Humoral immunity to tetanus, measles and rubella in children with acute lymphoblastic leukemia after chemotherapy

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ABSTRACT

Chemotherapy regimens and clinical support advances have improved survival in children with acute lymphoblastic leukemia. The after-effects of treatment are a reason for concern, including damage to the immune system induced by immunosuppressive therapy which is reflected in the loss of antibody protection provided by prior immunizations.

Our goal was to assess the presence of measles, rubella, and tetanus protective antibody titers among patients with acute lymphoblastic leukemia after completing chemotherapy.

Sixty-one children with acute lymphoblastic leukemia seen at the Hospital Garrahan were included; patients had finished their chemotherapy at least 6 months earlier and had a complete immunization schedule before diagnosis. The rates of protective antibodies were 46% (CI: 32-59) for measles, 53% (CI 40-67) for tetanus, and 60% (CI 47-63) for rubella.

These results strengthen the need to reconsider revaccination in this group of patients.

***Key words**: acute lymphoblastic leukemia, immunizations, humoral immunity, antibodies, chemotherapy.*

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INTRODUCTION

Over the past two decades, intensified chemotherapy regimens and advances in clinical support implementation have improved survival among children with acute lymphoblastic leukemia (ALL).[1]

The increasing number of survivors poses a challenge for pediatricians, especially in relation to the development of sequelae secondary to treatment. These include damage to the immune system induced by immunosuppressive therapy. Children with ALL who are treated with chemotherapy suffer from humoral and cellular immunosuppression, which may last for months, or even years, after they have finished treatment.[2-4]

Immunizations are highly important for the prevention of communicable infectious diseases. In this context, it is relevant to know the level of protection against vaccine-preventable diseases in these patients, who received immunizations in a timely manner and then underwent chemotherapy.

There is little evidence in the literature regarding the recovery of antibody protective levels provided by prior immunizations in children treated for ALL who completed their chemotherapy. Published studies report different results, so it is not possible to make a definite recommendation on a revaccination policy.[5] In our setting, no data have been published in this regard.

The objective of this study was to assess the presence of measles, rubella, and tetanus antibody protective titers among patients with ALL after chemotherapy.

POPULATION AND METHODS

We conducted a descriptive, observational, cross-sectional study.

Sixty-one patients diagnosed with ALL and seen at the Hospital de Pediatría Prof. Dr. Juan P. Garrahan between June 2008 and January 2013 were included. Inclusion criteria were having received first-line treatment as per the ongoing protocol, being 1 to 17 years old at the time of diagnosis, having completed chemotherapy 6 to 18 months before the study, and having received every vaccine indicated in the national immunization schedule.

Patients included in the study agreed to participate in a voluntary and informed manner and gave their consent and assent, if applicable.

Treatment corresponded to Protocol 11-ALLIC/BFM-2002.[6] Patients were classified into three risk groups (standard, intermediate and high) as per clinical, biological and treatment response parameters. Treatment intensity differed across risk groups.

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Compliance with immunizations was confirmed by checking the patients' vaccination card.

Children who had received the corresponding booster doses of tetanus, measles or rubella vaccine for their age after chemotherapy, patients with immune disorders prior to ALL diagnosis, and those who missed the corresponding booster doses for their age because they were receiving chemotherapy were excluded.

The main outcome measures were rubella, measles and tetanus antibody titers.

Antibody titers were measured 6 to 18 months after chemotherapy completion; for this reason, and given that no measurement was done prior to chemotherapy, the situation was defined as "absence" of protective levels instead of "loss." Although these results were not compared to antibody levels prior to chemotherapy, it was considered that, in the general population who have completed their immunization schedule, the prevalence of antibody protective titers against the studied diseases ranged between 90% and 95%.[7-10]

Immunoglobulin G (IgG) titers for rubella were determined using a quantitative method based on the microparticle enzyme immunoassay (MEIA) from Abbott® Laboratories.

IgG titers for measles were determined using a qualitative method which associated the two-step sandwich enzyme immunoassay to the enzyme linked fluorescent assay (ELFA) from bioMérieux®.

Antibody titers against the tetanus toxoid were determined at the immunology laboratory using the enzyme-linked immunosorbent assay (ELISA).

In addition, for each case, the child's age at the time of diagnosis, time (in months) elapsed after chemotherapy, and ALL risk group were recorded.

In all cases, a single determination was made from a blood sample drawn from a vein, which was requested together with the routine cancer control of these patients. No additional blood draws were made for the purpose of this study.

The study was approved by the Research Review Committee and the Ethics Committee of the hospital.

Statistical analysis

For the descriptive analysis of continuous outcome measures, mean, median and standard deviation were used as summary statistics based on data distribution. Categorical outcome measures were established as absolute and percent values.

Protective rates were expressed as percentage and 95% confidence interval (CI) to report on the accuracy of the value obtained.

The relationship among the presence or absence of protective titers and ALL risk groups, age at the time of diagnosis, and time elapsed after chemotherapy was also analyzed. The STATA 9.0 (StataCorp USA) statistical software was used for analysis.

RESULTS

Sixty-one children were included in the study: 31 girls and 30 boys. *Table 1* describes the main characteristics of the population.

The rate of protective antibodies was 46% (95% CI: 32-59) for measles, 53% (95% CI: 40-67) for tetanus, and 60% (95% CI: 47-63) for rubella.

The presence of protective antibodies by risk group was as follows:

- Measles: 53% in patients who had a standard risk, 50% in those who had an intermediate risk, and none in the six patients who had a high risk.
- Rubella: 53% in patients who had a standard risk, 65% in those who had an intermediate risk, and 50% in those who had a high risk.
- Tetanus: 53% in patients who had a standard risk, 57% in those who had an intermediate risk, and 33% in those who had a high risk.

The descriptive analysis of our results did not show a difference in the presence of protective antibodies and median age at the time of diagnosis or median time (in months) elapsed after chemotherapy completion (*Tables 2 and 3*).

TABLE 1. *General characteristics of the studied population (n= 61)*

Male sex, n (%)	30 (49)
Age (years old) at the time of antibody titer measurement; median (range)	10.3 (3.6-19.1)
ALL risk group, n (%)	
Standard	16 (26)
Intermediate	39 (64)
High	6 (10)
Time (months) elapsed after chemotherapy; median (range)	9 (6.2-17)

ALL: acute lymphoblastic leukemia.

DISCUSSION

In our study, it was observed that, depending on the antibody assessed, between 40% and 54% of children diagnosed with ALL who completed conventional chemotherapy lacked protective antibodies against measles, rubella and tetanus, although they had received these vaccines in accordance with the national immunization schedule before they started chemotherapy.

Children with ALL who are treated with chemotherapy suffer from humoral and cellular immunosuppression, which may last for months or even years after they have finished treatment.[2-4] Humoral immunity expressed by B cell function may be assessed measuring immunoglobulin serum levels. It has been observed that, at the end of chemotherapy, these levels are close to the 10th percentile and reach normal values within six months after completing immunosuppressive therapy.[2,4]

However, there is little evidence in the literature regarding the recovery of antibody protective levels provided by immunizations received prior to chemotherapy.

Nilsson et al.[11] analyzed antibody titers in 43 children after chemotherapy and demonstrated the persistence of protection against measles and rubella in 60% and 72% of patients, respectively. Brodtman et al.[12] studied antibody titers provided by several vaccines in 100 children with ALL and observed that the percentage of these children who had protective titers was remarkably lower than that expected for immunized control subjects. In the study conducted by Von der Hardt et al.,[13] more than 50% of patients lacked protective immunity to diphtheria and tetanus after chemotherapy.

Published studies describe different results and, although many show reduced protective antibody titers, some are under scrutiny due to their design.

Only one systematic review has been done, by Van Tilburg et al.,[5] and its results were described as protective rate ranges, which seemed adequate given study variety. The wide range of protective antibody titers among studies, which may be explained by their heterogeneity and limited sample size, prevented the chance of doing a meta-analysis. So it was not possible to make a definite recommendation on a revaccination policy.[5]

The United Kingdom and Spain recommend the administration of a booster dose of all vaccines received six months after completing chemotherapy. These recommendations are mainly based on expert opinions and a limited number of published studies.[14,15]

Some studies have demonstrated that the incidence of reduced protective antibody titers is higher among younger patients.[11]

The descriptive analysis of our results did not show a difference between the presence of protective antibodies and median age at the time of diagnosis or the median time (in months) elapsed after chemotherapy completion.

Although the percentage of protective antibodies has been described for the different ALL risk groups, one of the limitations of these results is that the high risk group included only six patients.

Table 2. *Presence of protective titers against measles, rubella and tetanus by age at the time of diagnosis (n= 61)*

Antibody protective titers		Age at diagnosis of ALL X SD	(95% CI)
Measles antibodies	+	6.9 ± 4.5	(5.1-8.6)
	–	6.9 ± 4.2	(5.5-8.4)
Tetanus antibodies	+	7.2 ± 3.8	(5.9-8.6)
	–	6.7 ± 5	(4.9-8.5)
Rubella antibodies	+	7.2 ± 4.3	(5.7-8.6)
	–	6.7 ± 4.4	(4.9-8.4)

ALL: acute lymphoblastic leukemia.
X SD: median and standard deviation. CI: confidence interval.
+ Presence of antibody protective titers.
- Absence of antibody protective titers.

Table 3. *Presence of protective titers against measles, rubella and tetanus by months elapsed after chemotherapy (n= 61)*

Antibody protective titers		Months elapsed after chemotherapy X SD	(95% CI)
Measles antibodies	+	8.9 ± 2.5	(7.9-9.9)
	–	9.2 ± 2.5	(8.4-10.1)
Tetanus antibodies	+	8.7 ± 2.2	(7.9-9.5)
	–	9.4 ± 2.7	(8.4-10.4)
Rubella antibodies	+	9.5 ± 2.6	(8.6-10.4)
	–	8.6 ± 2.3	(7.6-9.5)

X SD: median and standard deviation. CI: confidence interval.
+ Presence of antibody protective titers.
- Absence of antibody protective titers.

Therefore, although none of the high risk patients were observed to have protective antibodies against measles, the small sample size prevents us from detecting a significant difference.

It is worth noting that even patients with a standard risk did not evidence a high percentage of protective antibodies.

Therefore, the results of our study strengthen the need to reconsider revaccination policies for patients who receive chemotherapy for ALL, including those who are in the standard or intermediate risk group and receive a less intense chemotherapy regimen, and especially those who have a high risk and receive an intensified regimen. ■

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Prevalence and clinical course of typical hemolytic uremic syndrome among siblings

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ABSTRACT

Introduction. Hemolytic uremic syndrome (HUS) is an infectious disease caused by Shiga toxin-producing *Escherichia coli*. The objective of this study was to assess the risk of transmission and clinical course between siblings with typical HUS.

Population and methods. Medical records of children with typical HUS between 1997 and 2012 were reviewed. Sibling pairs were established as inclusion criteria. A severity score was defined.

Results. A total of 133 patients with HUS were recorded; 40 had siblings and 4 progressed to HUS (10%). The mean age of the 4 sibling pairs was 29.3 months old (SD ± 11.5); 5 (62.5%) were girls. The mean time between each case was 5.7 days (SD ± 3). HUS was more severe in the siblings who became infected in the second place.

Conclusion. The risk of HUS transmission between siblings was 10%, and the clinical course of the second sibling was less favorable.

Key words: *hemolytic uremic syndrome, siblings,* Escherichia coli*, risk, Argentina.*

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INTRODUCTION

Hemolytic uremic syndrome (HUS) is clinically defined by the clinical triad of thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney failure, and is characterized by the presence of thrombotic microangiopathy in the pathological examination. In 1964, Carlos Gianantonio, M.D., published a series of cases in Argentine children and provided a full description of the clinical aspects and course of HUS.[1]

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Survival of HUS patients improved with intermittent peritoneal dialysis in the acute phase and with kidney transplantation in the chronic stage. However, HUS is still a major health problem in Argentina. It is the leading cause of acute kidney failure and the second cause of chronic kidney disease, which accounts for approximately 20% of kidney transplants in children.[2]

HUS is caused, in 90% of cases, by Shiga toxin-producing *Escherichia coli* (STEC); this means it is an infectious disease, and is called typical HUS. Its incidence rate is variable, but in Argentina, the annual HUS incidence ranges between 10 and 12 cases every 100 000 children younger than 5 years old; and it is the highest rate reported worldwide.[3]

Risk factors associated with the development of typical HUS include eating meat outside the house, eating undercooked meat, living in or visiting a place with farm animals, and contact with children younger than 5 years old with diarrhea.[4]

Cattle are the primary reservoir for STEC, and food or water contaminated with cattle feces is often the most common source of infections in Argentina.

Secondary infection through person-to-person transmission may also occur.[5] It has been described that family members who come in contact with children with typical HUS commonly have STEC colonization, and Shiga toxin has been frequently identified in the members of the same family.[6,7] The development and severity of person-to-person transmission may also depend on other factors, such as the amount of inoculum ingested and individual susceptibility.

Our objective was to assess the risk of transmission and clinical course between siblings with typical HUS.

POPULATION AND METHODS

The medical records of children with typical HUS admitted to the Department of Pediatrics of Hospital Italiano between March 1st, 1997 and December 31st, 2012 were reviewed. Their

families were contacted by telephone to check recorded data.

Typical HUS was defined as the triad of thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney failure after a bloody or non-bloody diarrhea episode.

As of 2000, all cases are reported to the Ministry of Health.

All patients had a stool culture to look for STEC and/or detect verotoxin-1 and -2 in feces using specific cytotoxicity of Vero cells, an enzyme immunoassay, or an immunochromatographic rapid test, depending on the year of patient admission.

Sibling pairs (6 months to 6 years old) who had typical HUS in the same epidemiological period (2-14 days) were established as inclusion criteria.

Kidney involvement was defined as an increase in serum creatinine above the normal range adjusted for age or the presence of hematuria and proteinuria in urinary sediment; thrombocytopenia was defined as a platelet count below 150 x 10^9/L; and neurological involvement was established as lethargy, irritability, ataxia, seizures, or coma.

The following outcome measures were assessed: age, sex, date of onset of clinical and lab HUS signs between the first and the second siblings, lab tests at admission (white blood cell count, platelet count, hematocrit, creatinine, urinary sediment), clinical characteristics (oligoanuria, intermittent peritoneal dialysis, neurological involvement, and clinical course).

A severity score was established based on the mortality and chronic kidney involvement predictors described by Oakes et al.[8,9] in 2006 and 2008:

- White blood cell count equal to 20 000 cells per mm^3 or higher (1) and lower (0).
- Hematocrit equal to 23% or lower (0) and higher (1).
- Oligoanuria equal to 5 days or longer (2) or shorter (1), and no oligoanuria (0).
- Presence (1) and absence (0) of neurological involvement.

A score of 0 was considered less severe, whereas 5 accounted for a more severe case.

Categorical outcome measures were analyzed by frequency and continuous outcome measures with normal distribution were studied using Student's t test. A *p* value below 0.05 was considered significant.

RESULTS

A total of 133 patients with typical HUS were recorded. Their mean age was 24 months old (SD ± 9.4); 58% were girls. The mortality rate was

TABLE 1. *Clinical characteristics, lab tests at the time of admission and severity score in the 4 pairs of siblings with hemolytic uremic syndrome*

Family	**1**		**2**		**3**		**4**	
Year of diagnosis	1997		1999		2002		2006	
Age (months)	25	10	23	43	31	47	28	28
Sex	F	M	M	F	M	F	F	F
Diagnosis	Inicial	Subs	Inicial	Subs	Inicial	Subs	Inicial	Subs
Time until HUS development (days)	9		5		2		7	
Oligoanuria (days)	1	5	0	1	6	30	2	9
IPD (days)	0	6	0	0	5	32	0	9
Baseline creatinine (mg/dL)	2.1	3.5	0.8	1.2	3.4	1.2	1.7	3.7
Hematocrit (%)	21	25	30	29.6	23.6	31	21	26
Platelet count (cells/mm^3)	50 000	17 200	130 000	29 000	43 700	53 800	64 300	74 500
White blood cell count (cells/mm^3)	12 300	13 500	12 000	14 600	13 800	36 100	19 500	24 500
Neurological involvement	Yes	Yes	No	No	No	Yes	No	Yes
Course	Normal	Normal	Normal	Normal	Normal	P and CKF	Normal	P
Severity score	2	4	1	2	3	5	1	5

HUS: hemolytic uremic syndrome. M: male; F: female. Normal: normal creatinine, normal blood pressure and no proteinuria. P: proteinuria. CKF: chronic kidney failure. IPD: intermittent peritoneal dialysis. Subs: subsequent.

1.8%, and neurological involvement was the cause of death in all fatal cases.

Forty patients had siblings; 16 had diarrhea and 4 progressed to HUS (10%). There was a pair of twin girls.

The mean age of the 4 sibling pairs was 29.3 months old (SD ± 11.5); 5 (62.5%) were girls. No patient had HUS recurrence, and no case occurred in adults. The mean time between HUS transmission from the first to the second sibling was 5.7 days (SD ± 3), and the mean follow-up time was 11 years (SD ± 5.4).

The pairs of siblings diagnosed between 2002 and 2006 had STEC, which was confirmed by identification of verotoxin in feces.

The baseline clinical and lab characteristics of sibling pairs are described in *Table 1*.

Siblings who developed typical HUS in second place had a more severe score, as per the poor prognosis parameters assessed at disease initiation, with a higher frequency of neurological involvement and prolonged kidney failure. The mean severity score of siblings who developed typical HUS first was 1.75 (SD ± 0.95) and that of siblings who had the disease in second place was 4 (SD ± 1.4) ($p < 0.03$).

DISCUSSION

Ten percent of siblings of primary patients developed typical HUS, and the clinical course of the second sibling was less favorable.

Family members who are in contact with children with HUS are usually colonized by STEC and seroconversion frequently occurs in the family members of these children.[5,6]

Although gastrointestinal symptoms in family contacts were less common in our study, it has been reported that approximately 40% of household contacts of children with HUS have the free toxin identified in their feces.[6,7]

HUS outbreaks may start due to simultaneous exposure of several individuals to a common food source, although secondary person-to-person transmission may occur within small communities or families.[6,7]

In our study, patients who became sick in the second place had a more severe clinical course. This may be associated with virulence factors, the mode of transmission or a greater amount of inoculum.

Children with typical HUS and central nervous system, gastrointestinal or myocardial involvement have a higher morbidity and mortality rate during the acute phase of HUS.[8-10]

Between 20% and 30% of patients have long-term kidney sequelae, including proteinuria, high blood pressure, and a reduced glomerular filtration rate.[2,10-12]

Several studies have attempted to establish predictors of a poor prognosis in terms of mortality and kidney disease progression in patients with typical HUS.[8,9]

The studies conducted by Oakes et al. in 2006 and 2008 demonstrated that leukocytosis and mild anemia at the time of admission to the hospital were associated with mortality, and the duration of oliguria and/or anuria were predictors of kidney morbidity in the long term.[8,9]

In endemic regions, many family cases of HUS are caused by the Shiga toxin. Cases occurring in the second sibling appeared within 4 weeks in 3.4% of studied families in Utah, USA.[13]

Prior studies reported that strains of STEC O157 caused sporadic typical HUS cases in Argentina, and that different members of the same family became infected with symptomatic or asymptomatic STEC. Signs of infection were observed in 31.6% of members of studied families, and parents had a higher infection rate than siblings.[6]

Given STEC's incubation period (median: 8 days), it is very difficult to establish a difference between co-primary cases and secondary transmission across family members with a history of common exposure.

A retrospective cohort study assessed a STEC O157 outbreak in South Wales and the United Kingdom in the fall of 2005 and observed that the presence of a sibling and a difference in age of less than 5 years with the primary case were independent predictors for families with secondary cases. It was also demonstrated that hospitalization of STEC cases reduces the risk of household transmission.[14]

Family cases of HUS have been reported to be associated with genetic mutations or acquired deficiencies in complement regulation. This type is called atypical HUS; it is usually recurrent and, in general, is not related to exposure to the Shiga toxin, although some families with observed mutations in the complement system had a concomitant STEC infection which had triggered HUS.[15]

Our study poses several limitations, including its retrospective design and the small number of sibling pairs included. However, our results show the prevalence of typical HUS among siblings in the studied period and population. The course of the second case may be more severe.

We believe that, in the case of typical HUS diagnosis, it is necessary to provide close epidemiological surveillance of the siblings of children with HUS. ■

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