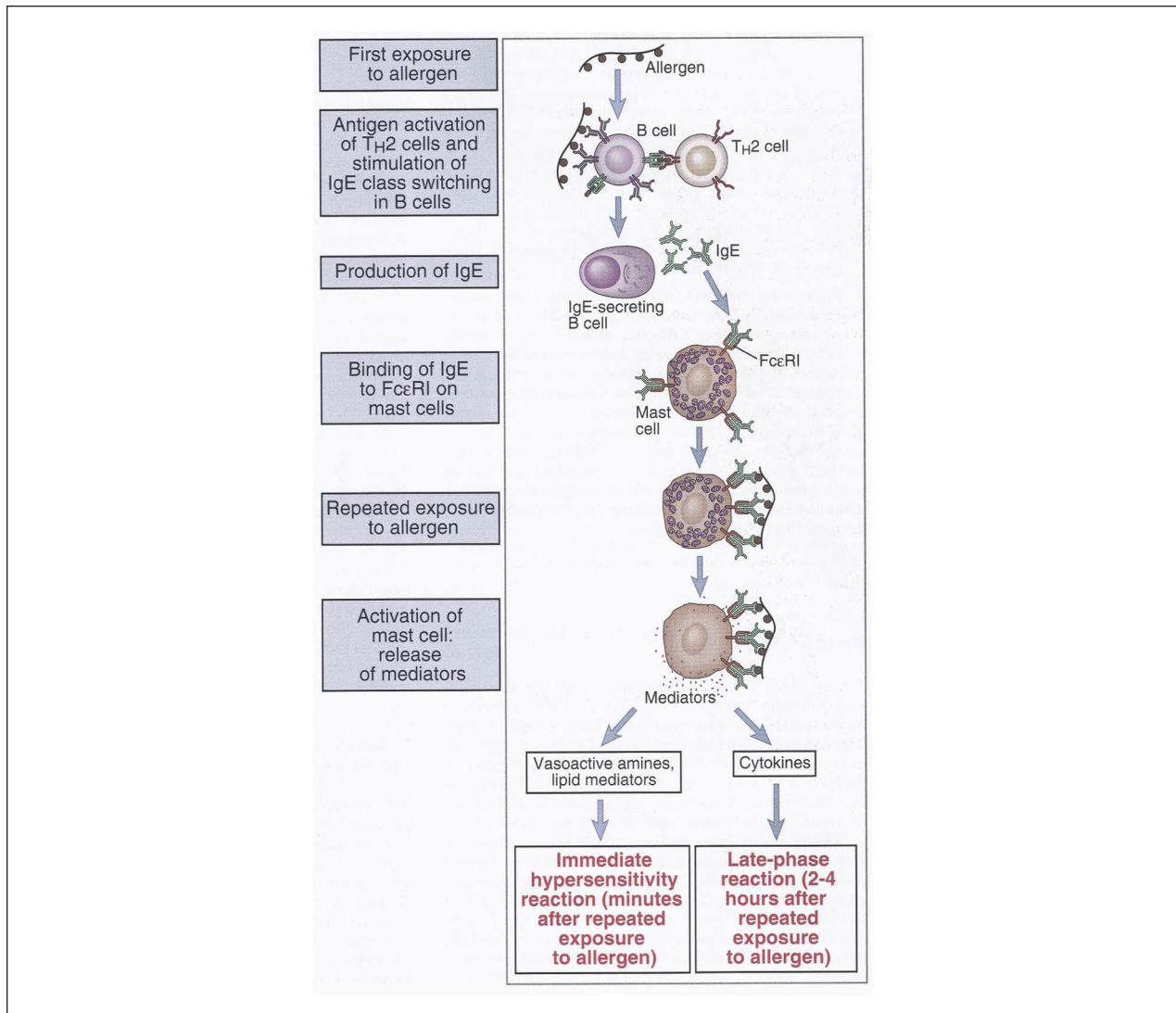


Figure 2. Sequence of events in immediate hypersensitivity reactions

SOURCE: Reprinted with permission from Abbas and Lichtman (2003).

NOTE: Most individuals who encounter an allergen do not produce antigen-specific IgE antibodies or develop harmful reactions. Genetic predisposition may lead to the development of IgE antibodies. IgE synthesis is dependent on the activation of $CD4^+$ helper T cells, subtype T_H2 , which secretes IL-4. T_H2 cells also secrete IL-5, which activates eosinophils and IL-13, which increases bronchial secretions. Individuals prone to allergies have larger amounts of IL-4 secreting T cells and more IgE antibodies in circulation than do nonallergic individuals, who are likely to produce IgM and IgG antibodies in response to allergens. T_H2 cells contribute to inflammation and have been found at the sites of immediate hypersensitivity reactions in the skin and bronchial mucosa. The allergen-specific IgE is produced by B-cells after stimulation by T_H2 cells and cytokines. The IgE antibodies are responsible for sensitizing mast cells and the recognition of an allergen in immediate hypersensitivity reactions. IgE binds to the Fc receptor specific for the epsilon heavy chain, known as $Fc\epsilon RI$, on mast cells, eosinophils, and basophils. On reexposure to the allergen, the mast cells proliferate and release mediators such as histamines, which cause vascular leak and bronchoconstriction; prostaglandin, which promotes inflammation and neutrophil chemotaxis; leukotrienes, which are associated with skin wheals and flare reactions; and cytokines, which trigger activation of other immune cells and further increase inflammation.

mild reactions will often go unreported (Pagani, 2010). Clinical hypersensitivity reactions to *E. coli* asparaginase have been reported to range from 0% to 45% (Woo et al., 2000). Allergic or hypersensitivity reactions can range from milder reactions of urticaria, fever, localized erythema, or pain at the injection site to severe symptoms, including systemic anaphylaxis (Chen et al., 2010; Graham,

2003; Müller & Boos, 1998). Allergic reaction incidence to asparaginase may be influenced by a number of factors, including different formulations of the drug, dose of the drug, prolonged asparaginase administration over multiple cycles of therapy, administration of drug after a break in cycles, and concomitant chemotherapy (Woo et al., 2000). In some cases, allergic reactions may be associated

Table 2. Classes of Immunoglobulins

Antibody Class	Subtypes	Function
IgA	IgA 1, 2	Provides mucosal immunity Resists stomach acid Found in breast milk
IgG	IgG 1-4	Fixes complement Triggers opsonization of bacteria Interacts with T-cells/NK cells Active in ADCC Crosses placenta
IgD	None	Receptor on naïve B-cells Interacts with basophils
IgE	None	Attaches to mast cells Leads to immediate hypersensitivity reactions, allergies and anaphylactic shock Defends against parasites
IgM	None	Receptor on naïve B-cells Activates complement Triggers opsonization of bacteria

SOURCE: Abbas and Lichtman (2003, pp. 41-64), Kang et al. (2009), Sompayrac (2008, p. 34).

NOTE: Ig, immunoglobulin; ADCC, antibody-dependent cellular cytotoxicity.

with an increased rate of enzyme inactivation or anti-asparaginase antibodies (Capizzi, 1993; Liu et al., 2012; Müller & Boos, 1998). Woo et al. (1998) found that anti-asparaginase antibody levels were higher in patients with hypersensitivity reactions than in those without a clinically identified allergic reaction.

Although most allergies are mild, the development of an allergy to one formulation of asparaginase could prompt a change to another formulation (Liu et al., 2012; Pagani, 2010). The three asparaginase products currently commercially available in the United States are derived from bacterial sources and each one is composed of four identical subunits, making them ideal candidates for an immune reaction (Müller & Boos, 1998). As numerous studies have demonstrated, any of the asparaginases may result in the formation of IgE antibodies in a percentage of patients (Pagani, 2010).

Reported frequency of anti-asparaginase antibodies is variable, with reports ranging from 79% in adults and up to 70% in children after the administration of native *E. coli* asparaginase (Woo et al., 2000). Anti-asparaginase antibody concentrations have been shown to increase with repeated asparaginase exposure and higher antibody levels have been reported in patients who exhibit overt allergic signs and symptoms (Woo et al., 2000; Zalewska-Szewczyk et al., 2007). These reactions frequently require discontinuation of the asparaginase product and subsequent substitution with another asparaginase preparation (Woo et al., 2000).

Differences in Preparations of Asparaginase

The 3 formulations of asparaginase, native *E. coli*, pegaspargase, and *Erwinia* asparaginase, differ in structure, drug clearance, half-life, dosing schedule, and anti-asparaginase antibody formation (Panetta et al., 2009). These factors all influence the activity of the drug.

Native *E. coli* Asparaginase (Asparaginase, Elspar, Lundbeck, Inc)

History. In the 1950s, guinea-pig serum was found to cause complete disease regression in lymphoma-bearing mice. The mechanism for the disease regression was the inhibition of asparagine incorporation into the lymphoma cell's nucleic acid metabolism, which affects RNA and DNA synthesis and ultimately leads to cell death. Subsequently, it was discovered that enzymes from different bacteria could inhibit asparagine but that the *E. coli* enzyme 2 (EC2) and *Erwinia carotovora*, later renamed *Erwinia chrysanthemi*, showed the highest asparaginase activity over the others tested (Avramis & Panosyan, 2005; Capizzi, 1993; Müller & Boos, 1998). The enzyme L-asparaginase catalyzes asparagine into aspartic acid and ammonia and thus depletes a crucial nutritional amino acid for leukemia cells. In the 1960s, a highly purified version of *E. coli* asparaginase was tested as a single agent in previously treated ALL patients and produced short remissions, resulting in a median survival of 122 days. *E. coli* asparaginase was subsequently combined with other chemotherapy agents to produce remissions in up to 98% of children with low-risk ALL (Avramis & Panosyan, 2005; Capizzi, 1993). The Food and Drug Administration approved *E. coli* asparaginase with the trade name Elspar in 1978 for use in ALL patients as part of a multiagent treatment regimen.

Dosing and half-life. *Escherichia coli* asparaginase has a half-life of 1.24 ± 0.17 days and thus must be given frequently in order to maintain the depletion of asparagine that is crucial to chemotherapeutic activity (Müller & Boos, 1998). The recommended dose is 6 000 IU/m² intramuscularly or intravenously 3 times a week (Lundbeck, Inc., 2010). In recent years, *E. coli* asparaginase has been incorporated into frontline ALL studies for pediatric patients in doses ranging from 5000 IU/m² to 25 000 IU/m² 3 times a week for multiple doses, ranging from 4 to 9 doses during induction and 30 or more doses after induction (Avramis & Tiwari, 2006; Panetta et al., 2009; Pieters et al., 2011; Woo et al., 1998).

Intravenous versus intramuscular administration. In a study by Nesbit, Chard, Evans, Karon, and Hammond (1979), 164 patients were treated with either intravenous or intramuscular native *E. coli* asparaginase.

Eighteen patients had an anaphylactoid-type reaction occurring after the intravenous administration. There was a greater incidence of major skin reactions in those receiving the intramuscular administration, although 8 of the 18 patients who had anaphylaxis with the intravenous administration also had a skin rash. The results of this investigation prompted the authors to conclude that intramuscular administration of native *E. coli* asparaginase produced less toxicity than the intravenous administration.

Reported rates of hypersensitivity reactions. Clinical hypersensitivity reactions to native *E. coli* asparaginase range from 32.5% to 75% (Lundbeck, Inc., 2010). Hypersensitivity reactions are more likely to be associated with antibodies, which in turn, increase clearance of the drug, and are more likely to occur with repeat dosing (Avramis & Tiwari, 2006; Lundbeck, Inc., 2010; Zalewska-Szewczyk et al., 2007). An increased incidence of hypersensitivity reactions and a shorter half-life have been reported with intravenous administration of native *E. coli* asparaginase as compared with intramuscular administration. Thus, less asparagine depletion, which is a surrogate marker of therapeutic benefit, may be achieved in patients experiencing a hypersensitivity reaction (Avramis & Tiwari, 2006; Lundbeck, Inc., 2010; Müller & Boos, 1998).

Pegylated *E. coli* Asparaginase (Pegaspargase, Oncaspar, Sigma-Tau Pharmaceuticals, Inc.)

History. Pegaspargase is formulated by covalently conjugating monomethoxypolyethylene glycol (PEG) to *E. coli* L-asparaginase. The mechanism of action for pegaspargase is the same as native L-asparaginase—depletion of serum asparagine. However, the addition of PEG to asparaginase confers pharmacological distinctions to the drug as compared with native *E. coli* asparaginase, namely—a longer half-life, prolonged asparagine depletion, and less immunogenicity, without changing the antineoplastic effect (Avramis et al., 2002; Masetti & Pession, 2009). An investigation performed by the Children's Cancer Group (CCG-1962) was a pivotal study to support the approval of the drug for the first-line treatment of ALL. This study showed that 3 doses of pegaspargase, administered by intramuscular injection, were able to safely and effectively replace 21 doses of native *E. coli* asparaginase. In this study, 118 newly diagnosed standard-risk ALL patients, aged 1 to 9 years, were treated with combination chemotherapy which included either native *E. coli* asparaginase or pegaspargase; differences in the incidence of "high-titer" antibody development were reported. Dinndorf, Gootenberg, Cohen, Keegan, and Pazdur (2007) summarized that

overall 11% of pegaspargase-treated patients as compared with 25% of native *E. coli*-treated patients developed anti-asparaginase antibodies at some time during the study. The Children's Oncology Group (COG) ALL trials now use pegaspargase rather than native asparaginase in their treatment protocols (Gaynon et al., 2010). Pegaspargase was given the trade name Oncaspar with the initial approval in 1994, with the indication that it be used as part of a multiagent chemotherapy regimen in ALL patients who experienced a prior hypersensitivity reaction to native *E. coli* asparaginase. Additional approval was granted in 2006, for use in both first-line treatment and for ALL patients experiencing a hypersensitivity reaction to native *E. coli* asparaginase (Sigma-Tau Pharmaceuticals, Inc., 2011).

Dosing and half-life. The recommended dose of pegaspargase is 2500 IU/m² either intravenous or intramuscular, no more frequently than every 14 days (Sigma-Tau Pharmaceuticals, Inc., 2011). Other adult and pediatric studies have used lower doses of pegaspargase with sufficient asparaginase activity (Müller & Boos, 1998; Sigma-Tau Pharmaceuticals, Inc., 2011). The half-life of pegaspargase is 5.73 ± 3.24 days in patients without a prior hypersensitivity to native *E. coli* asparaginase (Sigma-Tau Pharmaceuticals, Inc., 2011).

Reported rates of hypersensitivity reactions. Allergic reactions to pegaspargase have been reported to occur between 2%, after a single dose, and to up to 50% in patients receiving post remission consolidation therapy after having previously received native *E. coli* asparaginase (Stock et al., 2011). Because of the increased likelihood of developing an allergic reaction or neutralizing antibodies once exposed to native *E. coli* asparaginase, COG studies now incorporate pegaspargase into both induction as well as subsequent phases of therapy (Stock et al., 2011).

Intravenous versus intramuscular administration. August, Miller, Dalton, and Shinnick (2010) reported on 68 pediatric patients who received intravenous and/or intramuscular pegaspargase and found that 7 patients (10.3%) experienced a hypersensitivity reaction. In the group that received intravenous pegaspargase, 2 of 16 (12.5%) patients had a reaction. The hypersensitivity incidence in the intramuscular administration group was 3 of 27 (11.1%). Overall, 3 reactions occurred following 218 doses (1.4%) of intramuscular administration and 4 reactions occurred after 119 doses (3.4%) of intravenous administration of pegaspargase ($P = .25$). From this experience, the authors concluded that intravenous pegaspargase was well tolerated and did not appear to result in a significantly different incidence of hypersensitivity reactions as compared with the intramuscular administration.

Similar results were reported by Silverman et al. (2011) for patients treated according to the DFCI 05-01 protocol. Newly diagnosed pediatric ALL patients, age 1 to 18 years, who achieved a complete remission following induction therapy using pegaspargase, were eligible to participate in a randomized comparison of intramuscular native *E. coli* asparaginase or intravenous pegaspargase for the 30-week multiagent postinduction therapy. The authors reported no significant difference in the rate of allergy between the 2 groups—11 % allergic reactions with intravenous pegaspargase and 9% with intramuscular native *E. coli* asparaginase ($P = .44$).

Pidparti and Bostrom (2011) performed a retrospective review of 197 newly diagnosed pediatric ALL patients, treated at their institution between 2005 and 2010, who received pegaspargase and/or an investigational asparaginase product, EZN-2285. Allergic reactions were documented in 21 patients, including 17 of 186 (9%) who received intramuscular pegaspargase and 4 of 11 (36%) who received intravenous dosing ($P = .019$). The authors found that although there was an increase in the rate of allergic reactions, the severity of the reactions was not increased with intravenous dosing. They also found that allergic reactions occurred more frequently in high-risk patients, with 14 of 85 (16%) experiencing an allergic reaction compared with 7 of 112 (6%) standard-risk patients ($P = .034$).

Petersen et al. (2012) compared the incidence, time of onset of symptoms, and rates of hospitalization in 235 patients who received either intravenous and/or intramuscular pegaspargase. Allergy incidence occurred in 21 of 104 patients receiving solely intravenous pegaspargase as compared with 11 of 97 in the group receiving solely intramuscular pegaspargase ($P = .087$). For the 25 patients whose time of onset of allergic reaction was known, reactions occurred within 30 minutes of administration in 14 of 14 patients receiving the drug intravenously and in 1 of 11 patients in the intramuscular group ($P = .0001$).

***Erwinia chrysanthemi* Asparaginase (Asparaginase Erwinia, Erwinaze, Jazz Pharmaceuticals, Plc)**

History. *Erwinia chrysanthemi* asparaginase, previously termed *Erwinia carotovora*, was originally reported in 1968 by Wade, Elsworth, Herberg, Keppie, and Sargeant, and found to be antigenically and serologically distinct from the *E. coli* preparation. *Erwinia* was originally studied in 4 adult patients with ALL who previously had developed severe anaphylaxis from *E. coli* enzyme. All 4 patients tolerated the *Erwinia* therapy without incident as part of their continuation of multiagent chemotherapy for

treatment of ALL. Cortisol was given intravenously to 3 of the patients in an effort to allay anaphylaxis (Ohnuma, Holland, & Meyer, 1972).

Most recently, results of the COG AALL07P2 trial led to the approval of Erwinaze in the United States. This study was a single-arm, multicenter, open-label, safety, and clinical pharmacology trial of ALL patients who were unable to receive pegaspargase because of previous hypersensitivity reactions from asparaginase products. Fifty-eight patients received *E. chrysanthemi* asparaginase 25 000 IU/m² intramuscularly for 6 doses to replace each single dose of pegaspargase in their treatment plan. All of the 48 evaluable patients met the primary endpoint of trough asparaginase activity level of ≥ 0.1 IU/mL at 48 hours. For the higher serum trough level of asparaginase activity of ≥ 0.4 IU/mL at 42 and 72 hours, 80% and 38% met this end point (EUSA Pharma, Inc., 2011). Based on this study result, the Food and Drug Administration approved *Erwinia* asparaginase with the trade name of Erwinaze in 2011, to be used as a component of a multiagent chemotherapy regimen for the treatment of patients with ALL who have developed hypersensitivity to *E. coli*-derived asparaginase.

Dosing and half-life. *Erwinia* asparaginase has a much shorter biological half-life of asparaginase activity (0.65 days $\pm$ 0.13) than either native *E. coli* or pegaspargase (Asselin et al., 1993). To substitute for a single dose of pegaspargase the recommended dose of *Erwinia* asparaginase is 25 000 IU/m² administered intramuscularly 3 times a week (Monday/Wednesday/Friday) for 6 doses for each planned dose of pegaspargase. To substitute for native *E. coli* asparaginase the recommended dose is 25 000 IU/m² administered intramuscularly for each scheduled dose of native *E. coli* asparaginase within a treatment plan (EUSA Pharma, Inc., 2011).

Reported rates of hypersensitivity. Patients who develop an allergy to an asparaginase product are often switched to an alternative product. Second-line asparaginase treatment should be dictated by the protocol on which the patient is enrolled. *Erwinia* asparaginase is commonly used for second-line treatment in current pediatric cooperative group protocols in the United States.

Serious hypersensitivity reactions, including anaphylaxis have occurred after the use of *Erwinia* asparaginase in 9% of patients on the AALL07P2 trial (EUSA Pharma, Inc, 2011). Vrooman et al. (2010) enrolled 215 patients on a clinical trial to evaluate 30 weekly intramuscular doses of native *E. coli* asparaginase during consolidation therapy in newly diagnosed pediatric patients with ALL. If a clinical allergy developed, patients were switched to twice weekly intramuscular *Erwinia* asparaginase. Forty-two patients on the trial required a switch to *Erwinia* asparaginase and a subsequent allergy developed in 14 (33%)

patients at a median of 9 weeks following the change in formulation. Woo et al. (1998) reported on 154 newly diagnosed ALL patients treated on the St Jude Children's Research Hospital (SJCRH) study, Total XIII-HR. Patients were initially prescribed native *E. coli* asparaginase and were switched to *Erwinia* asparaginase if they developed clinical allergy. Fourteen percent of patients who reacted to native *E. coli* asparaginase eventually reacted to *Erwinia* asparaginase. On DFCI Protocol 95-01, 286 patients were randomized to receive either native *E. coli* or *Erwinia* asparaginase intramuscularly for 20 weeks during postinduction consolidation. Weekly *Erwinia* asparaginase was associated not only with a lower incidence of asparaginase associated allergy (6% vs 14 %; $P = .03$) but also with inferior EFS compared with weekly *E. coli* asparaginase ($78\% \pm 4\%$ vs $89\% \pm 3\%$, $P = .02$); (Moghrabi et al., 2007).

Management and Supportive Care of Hypersensitivity Reactions (Table 4)

The COG and two major centers, Dana-Farber Cancer Institute and SJCRH, have incorporated some form of asparaginase into pediatric protocols for years and have developed specific guidelines for managing toxicity associated with the asparaginase products. Below are excerpts from their current protocols, which include pegaspargase as part of a multichemotherapy regimen for treating pediatric ALL patients.

The Children's Oncology Group

Today COG protocols advise that since pegaspargase is long acting, hypersensitivity reactions may not appear until hours following administration. Clinicians should monitor vital signs as well as for signs of fever, chills or acute allergic reactions including anaphylaxis. Nurses should have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, corticosteroids, and antihistamines). Patients should be observed for one hour after administration of the drug for signs of hypersensitivity reactions. Parents and patients should be educated to observe for reactions at home post administration. Although rare, hypersensitivity reactions have been reported hours after drug administration.

Dose modifications recommended by COG include discontinuing pegaspargase if the patient

develops a systemic allergic reaction which is Grade 2 or greater as defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Table III). Premedication with antihistamines to decrease the risk of overt allergy symptoms is strongly discouraged since antihistamine use may mask the appearance of systemic allergy. Systemic allergy may be associated with the presence of asparaginase neutralizing antibodies, which renders asparaginase therapy ineffective.

Current COG trials have adopted pegaspargase as the asparagine-depleting preparation of choice based on the results of CCG 1962 (Avramis & Panosyan, 2005). If a patient develops an allergic reaction to pegaspargase, COG trials recommend substitution with *Erwinia* asparaginase. (Hunger & COG Pharmacy Committee, 2010).

Dana-Farber Cancer Institute

The DFCI currently defines mild reactions as a local reaction with erythema and/or pain at the injection site. Severe reactions are defined as any other allergic reaction, including rash, urticaria, lip/tongue swelling, respiratory symptoms, and hypotension. For either mild or severe hypersensitivity reactions, a switch in preparation should occur as follows: If initial asparaginase is *E. coli* given intramuscularly, switch to intramuscular pegaspargase. If a subsequent allergic reaction develops after an initial switch to pegaspargase, the patient should receive twice-weekly *Erwinia* intramuscularly. If initial asparaginase is pegaspargase, switch to twice-weekly *Erwinia* intramuscularly. If *Erwinia* is unavailable, asparaginase therapy should be discontinued. (Silverman et al., 2006)

St. Jude Children's Research Hospital

Currently patients with allergic reactions to pegaspargase subsequently will be given *Erwinia* intramuscularly at the SJCRH. Anaphylactic reactions can be characterized by laryngeal constriction, hypotension, diaphoresis, fever, chills, edema and loss of consciousness. Allergic reactions at the site of the intramuscular injections include pain, swelling, and erythema. The incidence of hypersensitivity reactions to pegaspargase may be less than with conventional *E. coli* derived asparaginase although cross sensitivity can occur. (Jeha et al., 2007)

Relationship Between Allergy, Antibodies, and Asparaginase Activity

Though many current practices assume a direct relationship between allergy, antibodies, and decrease in asparaginase activity, the picture is not nearly so clear when one reviews additional and recent published data on asparaginase hypersensitivity and antibodies. Avramis and Tiwari (2006) have reported that the risk of allergic reaction is reduced when a steroid and other immunosuppressive agents are administered concurrently with the asparaginase product. Asselin (2012) also theorized that pretreatment with glucocorticoids is expected to decrease the likelihood of developing anti-asparaginase antibodies and that “continuous” rather than “pulse” dosing of asparaginase may be less immunogenic. The rationale for preconditioning with a steroid and immunosuppression is to deplete helper-T-cells and subsequently decrease immune responsiveness to future asparaginase administrations. Avramis and Tiwari (2006) have noted that clinical allergic reactions may occur when the levels of circulating IgG antibodies, which are responsible for slight to moderate allergic reactions, become elevated after several doses of asparaginase. For this reason, they note the benefit of preconditioning to reduce an immune reaction. In an earlier publication, Avramis et al. (2002) noted that patients treated on the CCG 1962 study had received 3 days of high-dose prednisone prior to the asparaginase administration, either native or pegylated, and only 2 of 118 experienced an allergic reaction during their second exposure. In this study, patients treated with pegaspargase had more prolonged asparaginase activity compared with those patients treated with native asparaginase. Also, high-titer antibodies to asparaginase, which negated the activity of the drug, were associated with native asparaginase (26%) but not with pegaspargase (2%) during the first delayed intensification phase of treatment.

Strullu et al. (2010), prospectively evaluated the incidence of silent hypersensitivity (the phenomenon of antibody production in the absence of clinical allergy) to native *E. coli* asparaginase in 33 pediatric patients with newly diagnosed ALL. Patients were treated according to the FRALLE 2000 protocol (French chemotherapy protocol consisting of drugs for the treatment of ALL) and divided into two groups for this study—18 patients diagnosed with lower-risk B-cell ALL were part of the “A group” and 15 patients diagnosed with higher-risk B-cell and T-cell ALL were in the “B-T group.” Patients in the “A group” received less intensive chemotherapy overall, less prednisone therapy compared with dexamethasone, and higher doses of asparaginase at less frequent intervals

during the second intensification compared with the “B-T group.” A significant increase in clinical allergic reactions was noted in the “A group” as compared with the “B-T group,” 72% versus 13%, respectively. Silent hypersensitivity was observed in 18% of the study population, the majority of which occurred in the “B-T group” ($P = .07$). However, no significant differences between asparaginase activity or asparagine depletion between the silent hypersensitivity and clinical allergy groups were observed. Additionally, at a median follow-up time of 5 years, no difference in outcome between the silent hypersensitivity and clinical allergy groups had been detected. The authors note that the probability of an allergic reaction was increased in those patients who did not receive concurrent prednisone-vincristine and who had a longer period of time between asparaginase doses. They further suggest immunosuppression with concomitant chemotherapy and corticosteroid therapy may have prevented either the development of or lowered the anti-asparaginase antibodies. Thus, by maintaining low-antibody titers, which are insufficient to initiate an allergic reaction, silent hypersensitivity antibodies may be present, but they did not affect the activity of the asparaginase.

Other studies have indicated that allergic reactions are associated with the development of antibodies which increase asparaginase clearance and may neutralize asparaginase activity (Avramis et al., 2002; Panosyan et al., 2004). Willer et al. (2011) noted that although hypersensitivity reactions may limit the ability to administer asparaginase products, it is only when anti-asparaginase antibody levels become high, >200 AU/mL, that the drug activity level is diminished. In this case, they state that *Erwinia* asparaginase may be an appropriate alternative to *E. coli* asparaginase. As part of a retrospective review of 1221 samples from 329 patients treated on the ALL-BFM (Berlin Frankfurt Munster group) 2000 and ALL-REZ (Germany, Austria, Switzerland group) BFM 2002 trials, Willer et al. assessed anti-asparaginase antibody levels and drug activity levels for patients treated with native *E. coli* ($n = 403$), pegylated ($n = 453$), and *Erwinia* asparaginase ($n = 365$). The samples from patients who received pegaspargase or *Erwinia* asparaginase were taken after they had an allergic reaction to native *E. coli* asparaginase. In this review, they found that in 81 of 99 patients (82%) who received only native *E. coli* asparaginase, clinically overt allergic reactions were associated with anti-asparaginase antibodies. Anti-asparaginase antibodies continued to increase in patient samples when switched to either pegaspargase or *Erwinia* asparaginase. Sufficient asparaginase activity, >100 U/L, was detected in 65.1% of pegaspargase samples, measured 14 days after administration, and in 55.1% of *Erwinia* asparaginase samples, measured 2 days after administration. For

patients with anti-asparaginase antibodies being treated with native asparaginase, a switch to pegaspargase increased the rate of samples with sufficient and borderline asparaginase activity, unless the antibody level was >200 AU/mL. In this case, asparaginase activity was determined to be insufficient during the first and second weeks after administration of pegaspargase. For samples from patients switched to *Erwinia* asparaginase, no significant association between drug activity level and anti-asparaginase antibody level was found. In this review, the authors found that for patient samples with serum asparaginase activity levels >100 U/L (considered sufficient for asparagine depletion from both serum and cerebral spinal fluid) and with intermediately positive antibody levels (20-200 AU/mL), patients treated with pegaspargase had higher drug activity levels, 75%, as compared with those samples from patients treated with *Erwinia* asparaginase, whose drug activity levels were 55%. The authors stress that when symptoms of clinical allergy are mild, antibody levels should be measured prior to changing to another asparaginase product.

In an adult cooperative group study reported by Wetzler et al. (2007; Cancer and Leukemia Group B 9511), the differences in disease-free survival (DFS) and overall survival (OS) were compared for 85 newly diagnosed ALL patients based on asparagine depletion levels, defined as asparaginase activity levels of >0.03 U/mL. Asparaginase levels were collected at multiple time points. The authors suggest that based on univariate analysis, the 22 patients who did not achieve asparagine depletion at some time point had inferior OS and DFS. More anti-asparaginase antibodies were detected in patients who did not achieve asparagine depletion as compared with patients who did, 7 of 22 (31.8%) versus 6 of 63 (9.5%), respectively ($P = .012$). Although anti-asparaginase antibodies were more prevalent in patients who did not achieve asparagine depletion, using multiple predictive models, the authors noted that they could conclude no meaningful association between antibodies and outcome. From this, the authors stated that even though patients eventually developed antibodies to asparaginase, which presumably may have had a neutralizing effect on the asparaginase, no decrease in antileukemic effect was noted. They did find that increasing age was associated with fewer pegaspargase doses being administered.

Discussion/Conclusion

Significant progress has been made during the past 50 years in the treatment of pediatric and adolescent patients with ALL. During this time asparaginase therapy has been a cornerstone in multimodal chemotherapy regimens used to achieve current cure rates nearing 90%. Much has been learned about the three commercially

available asparaginase products in the United States as a result of extensive study in investigational protocols and during the evolution of ALL regimens. However, despite how much we currently know about asparaginase agents, questions persist about their optimal use within ALL regimens and precise adverse event profile with corresponding management.

It is becoming more evident that asparagine depletion directly correlates with outcome in both pediatric and adult patients. In vitro response versus nonresponse rates to asparaginase in pediatric ALL patients have been correlated with relapse rates—5% versus 57%, respectively ($P = .0008$; Asselin et al., 1999). Silverman et al. (2001) demonstrated improved survival in pediatric patients receiving at least 26 of 30 weeks of planned therapy compared with patients receiving 25 or fewer weeks. Analogous results were reported by Wetzler et al. (2007) in adult patients. This group looked at outcomes relative to asparagine depletion. Superior DFS and OS were realized in patients achieving adequate asparagine depletion (as defined as an asparaginase level >0.03 U/mL) compared with those patients failing to achieve the minimum threshold of depletion. Although specific serum thresholds for asparagine and asparaginase concentrations as well as length of time for asparagine depletion remain unknown, asparagine depletion in ALL patients affects patient outcomes.

Data are less well elucidated with asparaginase therapy as it relates to allergy, anti-asparaginase antibody production, and outcome. As part of the CCG 1961 study, anti-asparaginase antibodies and asparaginase enzymatic activity were investigated in 1001 patients receiving either intramuscular native *E. coli* asparaginase or pegaspargase. Serum samples were assayed for determination of asparaginase antibody titers and enzymatic activity. Six hundred and eleven patients (61%) had a positive antibody titer (defined as $>110\%$ over negative control). Among these 611 patients, 447 had no measurable asparaginase activity during therapy. In a small subset of patients ($n = 280$) evaluated for outcome relative to the presence of antibodies, 29% of patients experienced silent hypersensitivity and represented 25% of patients relapsing after therapy. Thus, antibody measurement could be a surrogate marker for poor outcome of the disease. The authors concluded that anti-asparaginase antibody was associated with undetectable asparaginase activity and may be correlated with adverse outcomes in high-risk ALL (Panosyan et al., 2004).

In contrast to the above findings, research by other groups has failed to correlate anti-asparaginase antibody production to outcome. Strullu et al. (2010) observed both clinical allergy and silent hypersensitivity in pediatric patients with newly diagnosed ALL treated with

intramuscular or intravenous native *E. coli* asparaginase. There were no reported differences in asparaginase activity, asparagine depletion, and outcomes in patients regardless of allergy type. Wetzler et al. (2007) could not correlate outcomes with antibody production despite observing a higher prevalence of antibody production in patients failing to achieve adequate asparagine depletion.

Prevention of allergies with prophylactic use of corticosteroids, antihistamines, and/or acetaminophen remains controversial. Most pediatric patients do not receive routine prophylactic medications so as not to potentially mask an allergic reaction. However, this practice of avoiding an antihistamine or steroid preparation may expose patients to a risk of hypersensitivity reactions and possibly anaphylaxis. Use of prophylactic medications is more common in adult patients. Specifically, in the adult cooperative group study, CALGB (Cancer and Leukemia Group B) 10403, one researcher has indicated that she has observed that “corticosteroid premedication has reduced the rate of toxicity allowing more patients to complete their asparaginase courses” (W. Stock, personal communication, July 29, 2012).

Finally, the importance of careful monitoring and meticulous documentation of hypersensitivity reactions is vital to our continued understanding and characterization of asparaginase hypersensitivity reactions. Allergic reactions to asparaginase products are diverse, ranging from grade 1 to grade 4 reactions (Table 3) and often not well documented in the patients’ medical records. However, patients are often considered “allergic” to asparaginase therapy, regardless of the severity of the reaction. Since studies suggest that stopping therapy with asparaginase or delivering less than 80% of the planned asparaginase dose might lead to decreased EFS (Silverman et al., 2001), it would seem wise to confirm any allergic reactions prior to discontinuing the drug. Tools exist to aid clinicians in classifying the severity of reactions (Table 3) and management strategies, often dictated by research protocol or institutional guidelines, are available to ameliorate adverse events (Table 4; Stock et al., 2011). Complete description of reactions, including grade of reaction, route of administration, time to onset, and concomitant medications before and during an event, will not only guide future asparaginase therapy but will also assist clinicians in gaining a better understanding of asparaginase hypersensitivity reactions. To ensure the capture of such information, the nurse should perform and document the allergy assessment at time of the reaction.

Future directions in the area of hypersensitivity reactions associated with asparaginase products are exciting. With the recent commercial availability of *Erwinia* asparaginase, characterization of hypersensitivity reactions with this product will undoubtedly be increased and comparisons with native *E. coli* asparaginase and pegaspargase will be easier to

Table 3. Grading of Allergic Reaction/Hypersensitivity

Version 3 Allergic Reaction/Hypersensitivity	Version 4.03 Allergic Reaction
Grade 1	
Transient flushing or rash	Transient flushing or rash
Drug fever <38°C or <100.4°F	Drug fever <38°C or <100.4°F Intervention not indicated
Grade 2	
Rash, flushing	Intervention or infusion interruption indicated
Urticaria	Responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics)
Dyspnea	Prophylactic medications indicated for ≤24 hours
Drug fever ≥38°C (≥100.4°F)	
Grade 3	
Symptomatic bronchospasm with or without urticaria	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion)
Parenteral medication or medications indicated	Recurrence of symptoms following initial improvement
Allergy-related edema/angioedema	Hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)
Hypotension	
Grade 4	
Anaphylaxis	Life-threatening consequences Urgent intervention indicated
Grade 5	
Death	Death

SOURCE: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Cancer Therapy Evaluation Program (2006, 2010).

ascertain. Questions remain about the relationship of antibody production and clinical outcomes in patients exhibiting silent hypersensitivity reactions. Monitoring patients throughout therapy for antibody production and making therapeutic decisions on which asparaginase product to subsequently administer, if any, remains investigational. Prophylactic use of corticosteroids, antihistamines, and/or acetaminophen requires further evaluation, particularly, in relation to the ability to deliver planned asparaginase therapy. By working to address these and other facets of asparaginase hypersensitivity reactions, we will have a greater understanding of how to optimize asparaginase therapy in ALL patients and ultimately improve outcomes.

Table 4. Comparison of Three Major Pediatric Cooperative Groups' Definition and Management of Hypersensitivity Reactions Related to Asparaginase Products^a

	COG ^b	DFCI ^c	SJCRH ^d
Define hypersensitivity	Use CTCAE Version 4.0	Mild reactions are defined as local reaction: erythema and/or pain at injection site. Severe reactions are defined as any other allergic reaction, including rash, urticaria, lip/tongue swelling, respiratory symptoms, and hypotension	Laryngeal constriction, hypotension, diaphoresis, fever, chills, edema, and loss of consciousness. Allergic reactions at the site of the intramuscular injections include pain, swelling, and erythema
Change/stop preparation	Discontinue pegaspargase and substitute with <i>Erwinia</i> asparaginase if the patient develops a systemic allergic reaction which is grade 2 or greater as defined by the CTCAE Version 4.0 Substitution with <i>Erwinia</i> asparaginase is dose at 25 000 IU/m ² /dose intramuscularly M/W/F [Monday/Wednesday/Friday] × 6 doses for each dose of pegaspargase If a patient develops a grade 2 or greater allergy to <i>Erwinia</i> asparaginase, discontinue future asparaginase therapy	For either mild or severe hypersensitivity switch preparation as follows: If initial asparaginase is intramuscular <i>E. Coli</i> , switch to intramuscular pegaspargase. If a subsequent allergic reaction develops after switching to pegaspargase, patient should receive twice-weekly <i>Erwinia</i> intramuscularly. If initial asparaginase is pegaspargase, switch to twice-weekly intramuscular <i>Erwinia</i> . If <i>Erwinia</i> is unavailable, asparaginase should be discontinued	Patients with allergic reactions to pegaspargase subsequently will be given <i>Erwinia</i> intramuscularly

NOTE: COG, Children's Oncology Group; DFCI, Dana-Farber Cancer Institute ALL Consortium SJCRH, St Jude Children's Research Hospital; CTCAE, common terminology criteria for adverse events.

a. The Prescribing Information for native *E. coli* asparaginase, pegaspargase and *Erwinia* asparaginase advise for "anaphylaxis and serious allergic reactions" that the patient be observed for 1 hour after the drug administration, in a setting with available resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine, oxygen, intravenous steroids, antihistamines). The drug should also be discontinued in patients with serious allergic reactions.

b. Hunger and COG Pharmacy Committee (2010).

c. Silverman et al. (2006).

d. Jeha et al. (2007).

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