

## **Measles and rubella antibody status in children after treatment for acute lymphoblastic leukemia**

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### **Abstract**

**Objective:** To assess the vaccination history and the status of vaccine-induced protection from measles and rubella in children after treatment for acute lymphoblastic leukemia.

**Methods:** Measles and rubella immunological status was assessed by the ELISA technique for 22 children previously treated for acute lymphoblastic leukemia.

**Results:** From the total of 22 patients, 20 had been given two doses of measles vaccine and 18 had had one dose of rubella vaccine. The percentage of patients seropositive for measles and rubella were 65 and 88.9%, respectively, with no correlation with age of patient, aggression of treatment or the time passed between the end of treatment and sample collection.

**Conclusions:** We detected that vaccination had failed against measles and rubella in 35 and 11.1% of cases, respectively. We recommend that a measles booster be given after the completion of treatment for acute lymphoblastic leukemia and that rubella immunity status should be assessed at this point, with revaccination performed when necessary.

*J Pediatr (Rio J). 2006;82(6):481-4: Immunization, immunosuppression, chemotherapy.*

### **Introduction**

Specific immunoresponse abnormalities, both cellular and humoral, have been detected in around 80% of children after conventional treatment for malignant neoplasms, including acute lymphoblastic leukemia (ALL).<sup>1</sup> The underlying disease and the treatment itself both result

in significant immunosuppression, which can remain even after white blood cell counts have returned to normal.<sup>2</sup>

Assessment of the immune status of these patients with reference to common childhood diseases, after completion of their treatment, is a subject that, while relevant, has received little study. Such assessment allows the immunological status of these children to be investigated through their serological status for diseases against which they have previously been immunized. It is on this analysis that recommendations on the immunization of these patients will be based, since the ideal revaccination schedule is still the subject of discussion.<sup>3</sup>

In this study we assess the impact that treatment for ALL has on vaccine-afforded protection against measles and rubella and we also verify whether or not it is necessary to revaccinate these patients at the end of their treatment.

### **Methods**

Twenty-two patients who had completed treatment for ALL between September 1999 and August 2002 were assessed. Twelve patients received treatment according

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Manuscript received Dec 29 2005, accepted for publication Jun 26 2006.

**Suggested citation:** Volc SM, Almeida MT, Abadi MD, Cornacchioni AL, Odone Filho V, Cristofani LM. Measles and rubella antibody status in children after treatment for acute lymphoblastic leukemia. *J Pediatr (Rio J)*. 2006;82:481-4.

to a high risk program, and 10 patients were treated according to a low risk program. All had completed anti-leukemia treatment and were in complete remission from the disease.

A 6 mL blood sample was collected from each patient and centrifuged at 3,000 rpm for 15 min, separated into 500 µL aliquots and stored at -20 °C.

At the end of the collection phase, serology was run for rubella and measles by the ELISA (enzyme-linked immunosorbent assay) method.<sup>4</sup> Serological tests for rubella were run using a commercial kit, Enzygnost® Anti-Rubella-Virus/IgG (Dade-Behring).

Efficacy of measles vaccination was assessed by measuring immunoresponse by means of seroconversion titers or from the geometric mean of post-vaccination sample titers.<sup>5</sup>

## Results

The 22 children suffering from ALL were assessed. Age at assessment varied from 4 years and 7 months to 17 years and 7 months, with a median of 8 years. The mean time since completion of treatment was 13 months, varying from 1 to 36 months.

We observed that all 22 patients' vaccination histories included the first dose of measles vaccine, which is compulsory throughout Brazil.<sup>6</sup> The same was not true of

the second measles vaccine dose, since two patients had not received it; the rubella vaccine had not been given to four patients. Thus, 4/22 (18.2%) patients analyzed had not followed the vaccination schedule correctly, while the vaccination histories of 18/22 (81.2%) were adequate. Table 1 shows the vaccination and serological status of the patient sample.

When we assessed the patients' humoral immunity to measles, we observed that 20/22 patients had been given two doses of the measles vaccine. In this group, 13/20 (65%) exhibited positive serology for measles, and 7/20 (35%), negative serology. Just 2/22 patients received only one dose of the measles vaccine and serology was positive for one of these patients and negative for the other. There was no significant difference in terms of measles immune status between the group who had received one and the group given two doses, according to Fisher's exact test ( $p = 0.135$ ), although we emphasize that the number of patients who had only had one dose was small.

With relation to specific immunity against rubella, 18 (81.9%) cases had had the vaccine and four (18.2%) had not been vaccinated. Sixteen (88.9%) of the 18 vaccinated patients exhibited positive serology and two (11.1%) negative. Two of the four cases who had not been vaccinated against contra rubella exhibited positive serology for the disease and two were negative.

**Table 1** - Age, time since end of treatment, vaccination history and serology results for the patients studied

| Patient | Age at diagnosis | Time off chemotherapy | 1 dose measles vaccine | 2 doses measles vaccine | Rubella vaccine | Measles serology | Rubella serology |
|---------|------------------|-----------------------|------------------------|-------------------------|-----------------|------------------|------------------|
| 1       | 2 yrs 3 m        | 24 m                  | +                      | +                       | +               | +                | +                |
| 2       | 2 yrs 6 m        | 26 m                  | +                      | +                       | +               | +                | +                |
| 3       | 3 yrs            | 6 m                   | +                      | +                       | +               | -                | +                |
| 4       | 1 yr 5 m         | 30 m                  | +                      | +                       | +               | +                | +                |
| 5       | 3 to 7 m         | 15 m                  | +                      | +                       | +               | +                | +                |
| 6       | 4 yrs 7 m        | 1 m                   | +                      | -                       | -               | +                | +                |
| 7       | 4 yrs 2 m        | 21 m                  | +                      | +                       | +               | +                | +                |
| 8       | 2 yrs 2 m        | 16 m                  | +                      | +                       | +               | +                | +                |
| 9       | 1 yr 6 m         | 36 m                  | +                      | +                       | -               | -                | -                |
| 10      | 1 yr 6 m         | 16 m                  | +                      | +                       | +               | +                | +                |
| 11      | 4 yrs 10 m       | 2 m                   | +                      | +                       | +               | +                | +                |
| 12      | 1 yr 11 m        | 5 m                   | +                      | +                       | +               | +                | -                |
| 13      | 10 yrs           | 9 m                   | +                      | -                       | -               | -                | -                |
| 14      | 2 yrs 6 m        | 10 m                  | +                      | +                       | +               | +                | +                |
| 15      | 7 yrs            | 8 m                   | +                      | +                       | +               | +                | +                |
| 16      | 1 yr 9 m         | 5 m                   | +                      | +                       | +               | -                | +                |
| 17      | 15 yrs           | 8 m                   | +                      | +                       | -               | +                | +                |
| 18      | 7 yrs 4 m        | 5 m                   | +                      | +                       | +               | +                | +                |
| 19      | 1 yr 9 m         | 4 m                   | +                      | +                       | +               | -                | +                |
| 20      | 7 yrs            | 4 m                   | +                      | +                       | +               | -                | +                |
| 21      | 2 yrs 5 m        | 10 m                  | +                      | +                       | +               | -                | +                |
| 22      | 3 yrs            | 29 m                  | +                      | +                       | +               | -                | -                |

We used the Mann-Whitney non-parametric test to assess the effect of the age of patients at disease diagnosis on the results of serology, observing that there was no significant difference between the groups with positive and negative serology, either for measles ( $p = 0.6569$ ) or for rubella ( $p = 0.7655$ ).

We also verified whether there would be a correlation between the time passed since the end of treatment and collection of samples and the results of serology. According to the Mann-Whitney non-parametric test there were no differences between groups, whether for measles ( $p = 0.7323$ ), or for rubella ( $p = 0.2862$ ).

Comparing the patients treated on the more intensive (high risk) program with those treated on the basic risk program, we found that there was no association between the aggressiveness of treatment and the serological results observed, either for measles ( $p = 0.274$ ) or for rubella ( $p = 1.000$ ).

### **Discussion and conclusions**

On completion of antineoplastic treatment, children who have had cancer return to all the activities normal for their age group. During this phase, recognition of the immunological status of these children, particularly in terms of protection from common childhood diseases, becomes relevant. Nevertheless, there is no consensus on the measures that should be taken and references to the subject in published literature are scarce.

Feldman et al. assessed 39 previously vaccinated children, before and after chemotherapy. At leukemia diagnosis, positivity for IgG specific to measles was over 90% and, for rubella, it was 85%. After treatment, seropositivity rates for measles dropped by 13% (from > 90 to 77% seropositive) and by 21% for rubella (from 85 to 64% seropositive). These authors consider that leukemia treatment is the greatest contributor to the loss of antibodies, since at diagnosis levels were close to those observed in the normal population.<sup>7</sup>

Nilsson et al. assessed 43 children who had completed treatment for ALL, all of whom had been vaccinated against measles and rubella. They found just 60% seropositivity for measles and 72% for rubella; levels below those expected for the healthy population. They suggested that all children be revaccinated at the end of treatment.<sup>8</sup>

Brodman et al. observed 52% positivity for measles and 76% for rubella among 99 children treated for ALL and off therapy for 1 year.<sup>9</sup>

In our study we observed that 65% of the children had maintained adequate measles antibodies after completion of treatment, which is very similar to the results reported by the authors cited above. Nevertheless, positivity of

60-65% is well below the 95-99% seroconversion after the basic measles vaccination schedule expected for the healthy general population,<sup>10</sup> and means that more than 25% of our patients were vulnerable to measles.

This reduction in seropositivity rates is probably the result of the loss of protective antibody that had been induced by previous vaccination during leukemia treatment, as described by Feldman et al.<sup>7</sup> In our study this statement is an inference since we are limited by the fact that antibodies against measles and rubella were not assayed at leukemia diagnosis, which would have allowed us to compare baseline positivity with that at the end of treatment, confirming the loss of antibodies. Other authors have also suggested that the loss of antibodies is induced both by the underlying disease and by antineoplastic treatment, being more intense the more aggressive the treatment employed.<sup>11</sup> In this study, however, the aggressiveness of treatment did not influence positivity of immunity to measles or rubella. Nor was there any correlation between the age of patients at diagnosis of leukemia and seropositivity, or between seropositivity and the time passed between the end of treatment and sample collection.

Despite the low levels of measles antibodies observed in 35% of our ALL survivors, we did not observe any cases of the actual disease.

In view of the considerations above, we recommend that patients who complete treatment for ALL be revaccinated against measles, since the epidemiological status of this disease in our country, while under control, has not yet been resolved. The measles virus has not been eradicated from all countries, and there is a risk of fresh epidemics, if regional ones.

Our assessment of vaccine-induced protection against rubella revealed high rates of maintenance of protection (88.9%), which leads us to suggest the investigation of rubella antibody serology after completion of treatment for ALL and the revaccination of unprotected individuals only.

Immunization guides only exist for bone marrow transplantation patients.<sup>12</sup> Mahajan Assessed the vaccination policy for children given antineoplastic treatment at 15 child cancer treatment centers. All of the centers suspended immunization during treatment and restarted from 6 to 12 months after completion. Patients whose basic vaccinations were not complete were not vaccinated at 11 of the centers, two centers repeated the entire basic vaccination course (DPT/DT, OPV, HiB and triple viral vaccine) and two centers gave boosters of DPT, OPV, HiB and the triple viral vaccine.<sup>13</sup>

As we have observed, the conduct of immunizations with conventional chemotherapy patients is controversial. In the face of the level of aggression of current

chemotherapy protocols, we recommend measles booster vaccination for all children with ALL after completion of treatment. Each patients' serological status should be assessed separately for rubella, with vaccination of unprotected patients.

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