

Ammonia level as a proxy of asparaginase inactivation in children: A strategy for classification of infusion reactions

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Abstract

Introduction: Allergic hypersensitivity reactions related to enzyme asparaginase may occur during intravenous infusion of drugs and other adverse reactions (non-allergic hypersensitivity and hyperammonemia), which do not require discontinuation of therapy as the first case. It makes differential diagnoses between infusion reactions essential to assure the team regarding the right decision to make after the adverse event. This study evaluated a pharmacovigilance strategy of differentiating infusion reactions to asparaginase in pediatric patients, based on the measurement of serum ammonia and the classification of the reactions by clinical symptoms and severity.

Methodology: We included children, diagnosed with ALL, and treated with native *Escherichia coli* asparaginase in a university hospital. The professional team monitored and evaluated all asparaginase infusions for continuity of treatment (rechallenge), seeing the measurement of serum ammonia and classification of reactions for type and severity grade. Data from this monitoring was collected retrospectively. Chi-square and Mann-Whitney tests were used to compare the ratios between serum ammonia concentration posterior and before asparaginase infusion.

Results: 245 infusions in 32 patients were monitored, and 19 reactions were observed in 17 children (53%). Three children have hyperammonemia and continue their treatment. The variation of the serum ammonia levels before and after the infusion was statistically significant, comparing the groups with no reaction or hyperammonemia versus the group with the hypersensitivity reaction.

Conclusion: The pharmacovigilance strategy applied in the hospital investigated was a useful and inexpensive tool that supported clinical decision-making and enabled the maintenance of asparaginase therapy for three (9,4%) patients followed up.

Keywords

Acute lymphoblastic leukemia, asparaginase, adverse reaction, infusion reactions, ammonia

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Introduction

Asparaginase enzyme, which leads to asparagine depletion in leukemic blasts by asparagine cleavage in aspartic acid and ammonia, is used in all treatments of pediatric Acute Lymphoblastic Leukemia (ALL), the most common childhood cancer.^{1–3} However, its full use is limited by adverse reactions, especially those of allergic hypersensitivity that affect, on average, 30% of the patients.⁴

Allergic hypersensitivity can range from mild local infusion reactions to severe systemic events, including anaphylaxis, especially for native asparaginase from

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Escherichia coli (EcA). In these cases, the enzyme activity is almost always reduced (asparaginase inactivation) and mediated by the production of neutralizing antibodies. It may occur in the absence of a clinically evident allergic reaction,^{5–7} and this phenomenon is called “silent inactivation”. In general, the presence of anti-asparaginase antibodies is associated with reduced asparaginase activity.⁸ However, observation of infusion reactions during infusion does not require discontinuation of therapy if properly managed.^{8,9}

Burke and Rheingold¹⁰ suggested a pathway to classification and management of adverse reactions to asparaginase based on clinical symptoms, therapeutic drug monitoring (asparaginase activity), and previous enzyme exposure. The evaluation of elevated ammonia serum after asparaginase infusion (hyperammonemia) is evidence of non-antibody mediated reaction indicated by these authors.⁸ Therefore the measurement of plasma ammonia might be a proxy of asparaginase activity useful for analysis of adverse reactions due to its easy availability, speed, and low cost.^{9,11} During asparaginase administration, plasma ammonia increases significantly, as it is a direct product of the enzyme-catalyzed reaction, causing signs and symptoms similar to mild hypersensitivity reactions, a specific infusion reaction, the hyperammonemia.^{11,12}

This study aimed to evaluate the strategy of differentiating the reactions to EcA in pediatric patients, implemented at a Brazilian hospital, based on the measurement of serum ammonia and the classification of reactions for type and severity grade (CTCAE).⁹

Methodology

Design and setting

A cohort study was conducted at a pediatric university hospital, qualified for the treatment of pediatric hematologic cancer, located in the city of Rio de Janeiro (Brazil).

Eligibility criteria

All children from zero to 12 years old, diagnosed with ALL, first time, or relapsed, treated with native *E. coli* asparaginase (EcA) between August 2016 and March 2018, were monitored with a new pharmacovigilance strategy,⁹ and retrospectively enrolled in this study. No exclusion criteria were applied. Native EcA was the only type of asparaginase provided by the Unified Health System (*Sistema Único de Saúde*, SUS) during the study period and was used by all patients undergoing treatment.

Data collection

Retrospective data was collected from adverse reaction monitoring related to (i) patient characterization, (ii) treatment phase and drugs used, (iii) suspected adverse reaction and reaction characteristics, (iv) serum ammonia levels before and after infusion, (v) reaction management and (vi) continuation of treatment.

Pharmacovigilance strategy description

The monitored infusion of asparaginase, recommended by the institution, was based on the measurement of serum ammonia before (to rule out other possible causes of elevated ammonia levels, unrelated to asparaginase infusion) and immediately after asparaginase infusion by dry chemistry colorimetric method^{13,14} for all patients with transportation of sample and test execution right away to collect, according to Figure 1.

The monitored infusion of asparaginase, recommended by the institution, was based on the assessment of (i) serum ammonia measurement before and after asparaginase infusion by dry chemistry colorimetric method^{13,14} and (ii) grade of signals and symptoms of the reaction, according to Figure 1.

If there was any reaction, it was analyzed and classified, indicating or not suspicion of silent inactivation and the conduct adopted in each situation.

Reactions were classified as allergic hypersensitivity or hyperammonemia according to signs and symptoms presented and serum ammonia levels. Infusion time until the onset reaction and management and its response were used as additional tools in defining the type and grade of reaction, considering that those that occurred at the beginning of infusion and responded quickly to epinephrine and corticosteroids were antibody-mediated.¹⁵ The reaction grade was determined, by consensus between a pharmacist and a pediatric hematologist, according to the Common Terminology Criteria for Adverse Events (CTCAE) 3/4.03 version, which classified the reactions by 1 to 5, being grade 1 the mildest (transient flushing, rash) to grade 5 the most severe (death).¹⁶

In cases of reactions classified as hyperammonemia, asparaginase treatment continued (rechallenge) because the increase in serum ammonia concentration indirectly indicated the enzyme's action. Ammonia is a product of the hydrolysis of asparagine by asparaginase, and the plasma ammonia level might reflect the biological activity of asparaginase.¹⁷ In cases of hypersensitivity reactions classified as grades 1 and 2, with increased serum ammonia (concentration after administration higher than 100 μmol and previous concentration equal to or less than 30 μmol ^{11,13}) there was also the continuity of treatment, because according to the

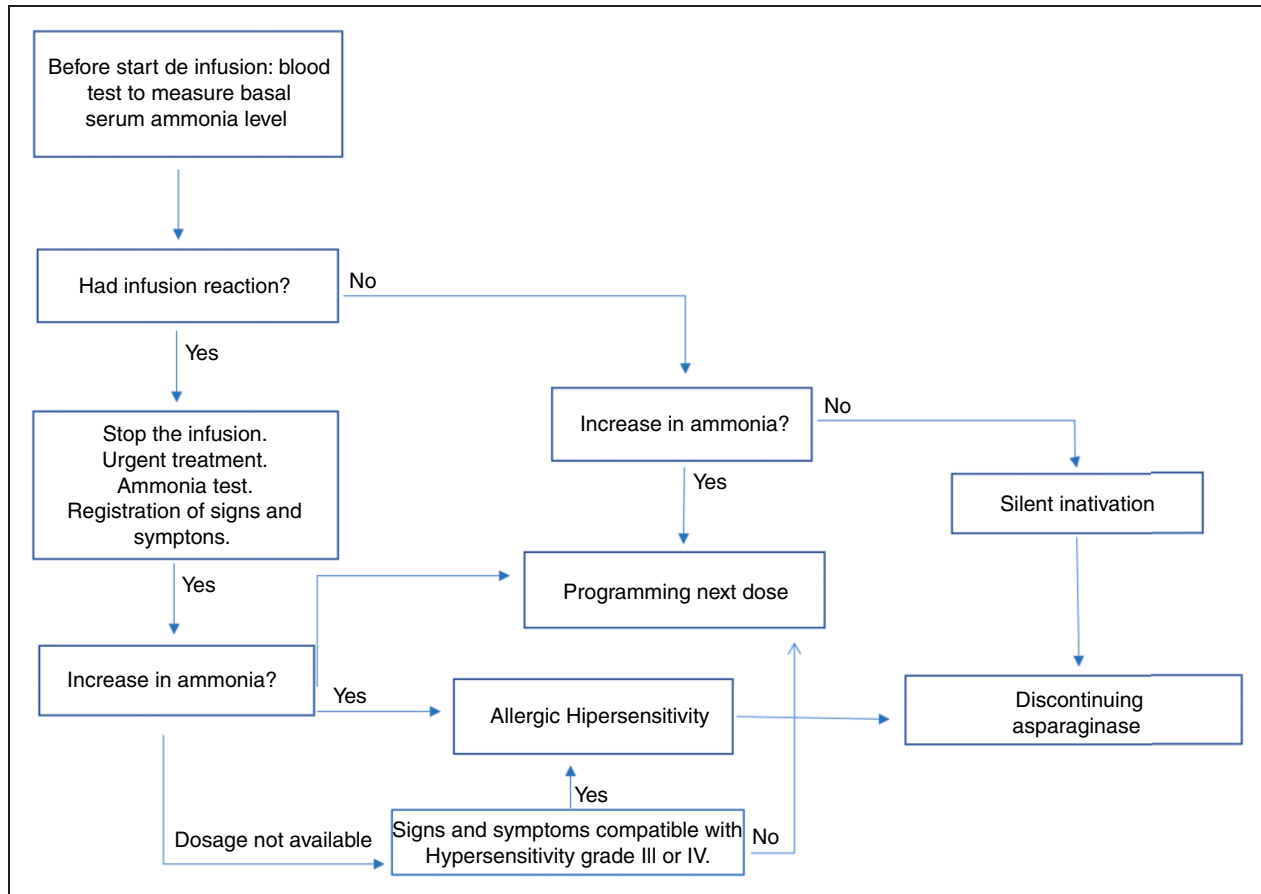


Figure 1. Asparaginase monitored infusion flowchart.

recommendation of Van der Sluis (2016) if there is not inactivation the treatment with asparaginase must be continued.⁸

When there was no change in the serum ammonia levels after the administration of asparaginase, regardless of any event, treatment was discontinued due to suspected asparaginase inactivation.⁸ The same happened in high-risk reactions, classified as grades 3 and 4, irrespective of the ammonia levels.⁸

During the follow-up of some patients, there was no ammonia test due to the reagent's unavailability or the impossibility of adequate central access. In the latter case, it was decided only to collect ammonia in case of a reaction to assist in the differential diagnosis since collection in peripheral access is painful. Regardless of ammonia values, all reactions were classified with the available data.

In addition to the monitored infusion of asparaginase, the minimum 12-hour interval between vincristine and asparaginase infusions was adopted, as provided for in the German protocol chosen for the treatment of ALL, to avoid possible drug interactions. Vincristine

undergoes hepatic metabolism, and asparaginase is hepatotoxic, increasing the risk of reaction to vincristine.^{9,13}

Statistical analysis

For variables tested as possible risk factors, the odds ratio, the confidence interval (95% CI), and p-value were calculated.

Chi-square and Mann-Whitney tests were used to compare the ratios between post and pre ammonia in infusions without any reactions, with hyperammonemia and hypersensitivity reactions, and also in hypersensitivity reactions of different grades. Statistical analyses were performed using the SPSS program.

Ethical issues

This research project was submitted and approved by the Research Ethics Committee of the institution (2.787.464).

Results

During the study period (2016 - 2018), 245 infusions were monitored in 32 patients. Among the patients followed, 62,5% were boys, the predominant type of ALL was B-cell precursor acute lymphoblastic leukemia BCP-ALL (87,5%), and the high-risk cases were the most observed (56,3%). Infusion reactions were observed in 7% of these infusions. Table 1 presents the characterization of the included patients.

Seventeen (53.1%) patients had at least one adverse reaction during the study period. Two had two reactions, totaling 19 reactions during the period. Seven reactions (36.84%) occurred in the induction phase and seven in the consolidation phase. Five reactions (26.4%) occurred in the re-induction phase.

As for the risk factors analyzed, the disease risk rating was considered statistically significant (Table 1).

Description of signs and symptoms in all the reactions allowed their classification to grade and previous and post ammonia values ($\neq$ serum level). When available, they helped distinguish between low-grade hypersensitivity reactions and hyperammonemia well as the percentage of solution infused. Among the 19 reactions observed during the study period, 15 were classified as hypersensitivity and four as hyperammonemia (Table 2).

Cases of hyperammonemia: three patients

Three children presented hyperammonemia reactions. All these events were observed after the infusion of more than 50% of the dose. One of these children, which had rechallenged asparaginase and got to complete all the doses anticipated in the clinical guideline, presented two hyperammonemia reactions in different treatment phases (cases 14 and 15). Another child with reactions classified as hyperammonemia also received

the whole therapy without any complications. The third patient presented a hyperammonemia reaction, continuing with the treatment. However, after three doses, there was a grade-3 hypersensitivity reaction, and then the treatment was discontinued. One case was classified as hyperammonemia, without the serum level, because it was an absence of test on the moment of infusion, but the symptoms observed and the temporality of the reaction was used to classify.

Thus, the differential diagnosis allowed for the completion of the asparaginase treatment for two patients and the possibility of administering another three doses for one patient.

Hypersensitivity cases: 14 patients

Grade 3 and 4 reactions: Nine reactions were classified as grade-3 hypersensitivity. In five, the ammonia level indicates a possible inactivation of asparaginase due to a small difference in the concentration subsequent and previous to the asparaginase infusion (a difference of less than 70 $\mu\text{mol/L}$). In one case, the difference between post and pre ammonia was 118 $\mu\text{mol/L}$, so there was no inactivation. However, considering the severity of the reaction, it was decided to permanently discontinue the treatment.

In another three events, it was not possible to measure the ammonia level; however, the treatment was discontinued due to the severity of the reaction.

In the only reaction classified as grade 4, no significant ammonia increase was observed. All of these reactions led to discontinuation of the treatment, totaling nine children who had severe reactions, then the asparaginase treatment was discontinued.

Grade 2 reactions: Of the five grade-2 hypersensitivity reactions, the inactivation of the enzyme was observed in four due to little variation of the serum

Table 1. Risk factors for asparaginase-related reactions.

Reactions during asparaginase infusion					
Risk factor	Yes	No	Odds ratio	CI (95%)	p-value
Gender					
Female	8	4	3	0.671–13.404	0.144
Male	8	12			
Type of ALL					
BCP-ALL	16	12	4	0.369–43.383	0.228
T-ALL	1	3			
Risk rating					
HR	10	4	5	1.096–22.820	0.033
Non-HR	6	12			
Age			0.836 ^a	2.84–6.41	0.399

HR: high risk; Non-HR: medium and low risk, CI: confidence interval.

^aFor each year of life.

Table 2. Description of the reactions reported according to Ammonia serum level before and after asparaginase infusion and the signals and symptoms grade (n = 17 patients; 19 reactions, Rio de Janeiro, Brazil, 2016-2018).

Case	Description of the related symptoms	%Vol. adm/ Vol. prescribed	Serum level difference	Reaction management	Reaction classification	HR grade
1	Nausea, tachycardia, rash, hives, colic, sweating, vomiting, perioral angioedema	14	19	Administration of epinephrine and corticosteroid	HS	3
2	Agitation, nausea, broncho-spasm, dyspnea	33	19	Administration of epinephrine and corticosteroid	HS	3
3	Agitation, bronchospasm, dyspnea, nausea and hives	24	ND	Administration of epinephrine and corticosteroid	HS	3
4	Agitation, bronchospasm, cough	36	19	Administration of epinephrine and corticosteroid	HS	3
5	Agitation, tachycardia, dyspnea, rash, flushing, hives, sweat	17	9	Administration of epinephrine and corticosteroid	HS	2
6	Agitation, glottic edema, and difficulty breathing	16	ND	Administration of epinephrine and corticosteroid	HS	3
7	Agitation and irritability	100	ND	Decreased infusion rate	HA	NA
8	Agitation, tachycardia, rash, flushing, edema	38	118	Administration of epinephrine and corticosteroid	HS	3
9	Nausea, cough, bronchospasm	37	ND	Administration of epinephrine and corticosteroid	HS	3
10	Agitation, cough and cyanosis	11	0	Administration of epinephrine and corticosteroid	HS	2
11	Agitation, fatigue, bronchospasm, flushing and sweating	11	18	Administration of epinephrine and corticosteroid	HS	3
12	Irritation, mild dyspnea, cough	76	130	Interruption of the infusion	HA	NA
13	Abdominal pain, cough, flushing and sweating	25	ND	Administration of epinephrine and corticosteroid	HS	2
14	Vomiting	100	308	Decreased infusion rate	HA	NA
15	Vomiting, abdominal pain and agitation	100	350	Decreased infusion rate	HA	NA
16	Agitation, colic, dyspnea, headache and rash	2	9	Administration of epinephrine and corticosteroid	HS	2
17	Tachycardia, chills, colic, sweating, prostration, high fever after infusion and backache	20	39	Administration of epinephrine and corticosteroid	HS	4
18	Colic, diarrhea, dyspnea, nausea, sweating, tachycardia, vomiting, tremors, and pale lips	8	34	Administration of epinephrine and corticosteroid	HS	3
19	Agitation, tachycardia, hives	6	42	Administration of epinephrine and corticosteroid	HS	2

NA: not applicable; ND: ammonia not dosed; HA: hyperammonemia; HS: hypersensitivity; HR: hypersensitivity reaction; %Vol. adm/ Vol. prescribed: percentual of solution volume administered until adverse reaction started/ infusion volume total prescribed

ammonia level. However, there was no dosage of ammonia in one case, making it difficult to distinguish the type of hypersensitivity reaction (allergic or not) and possibly the continuation of the treatment. Unfortunately, the patient later died of the disease, making it impossible to re-administer the drug. The fact that the event occurred with 25% of the infusion suggested, however, the inactivation of the enzyme, and the reaction was classified accordingly. Four grade-2 hypersensitivity reactions led to discontinuation of

the treatment. No grade-1 reactions were observed during the study period.

Cases of silent inactivation of asparaginase were also not observed by measuring the serum ammonia levels.

Hypersensitivity reactions occurred early in the infusion, all with less than 40% of the infused asparaginase dose. In addition to the immediate discontinuation of the administration, epinephrine and corticosteroid were used.

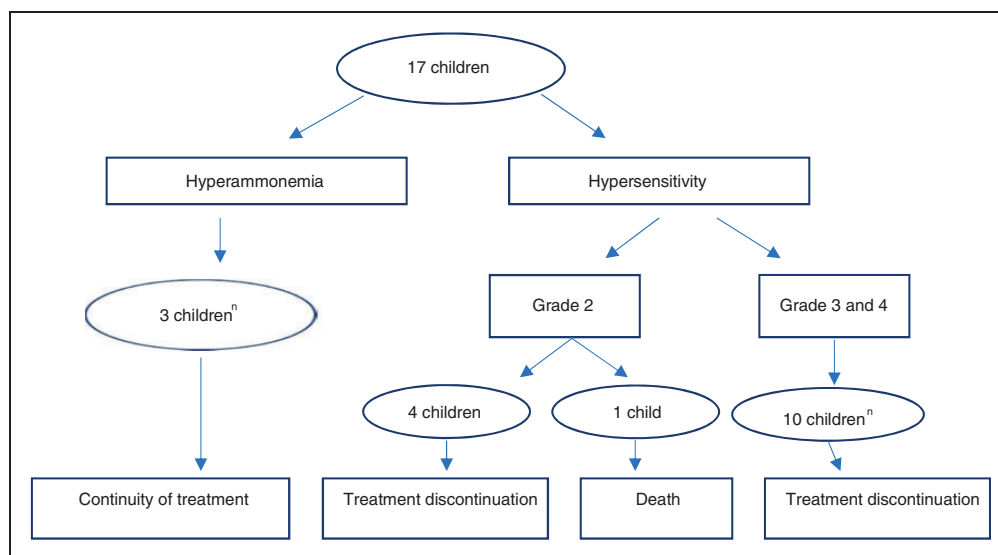


Figure 2. Monitored infusion of asparaginase (17 patients).

n: same patient accounted for in both groups due to initial hyperammonemia reaction and, after administration of another three doses, hypersensitivity reaction.

Figure 2 summarizes the result of monitoring the use of asparaginase in the 17 patients with infusion reaction.

Evaluation of the serum ammonia levels

Figure 3 indicates the sum of the ratio found between the increase in the serum ammonia level in cases of patients diagnosed with a hypersensitivity reaction and without this reaction during infusions (A) and the sum of the ratio found between the increase in the serum ammonia level of patients who did not have a reaction, with hyperammonemia reaction and hypersensitivity reactions of any grade in the 173 infusions in which it was possible to collect and evaluate serum ammonia before and after the infusion (B).

In 173 cases, it was possible to calculate the median of the post/pre-asparaginase ratio, the maximum and minimum values found, and the interquartile ranges (Table 3).

Discussion

A larger number of male children were included in the study. Some studies point to a slight predominance of cases in boys, as well as better event-free survival in girls.^{8,9,12,18} Regarding the type of ALL, the incidence of BCP-ALL (87.5%) and T-ALL (12.5%) was similar to other studies indicating a mean of 85% of BCP-ALL cases and 15% of cases of T-ALL.^{8,9,12,18}

A high number of cases diagnosed and treated as high risk (43.7%). It was consistent with previous work carried out at the same setting (in which found

41.2% of the cases were also classified as high risk), though do not consist with the German study ALL-BFM-IC (guideline used at the studied hospital) where only 17% of the cases were considered high risk.^{9,18} Specifically, in this study, such findings may have been one of the causes of this apparent discrepancy because relapsed patients were also included in the study, as long as they had used asparaginase during the study period, unlike previous studies.

Seventeen patients (53.1%) had a reaction during asparaginase infusion. For three (9.4%) of these patients, a full or partial continuation of the predicted asparaginase treatment was possible in the treatment regimen. This may have contributed to a response to the treatment, as Silverman et al. (1997)¹⁹ showed that shorter treatments with asparaginase (less than 25 weeks) might reduce event-free survival. The decrease of asparaginase doses was the only significant prognostic factor in multivariate Cox proportional hazards analysis when compared to covariates age, leukocyte count, and immunophenotype.

Fifteen patients had a reaction classified as hypersensitivity, and 14 (43.8%) had their treatment with asparaginase discontinued. This percentage of treatment interruption due to infusion reaction was above the mean of 30% described by Burke et al. (2014) in an American study, but lower than that found in the previous analysis (60.5%) site.^{9,21}

The differentiating the reactions to EcA, based on serum ammonia dosage and reaction classification,⁹ ensured treatment keeping with EcA for three children among 17 included in this study. This easy and

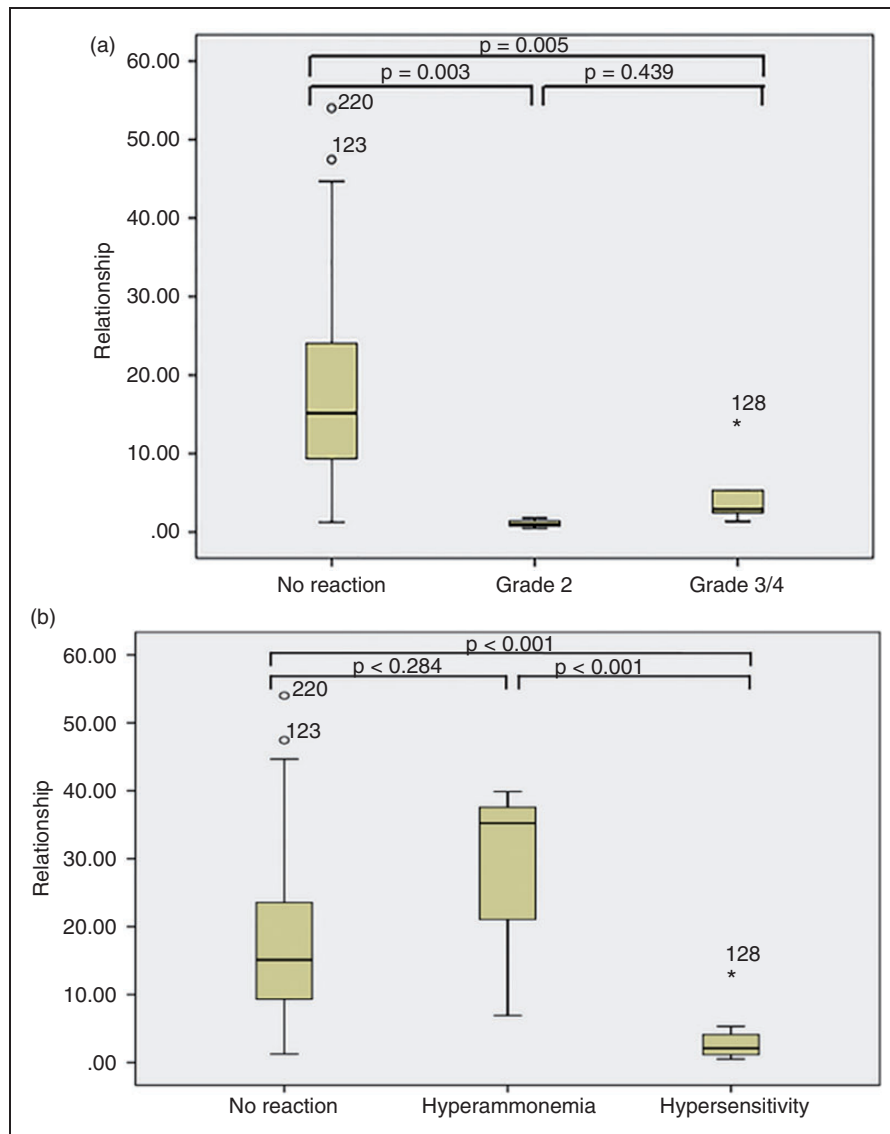


Figure 3. (a) Relationship between serum ammonia level and hypersensitivity reaction. (b) Relationship between serum ammonia level and infusion-related reactions.

Table 3. Median of the ratio of the serum ammonia levels in patients without HR and with different grades of HR.

Ratio between the post- and pre- asparaginase serum ammonia levels

Group	Median	Minimum	Maximum	IR
Without HR	15.1	1.26	54.00	14.28
HR grade 2	1.75	0.5	2.9	
HR grade 3/4	1.9	1.34	14.11	7.82

IR: interquartile range (25%-75%); HR: hypersensitivity reaction.

inexpensive strategy represents an effective alternative for adverse reaction assessment given that asparaginase activity assay is not available in most of the facilities in health services.

In addition to the differential diagnosis of infusion-related reactions, it is believed that following predicted interval between the doses and at least 12 hours between the administration of vincristine and

asparaginase contributed to the reduction of early discontinuation of the treatment with asparaginase due to adverse reaction during infusion. Longer intervals between administrations increase the risk of hypersensitivity reaction. In Santos et al. (2017)⁹ overwritten, 60.5% of the patients had infusion reactions, and all of them were considered hypersensitivity reactions due to lack of a differential diagnostic tool, leading to treatment discontinuation in all cases.

We found that 53.1% of the patients had some infusion reaction, but only 43.8% had evidence of allergic hypersensitivity reactions during monitored asparaginase infusion and discontinued their enzyme treatment. Differential diagnosis of the reactions (with ammonia dosage and classification of reactions by grade) was especially important for the cases of hyperammonemia and grade 2 hypersensitivity reactions since, of the three children with hyperammonemia, two completed the treatment and the third received more doses until the onset of the grade 3 hypersensitivity reaction. Also, the only grade-2 reaction that did not have an ammonia level raised doubts about the possibility of asparaginase inactivation.

Regarding the phase of the treatment in which the reactions occurred, seven patients had reactions still in the remission induction phase, one of hyperammonemia and six of hypersensitivity (31.6%). Five patients had hypersensitivity reactions in the consolidation phase, and two had hyperammonemia, and in the re-induction step, four had hypersensitivity reactions, and one had hyperammonemia. The incidence of hypersensitivity reactions in the remission induction was high in this study, as this type of reaction is more common in the post-induction phases. However, as a dose-dependent reaction, the incidence of hyperammonemia is more likely to occur in the consolidation or re-induction phases of remission, where asparaginase doses are five and two times higher than the induction phase doses, respectively.^{20–22} Concerning risk factors for the occurrence of reactions, only the risk rating of the disease proved to be statistically significant. In the previous study,⁹ high-risk scores and low age were considered risk factors for the occurrence of reactions. The low incidence of hyperammonemia reactions among infusion reactions in this study is consistent with the non-appearance of age as a risk factor since younger individuals are more susceptible to such reactions due to childhood pharmacokinetic differences.²³ The permanence of risk rating as a risk factor with an odds ratio higher than that found in Santos et al. (2017)¹⁰ was consistent with Hasan et al. (2016)²⁴ finding for PEG-asparaginase. The intravenous route seems adequate for the administration of PEG-asparaginase in low and intermediate-risk patients; however, for

high-risk patients, the same way represents a 35% increase in the probability of reaction.²⁴

Previous and posterior asparaginase ammonia level was useful for differential diagnosis of reactions. It confirmed little variation in serum ammonia levels in patients with a hypersensitivity reaction, as the median ratio of previous and posterior asparaginase serum ammonia levels in patients without reaction during the asparaginase infusion (median ratio without reaction: 15.1) is five (median ratio with grade 2: 2.9) and seven times (median ratio with grade 3: 1.9) higher than in patients with grade 2 and grade 3 or 4 hypersensitivity reaction, respectively. Mann-Whitney test between pairs of groups showed a statistically significant difference between the groups without reaction and the hypersensitivity reaction.

The variation in the serum level of ammonia can also be an indication of silent inactivation,²⁵ because when applying such a tool, cases can be identified in which there was no variation in ammonia levels and neither infusional reaction, demonstrating enzyme inactivation, besides allowing the identification and treatment, when necessary, of the hyperammonemia reaction.¹³

As the differential diagnosis protocol was implemented as a routine of the service and not as a clinical trial, it was subject to limitations of materials and ideal conditions for the study of the children included, such as lack of reagent for ammonia dosage and difficulties in collecting samples due to child's health. This fact led to the non-dosage of ammonia in 72 (29.4%) of the 245 monitored infusions. However, even without this tool, reactions' signs and symptoms were considered to obtain, with the best possible accuracy, the differential diagnosis of the reactions. It is believed that the study offers a viable strategy for application in cancer care in children in middle and low-income countries.

Conclusion

Monitoring asparaginase infusion-related reactions, based on risk rating and use of the serum ammonia test, proved a useful and inexpensive tool combined with administration interval between vincristine and asparaginase, allowed maintaining enzyme treatment for 9.4% of the patients. Differential diagnoses of infusion reactions contributed to support clinical decisions regarding continuity of therapy, based not only on adverse reactions but also on the ineffectiveness of drugs after the event.

Declaration of Conflicting Interests

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