

Allergic Reactions to *Erwinia* Asparaginase in Children With Acute Lymphoblastic Leukemia Who Had Previous Allergic Reactions to *Escherichia coli* Asparaginase

Amy Louise Billett, M.D.,*†‡ Alexa Carls, M.D.,* Richard D. Gelber, Ph.D., §||
and Stephen E. Sallan, M.D.*†‡

Background. *Escherichia coli* asparaginase is an active antileukemia agent in the treatment of childhood acute lymphoblastic leukemia. Allergic reactions occurred in 31 of 125 patients (24.8%) treated with weekly high-dose (25,000 IU/m²) intramuscular *E. coli* asparaginase and necessitated discontinuation of the drug.

Methods. The authors evaluated the toxic effects of *Erwinia* asparaginase in the 31 children who had allergic reactions to the *E. coli* preparation.

Results. Subsequent allergic reactions to *Erwinia* asparaginase occurred in 7 of the 31 children (22.6%). In contrast to previous reports with intravenous administration, most allergic reactions to both asparaginase preparations were characterized by mild urticaria that responded to use of diphenhydramine; none of the reactions was life-threatening.

Conclusions. In summary, the authors found *Erwinia* asparaginase to be an acceptable substitute for *E. coli* asparaginase for most children who had allergic reactions. Through the use of both *E. coli* and *Erwinia* asparaginase, 94% of children could receive their intended asparaginase. *Cancer* 1992; 70:201-206.

Key words: childhood acute lymphoblastic leukemia, asparaginase, allergic reaction, toxic effects.

From the Departments of *Pediatric Oncology and §Biostatistics, Dana-Farber Cancer Institute, Boston; the †Division of Hematology/Oncology, Children's Hospital, Boston; the ‡Department of Pediatrics, Harvard Medical School, Boston; and the ||Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts.

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Address for reprints: Amy Louise Billett, M.D., Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115.

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Since the antitumor effect of guinea pig serum first was demonstrated in 1953¹ and subsequently shown to result from the enzyme asparaginase,² the clinical use of asparaginase in the treatment of leukemia has increased. A number of studies have shown this agent to be effective in the treatment of acute lymphoblastic leukemia (ALL), either as a single agent or as part of multiple-agent chemotherapy.³⁻⁸

Although asparaginase causes minimal myelosuppression, it is associated with multiple toxic effects, which include hepatic dysfunction, coagulopathy, hyperglycemia, pancreatitis, hypocholesterolemia, central nervous system abnormalities, nausea, vomiting, and anorexia and hypersensitivity reactions.⁹⁻¹¹ Severe hypersensitivity, particularly after intravenous administration of this drug, has limited use of the enzyme.^{4,5,12}

Intramuscular administration of asparaginase, which affects neither the efficacy nor the occurrence of nonallergic toxic effects, has become the standard of practice because it results in fewer allergic reactions than intravenous administration.¹³ Unfortunately, 6-18% of children who receive asparaginase intramuscularly will have allergic reactions.^{6,13}

Clinically active asparaginases have been derived from *Escherichia coli* and *Erwinia carotovora* (also known as *Erwinia chrysanthemi*).^{14,15} *E. coli* asparaginase is commercially available in the United States, and *Erwinia* asparaginase in Canada and the United Kingdom. In the United States, the clinical use of *Erwinia* asparaginase has been limited to patients who were allergic to the *E. coli* preparation. Previous studies found the *Erwinia* preparation to have comparable efficacy and no cross-reactivity with *E. coli* asparaginase.^{16,17}

Because asparaginase is an effective antileukemic drug, the use of the alternative *Erwinia* preparation in patients who are allergic to the *E. coli* preparation is

important. The incidence of allergic reactions to intravenous *Erwinia* asparaginase after a previous reaction to *E. coli* asparaginase has been reported.^{12,16-19} We evaluated the incidence and severity of allergic reactions to intramuscular *Erwinia* asparaginase in children with ALL who had previous allergic reactions to intramuscular *E. coli* asparaginase.

Materials and Methods

One hundred thirty-five children with newly diagnosed ALL in whom the ALL was diagnosed and treated at the Dana-Farber Cancer Institute as part of multicenter protocol 81-01⁸ were included in this retrospective analysis of asparaginase toxicity. Children with ALL were assigned prospectively to receive one of two treatment programs on the basis of their risk of relapse. The criteria for risk-group classification have been described previously.⁸ Patients in the standard-risk and high-risk groups were treated with intensive remission-induction therapy, central nervous system treatment, weekly administration of high-dose asparaginase, and multiple-drug continuation therapy, which, in the high-risk group, included doxorubicin and higher doses of prednisone.⁸

The asparaginase dosage schedule for the standard-risk children was 25,000 IU/m² (825 IU/kg) intramuscularly once weekly during weeks 5-24, for a total of 20 consecutive doses. High-risk patients received the same dose of asparaginase starting at week 5, but asparaginase treatment then was continued weekly until patients had received doxorubicin (30 mg/m² every 3 weeks) to a cumulative dose of 345 mg/m² (11.5 mg/kg). The usual duration of weekly asparaginase treatment in the high-risk group was 9-11 months. When an allergic reaction attributable to the administration of *E. coli* asparaginase occurred, the *Erwinia* asparaginase preparation was substituted routinely. For other adverse reactions, *Erwinia* asparaginase was substituted or asparaginase therapy was stopped.

The number of doses of *E. coli* and/or *Erwinia* asparaginase was determined for all 135 patients. All patients who had adverse reactions to intramuscular *E. coli* asparaginase and subsequently were treated with intramuscular *Erwinia* asparaginase were specified. Data were collected retrospectively to assess the date of the final administration of *E. coli* asparaginase that precipitated the adverse reaction, the character of that reaction, the therapy initiated for that response, the number of doses of asparaginase to that date, the number of subsequent doses of *Erwinia* asparaginase, the date and character of any subsequent adverse response to the *Erwinia* preparation, the therapy initiated for that re-

sponse, and whether the second allergic reaction necessitated cessation of asparaginase chemotherapy.

An allergic response was considered to have occurred if any of the following signs or symptoms were observed that were temporally associated with the administration of asparaginase: urticaria, rash, swelling, erythema, tenderness, tachypnea, shortness of breath, or wheezing. A local response was defined by the presence of pain, pruritus, tenderness, erythema, rash, urticaria, or swelling at the site of injection. A systemic response was defined as any of the above signs and symptoms occurring at a site away from the asparaginase injection site or any respiratory or cardiovascular symptom. Thus, a patient could have a local, local and systemic, or systemic reaction. Therapeutic interventions prompted by these reactions also were recorded to assess the morbidity of the allergic reaction. The interventions included observation only; use of diphenhydramine, epinephrine, or steroids; and hospitalization.

Commercially available *E. coli* asparaginase was reconstituted in 0.9% sodium chloride according to the instructions of the manufacturer and administered intramuscularly in doses less than 50,000 IU (2 ml) at each site. *Erwinia* asparaginase (NSC #106977) was obtained from the National Cancer Institute and reconstituted and administered as above.

Statistical Methods

Comparisons between patient groups were performed with Fisher's exact test for discrete variables and the Wilcoxon rank-sum test for continuous variables. Curves for time to asparaginase reaction were estimated with the Kaplan-Meier method.

Results

Patient Population and Characteristics

One hundred thirty-five patient records were reviewed. Ten patients were excluded from the analysis: 2 patients with inadequate data regarding asparaginase dosing, 4 who died or were removed from protocol before asparaginase was administered (3 patients died, 1 was removed from protocol), 3 whose therapy was changed after less than four doses of asparaginase because of persistent leukemia, and 1 whose asparaginase treatment was stopped after two doses because of pancreatitis. Thus, 125 patients received at least three doses of asparaginase and were considered at risk for an allergic reaction. A minimum of three doses was chosen because no allergic reactions were seen before administration of the third dose. The median number of aspara-

Table 1. Comparison of Patient Characteristics According to Occurrence of an Allergic Reaction to *Escherichia coli* Asparaginase

Characteristic	<i>Escherichia coli</i> asparaginase allergy	No <i>Escherichia coli</i> asparaginase allergy	P value
No. of patients	31	94	
Sex			
Male	16	55	0.54
Female	15	39	
Risk group			
Standard	15	31	0.14
High	16	63	
Median age (yr)	5.0	5.0	0.37
Range	1.2–18.0	0.4–18.0	
Median leukocyte count ($\times 10^3/\mu\text{l}$)	10.3	12.1	0.37
Range	0.7–536	0.7–670	

ginase doses administered was 20 (range, 3–24) for standard-risk patients and 28 (range, 3–45) for high-risk patients. For 36 patients, treatment was switched from *E. coli* to *Erwinia* asparaginase. Five patients had pancreatitis, a nonallergic reaction, and were excluded from additional analysis.

Thus, 31 of 125 patients (24.8%) had allergic reactions attributable to *E. coli* asparaginase. Of the 31 children, 16 were male. The median age at the time of diagnosis was 5.0 years (range, 1.2–18.0 years), and the median leukocyte count was $10.3 \times 10^3/\mu\text{l}$ (range, 0.7–536 $\times 10^3/\mu\text{l}$). Fifteen were in the standard-risk group and 16 in the high-risk group. These characteristics were similar to those of the 94 assessable patients who did not have allergic reactions (Table 1). Fifteen of 46 patients (32.6%) in the standard-risk group had *E. coli* asparaginase reactions, compared with 16 of 79 patients (20.3%) in the high-risk group, a difference that was not statistically significant.

Reactions to *E. coli* Asparaginase

Although 25 patients reacted to *E. coli* asparaginase within the first 11 doses, reactions occurred as late as the 28th dose (Fig. 1). The reactions were local only in 5 patients, local and systemic in 3, and systemic only in 22. Details of the allergic reaction could not be determined for one patient who reacted to a dose of asparaginase administered at another institution. Most patients had more than one sign or symptom at the time of their reaction. Local manifestations at the injection site included erythema (7 cases), swelling (4 cases), urticaria (1 case), rash (3 cases), and pruritus (1 case). Systemic manifestations included urticaria (19 cases), pruritus (3 cases), rash (3 cases), tachypnea (2 cases), wheezing (2

cases), tachycardia (1 case) and shortness of breath (1 case).

Therapeutic interventions consisted of observation only (6 cases), diphenhydramine administration (24 cases), use of hydrocortisone (5 cases), and epinephrine administration (4 cases). Three patients were admitted to the hospital for management of bronchospasm. Two other patients were admitted with the diagnosis of cellulitis, which was excluded subsequently; their symptoms were attributed to an asparaginase reaction.

Reactions to *Erwinia* Asparaginase

Of the 31 patients with allergic reactions attributable to *E. coli* asparaginase who were treated subsequently with *Erwinia* asparaginase, 7 (22.6%) had allergic reactions to the latter. Thus, 118 patients (94%) could tolerate at least one form of asparaginase without an allergic

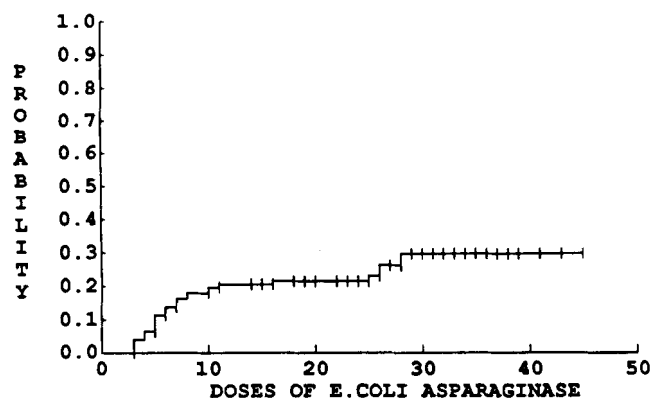


Figure 1. Risk of reaction to *Escherichia coli* asparaginase among the 125 patients at risk. Tick marks denote patients who did not have a reaction to *E. coli* asparaginase.

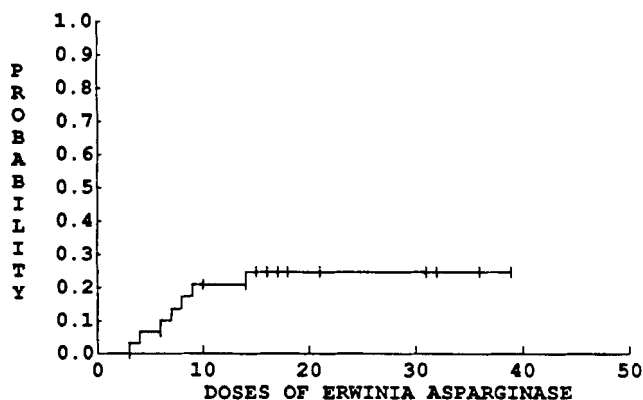


Figure 2. Risk of reaction to *Erwinia* asparaginase among the 31 patients at risk. Risk period began with the first dose of *Erwinia* asparaginase. Tick marks denote patients who did not have a reaction to *Erwinia* asparaginase.

reaction. The timing of the allergic reactions to *Erwinia* is shown in Figure 2. Three patients who had allergic reactions to *E. coli* asparaginase after more than 15 doses reacted to the *Erwinia* preparation after fewer than 10 doses (3, 4, and 9 doses). In contrast, three patients who reacted to *E. coli* asparaginase within the first 5 doses tolerated 6–14 doses of *Erwinia* before a subsequent reaction.

Two patients had limited local reactions, and five had systemic reactions without local manifestations. Local manifestations of the allergic reactions included urticaria in both patients and erythema and swelling in one. Systemic signs and symptoms consisted of urticaria (five cases), tachypnea (two cases), wheezing (two cases), shortness of breath (one case), pruritus (one case), and tachycardia (one case). Therapeutic interventions included observation only (two cases) and administration of diphenhydramine (five cases), steroids (two cases), or epinephrine (one case). No patient required hospitalization. In six of the seven patients, asparagin-

ase treatment was stopped before scheduled completion of therapy, and one patient reacted to the final dose of asparaginase and required no additional therapy.

Patients who had an *Erwinia* allergic reaction ($n = 7$) tended to be younger and have a higher initial leukocyte count compared with those who did not ($n = 24$) (Table 2). Male patients also tended to be more susceptible than female patients. With only seven reactions to *Erwinia*, however, these differences were not statistically significant. No factors, including *E. coli* reaction characteristics, were useful in predicting the probability, timing, or severity of a subsequent *Erwinia* reaction.

Discussion

The incidence of allergic reactions to intramuscular *E. coli* asparaginase was 24.8% (31 of 125 patients). Seven of the 31 patients who had allergic reactions to the *E. coli* preparation subsequently had allergic reactions to *Erwinia* asparaginase (22.6%). No life-threatening reactions occurred with either form of asparaginase. The most common manifestation of an allergic reaction to either preparation was urticaria, which responded to diphenhydramine therapy. We could not identify any patient, disease, or treatment characteristics that were predictive of an allergic reaction to either form of asparaginase. The timing of reactions to *E. coli* and *Erwinia* asparaginase was similar, with most reactions occurring within the first 11 doses of either preparation (Figs. 1 and 2). The timing of an allergic reaction to *E. coli* asparaginase did not indicate whether or when an *Erwinia* asparaginase reaction would occur. Three patients reacted to *E. coli* asparaginase after more than 15 doses but were able to tolerate only a few doses of *Erwinia* asparaginase. In contrast, three patients who reacted to the 3rd or 5th dose of *E. coli* asparaginase

Table 2. Comparison of Patient Characteristics According to Occurrence of an Allergic Reaction to *Erwinia* Asparaginase

Characteristic	<i>Erwinia</i> allergy	No <i>Erwinia</i> allergy	P value
No. of patients	7	24	
Sex			
Male	5	11	0.39
Female	2	13	
Risk group			
Standard	4	11	0.69
High	3	13	
Median age (yr)	3.1	5.5	0.18
Range	1.2–18.0	2.3–14.0	
Median leukocyte count ($\times 10^3/\mu\text{l}$)	18.9	9.85	0.16
Range	4.9–536.0	0.7–214.9	

tolerated 6–14 subsequent doses of *Erwinia* asparaginase.

It was difficult to compare the incidence of asparaginase allergic reactions in this patient group with those reported in the literature because most previous reports described patients who received intravenous asparaginase. The incidence of allergic reactions to *E. coli* asparaginase with intravenous administration ranges from 15% to 33%.^{3,19,20} Of 19 patients receiving intravenous *Erwinia* asparaginase after a severe allergic reaction to *E. coli* asparaginase, only 1 had an allergic reaction.^{12,16–18} In two reports from the Children's Cancer Study Group, the incidence of allergic reactions to intramuscular *E. coli* asparaginase ranged from 6% to 18% in children with ALL who had relapses.^{6,13} We found a higher incidence of allergic reactions to *E. coli* in our patients. It is significant that our patients received higher doses of asparaginase and more prolonged courses than did the Children's Cancer Study Group patients. Another group reported anaphylaxis to intramuscular asparaginase in 1 of 275 patients who received *Erwinia* asparaginase and 1 of 483 who received the *E. coli* preparation but did not report the incidence of less severe allergic reactions.²¹

The Pediatric Oncology Group reported severe local reactions, systemic reactions, or anaphylaxis to weekly intramuscular *E. coli* asparaginase administration in 48%, 22%, and 3% of patients, respectively.²² When these patients received subsequent *Erwinia* asparaginase, local and systemic reactions occurred in 13% and 11%, respectively. One possible explanation for the much higher incidence of allergic reactions in these patients is their less immunosuppressive concurrent therapy. Concurrent therapy for these patients was only intermediate-dose methotrexate, whereas all our patients received concurrent steroid pulses, 6-mercaptopurine, and either doxorubicin or conventional-dose methotrexate. Because all of our patients received concurrent steroid, we cannot assess the importance of this drug in preventing the occurrence of allergic reactions to asparaginase.

A prospective, randomized study found that allergic reactions to intramuscular asparaginase were less severe than reactions to intravenous asparaginase, with no anaphylactic reactions in the 73 patients who received intramuscular asparaginase.¹³ Our data concurred with this observation. As in our study, Evans et al. found no predictive factors for allergic reactions to *E. coli* asparaginase.¹⁹ The only predictive factor for a reaction to *Erwinia* asparaginase in their study was a prior allergic reaction to *E. coli* asparaginase. We observed a trend showing that allergic reactions to *E. coli* asparaginase were more common in standard-risk patients

(33%) than in high-risk patients (20%) and hypothesize that the more intensive therapy in the latter group might have resulted in greater immune suppression and an impaired allergic response.

Because this was a retrospective study, certain data were not recorded in the patient charts at the time of the asparaginase reaction. For example, a secondary symptom such as a rash in the presence of urticaria or subtle changes in vital signs may not have been recorded. We presume that it would be unlikely that major data such as the primary symptom, location, treatment, and outcome would not be recorded.

Asparaginase remains a major component of therapy for children with ALL. Although intramuscular administration significantly reduces the likelihood of a severe allergic response, 6–28% of children will have an allergic reaction to *E. coli* asparaginase.^{6,13} Therefore, alternative forms of therapy, such as the use of polyethylene glycosylated asparaginase²³ or the *Erwinia* preparation, are important. Previous reports have demonstrated the equal efficacy of *Erwinia* and *E. coli* asparaginase.^{16,17,24} Because of the shorter plasma half-life of the *Erwinia* species as compared with *E. coli* (Asselin BL. Personal communication, 1991),^{25,26} we have adopted a twice-weekly schedule for patients who require the *Erwinia* species.

In summary, asparaginase is an active agent in the treatment of ALL. One of its limitations, allergic toxic effects, can be overcome in most patients by the substitution of other asparaginase preparations. We believe that, in the near future, the greater number of treatment options will allow more patients to benefit from this effective drug.

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Erratum

A correction should be noted in the article, "Characterization of 21 Newly Established Esophageal Cancer Cell Lines," by Shimada et al. (*Cancer* 1992; 69:277-84). The figures on pages 280 and 281 have been reversed. The figures on page 280 are actually the facing page figures as described in the legend.
