Varicella at "Casa Garrahan", 2008-2013. Assessment of post-exposure prophylaxis measures

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ABSTRACT

Introduction. Casa Garrahan (CG) accommodates children with complex conditions referred nationwide; these children are seen in children´s hospitals located in the Autonomous City of Buenos Aires. Varicella is a highly-contagious disease, with attack rates of up to 90% among susceptible individuals. In closed communities, the implementation of outbreak control measures is critical.

Objectives. To describe the characteristics of children exposed to varicella at CG, the implemented prophylaxis measures and their effectiveness.

Methods. Prospective, cohort study. Children exposed to varicella at CG between 2008 and 2013, their demographic and clinical characteristics, immunization and/or history of varicella, prophylaxis measures, and secondary attack rate were assessed.

Results. N: 107. Fifty-three percent (n: 57) were girls. Their median age was 84 months old [interquartile range (IQR): 24-144]. Ninety-five percent (n: 102) had an underlying disease [hemato-oncological disease: 39% (n: 42); neurological disease: 18% (n: 19); congenital heart disease: 9% (n: 10); and post-operative period: 65 (n: 6)]. Fifty percent had some degree of immunosuppression (n: 54). Twenty-nine percent (n: 31) referred to have had varicella; 27% (n: 29) indicated that they never had the infection; and 41% (n: 44) did not recall a history of varicella. Only 3% (n: 3) had been vaccinated. Based on their immune status, age and history of varicella, acyclovir was indicated as prophylaxis in 61% (n: 65); immunization in 10% (n: 10); and gamma globulin in 1 patient. No adverse effects were observed in relation to the different prophylaxis measures. No secondary cases were observed at 30 days.

Conclusions. Implemented measures were effective to prevent secondary cases. Among healthy and immunocompromised children, prophylaxis with acyclovir was effective and well-tolerated.

Key words*: varicella, post-exposure prophylaxis, acyclovir.*

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INTRODUCTION

Varicella zoster virus (VZV) infection is a common cause of pediatric consultation. The rate of secondary attack is over 90%. Patients with immunosuppression, chronic obstructive pulmonary disease, skin conditions or receiving long-term salicylate therapy may develop severe forms of varicella with a higher risk of morbidity and mortality. In these cases, post-exposure prophylaxis is recommended. There are different prophylaxis strategies: VZV immunization, specific or hyperimmune gamma globulin, or acyclovir.[1]

The measure of choice is active immunization for patients who can be vaccinated. Gamma globulin is used in immunocompromised patients. The use of post-exposure acyclovir has been reported both in immunocompetent[2] and immunocompromised[2,3] hosts. Different experiences regarding varicella outbreaks have been published; however, in our setting, information in relation to daycare centers and closed communities is scarce.[4,5]

Casa Garrahan (CG) is an institution where children who live more than 100 km from the City of Buenos Aires and their mothers can be accommodated. These children are seen at the following children's hospitals: "Prof. Dr. Juan P. Garrahan", "Dr. Pedro de Elizalde" and "Ricardo Gutiérrez", either as outpatients or to undergo procedures for complex conditions that do not require hospitalization. Most patients have significant comorbidities and receive immunosuppressive therapy. CG is located in a three-story building. It has 46 rooms with private bathrooms for each family group, a shared kitchen, living room, playroom, computer room, a library, laundry and playgrounds. Patients and their mothers share com-

mon areas (halls, stairs, kitchen and dining room) and recreational activities organized by the institution. Every year, CG receives more than 1200 children referred from other Argentine provinces to be seen at different hospitals because of their complex conditions. They usually have comorbidities or are receiving immunosuppressive therapy. For this reason, and in the light of exposure to contagious diseases, it is essential to focus on prevention and an adequate management.

The objective of this study was to describe the characteristics of children exposed to varicella at CG between 2008 and 2013, the implemented prophylaxis measures and their effectiveness.

MATERIAL AND METHODS

This was an observational, descriptive and prospective cohort study. For every case of varicella at CG, demographic and clinical characteristics and the history of clinical varicella or immunization against VZV were prospectively recorded for all patients exposed to the index case using a database property of the Department of Epidemiological Control and Infectology. Patients were considered exposed if they had been staying at CG in the 48 hours prior to the onset of the index case and up to 4-7 days after or until all lesions turned to scabs. All cases of children exposed to varicella between January 1st, 2008 and December 31st, 2013 were recorded. An algorithm was designed based on international recommendations[2,6] and published studies[2,3] on how to manage people who came into contact with varicella (*Figure 1*). Although post-exposure prophylaxis has been proposed for immunocompromised patients with no history of varicella or immunization against VZV, based on the measures implemented in a closed community of patients in daily and close contact with the hospital, post-exposure prophylaxis was indicated to all immunocompromised patients (with primary immunosuppression or receiving immunosuppressive therapy in the past three months: corticosteroids, chemotherapy, immunemodulators, etc.) regardless of their history of varicella given the risk of reinfection reported in this group.[7]

The Department of Epidemiological Control and Infectology of Hospital "Prof. Dr. J. P. Garrahan" documented the prophylaxis measure implemented in each case and was in charge of follow-up at 30 days of exposure to the index case.

Each case was assessed in the first 24 hours of onset of lesions compatible with varicella in the index case, planning the right time to implement measures based on the adequate type of prophylaxis.

All varicella cases were considered hosts with risk of disseminated varicella, so they were hospitalized for management with IV acyclovir. Admission of new patients to CG was not restricted.

A cohort was established with patients who had been exposed and stayed at CG. Exposed children were located in two of CG's stories, and the third floor was reserved for new patients susceptible to varicella who arrived at CG in the 21 days following the index case outbreak or 28 days when one of the contacts received post-exposure gamma globulin.

Inclusion criteria to receive acyclovir chemoprophylaxis: 1) having shared CG with the varicella index case during the disease transmission period; 2) immunocompromised patients (with primary immunosuppression or receiving immunosuppressive therapy in the past three months: corticosteroids, chemotherapy, immunomodulators, etc.) with or without a history of varicella or immunization against VZV; 3) immunocompetent patients younger than 1 year old with no history of varicella.

Exclusion criteria to receive acyclovir chemoprophylaxis in immunocompetent patients: 1. history of varicella; 2. having received at least one dose of VZV vaccine in the five days prior to exposure; 3. infants younger than 3 months old whose mothers had a history of varicella. Exclusion criterion in immunocompromised patients: having received IV gamma globulin for any other indication in the 21 days prior to contact.

Oral acyclovir at a dose of 80 mg/kg/day was used as of the fifth day of contact and for seven days.

Gamma globulin was indicated only to patients with bone marrow transplant, considering both the time elapsed since the transplant and the patient's present clinical condition, and the decision was made together with the treating medical team.

Ethical principles for health research were followed to record data and prepare the manuscript containing this study's epidemiological results. Infectious assessment and post-exposure prophylaxis measures implemented in the observation period were performed on the basis of a consensus with the treating team, published studies and recommendations in force. No experimental

therapeutic interventions were conducted. Epidemiological results were published protecting patients' identity.

RESULTS

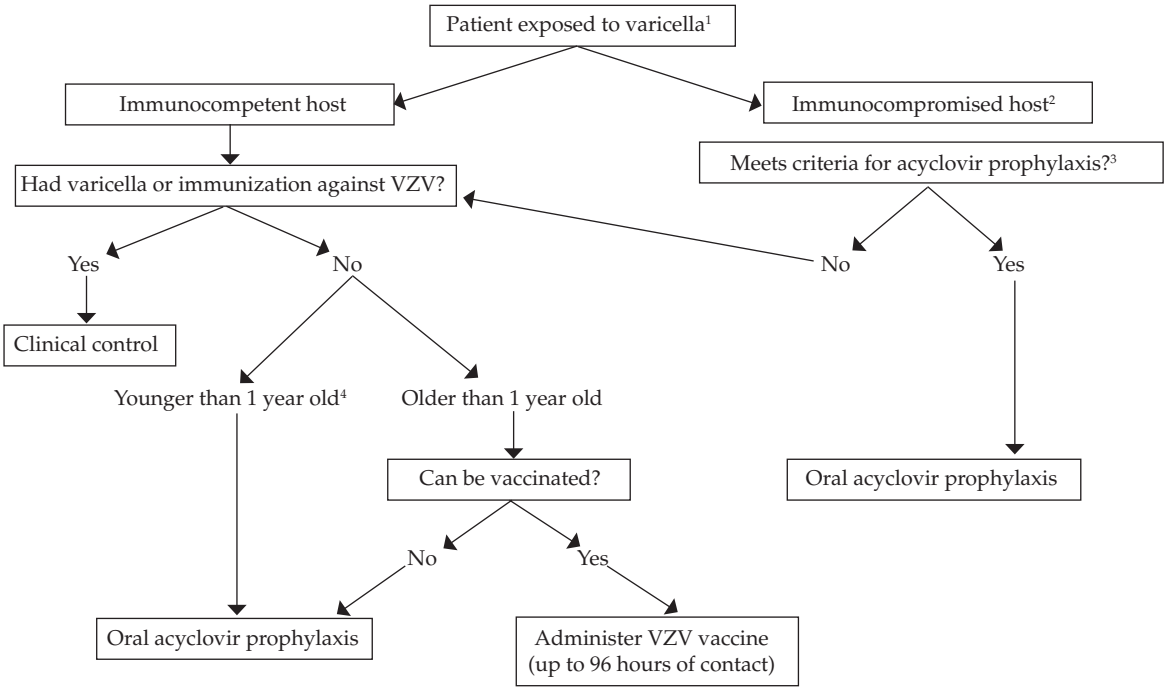
In the years included in the analysis, there were four unrelated cases of varicella among children staying at CG: in June 2008, November 2009, October 2010, and September 2013. A total of 107 patients were exposed to the four cases that presented (*Table 1*). Fifty-three percent (n: 57) were girls. The median age of exposed children was 84 months old (interquartile range [IQR]: 24-144). Ninety-five percent (n: 102) had an underlying disease. The most common comorbidities were hemato-oncological disease: 39% (n: 42); neurological disease: 18% (n: 19); congenital heart disease: 9% (n: 10); and post-operative period: 6.5 (n: 6). Fifty percent of exposed children had some degree of immunosuppression (n: 54). Forty-one percent (n: 44) were receiving chemotherapy; 8.4% (n: 9) were receiving corticosteroids; and one patient had received biologic immunomodulators.

The history of varicella was determined by questioning parents. Twenty-nine percent of exposed patients recalled having had varicella (n: 31). Twenty-seven percent (n: 29) referred that they never had the disease; and 41% (n: 44) did not recall a history of varicella.

Among exposed children, only 3% (n: 3) had been vaccinated against VZV.

Post-exposure prophylaxis was established as per the algorithm shown in *Figure 1*. Prophylaxis was indicated based on analyzed patients' age, history, underlying disease, type of treatment received and immune status.

FIGURE 1. *Algorithm for managing patients exposed to varicella in a closed community*



[1] Home contact: living in the same place; playmates: face-to-face contact for, at least, 5 minutes in the 48 hours before onset of rash and up to 4-7 days after or until all lesions turn to scabs.[1]

[2] Gamma globulin was indicated only to patients with bone marrow transplant, considering both the time elapsed since the transplant and the patient's present clinical condition, and the decision was made together with the treating medical team.

[3] Inclusion criteria to receive acyclovir in immunocompromised hosts: 1) having shared CG with the varicella index case during the disease transmission period; 2) having primary immunosuppression or receiving immunosuppressive therapy in the past three months (corticosteroids, chemotherapy, immunomodulators, etc.) with or without a history of varicella or immunization against VZV. Exclusion criterion to receive acyclovir in immunocompromised patients: having received IV gamma globulin for any other indication in the 21 days prior to contact.

[4] No post-exposure prophylaxis was administered to infants younger than 3 months old whose mothers had a history of varicella.

Acyclovir was indicated to 64% of exposed patients (n: 65); most were immunocompromised hosts.

Only 9% (n: 10) of patients received the VZV vaccine following exposure.

No post-exposure prophylaxis was required in one of four patients with bone marrow transplant because he was already receiving gamma globulin on a monthly basis. Together with the treating medical team and considering the time elapsed since the transplant and the individual clinical situation, gamma globulin was administered to one patient, and acyclovir to the other two.

Based on the questions made to parents, 53% (n: 28) of exposed immunocompetent children were considered immune based on their history of immunization against VZV or maternal reference of having had varicella. All patients were controlled during the 30 days following exposure to the index case by the Department of Epidemiological Control and Infectology of Hospital "Prof. Dr. J. P. Garrahan".

No adverse events were observed in relation to the administration of acyclovir, gamma globulin or VZV vaccine.

No new secondary case of varicella developed among exposed analyzed patients.

DISCUSSION

The etiologic agent of varicella is VZV: a highly contagious enveloped DNA virus.[8] It is transmitted through skin lesions and nasopharyngeal secretions from 48 h before the onset of blisters and up to 4-7 days after the onset of rash or until all lesions turn to scabs.[9]

In Latin America, the overall incidence of varicella in individuals younger than 15 years old reported by a meta-analysis is 42.9 cases every 1000 persons per year; children younger than 5 years old account for the most affected age group.[10] Epidemiological studies suggest that transmission is more likely to occur in the early stages of the disease, from 48 hours before the onset of rash. The rate of attack among people who share a household ranges between 80% and 90%,[11] which is a problem in closed communities, especially in susceptible patients and those with a risk of disseminated disease.

Before antiviral agents became available, the rate of varicella mortality was 7% among cancer patients, and 32% suffered disseminated varicella with visceral involvement.[12,13] For patients with a high risk of severe varicella, post-exposure prophylaxis is a need. In addition, in the case of closed institutions such as CG, which are useful

TABLE 1. *Demographic characteristics and type of underlying disease of children exposed to different cases of varicella (n: 107)*

Characteristic	N (%)
Patients exposed to case 1. June 2008	24
Patients exposed to case 2. November 2009	29
Patients exposed to case 3. October 2010	25
Patients exposed to case 4. September 2013	29
Male	50 (47)
Median age in months (IQR)	84 (24-144)
No underlying disease	5 (5)
Underlying disease	
Hemato-oncological*	42 (39)
Neurological disease	19 (18)
Autoimmune disease	3 (3)
Solid organ transplant	5 (5)
Heart disease	10 (9)
Post-operative period	6 (6)
Genetic disorder	4 (4)
Chronic lung disease	4 (4)
Bone marrow transplant	4 (4)
Others**	5 (5)

* Acute lymphoblastic leukemia, n: 20 patients (48%).
** Others: metabolic disease (1), renal failure (1), hemangioma (1), epidermolysis bullosa (2).

for complex patients seeking outpatient care, it is essential to implement post-exposure prophylaxis measures in order to prevent outbreaks and unit closedown. There are three measures which have an impact on the reduction of varicella transmission in case of contact: active or passive immunization and the use of antiviral agents.

The Ministry of Health has established National Immunization Standards that recommend active immunization of patients at risk with no contraindications to VZV vaccine and in case of outbreaks among closed population groups before the fifth day following exposure.[14] This strategy is useful for immunocompetent hosts and children older than 1 year old.[15] Vaccine effectiveness to prevent transmission is close to 90% when administered within 72 h of contact and is effective as prevention up to five days following exposure.[16] In this study, the varicella vaccine was indicated only to 10% of exposed patients because most were children with comorbidities and/or receiving immunosuppresive therapy.

For patients with contraindications to VZV vaccine or when more than five days have elapsed after exposure, acyclovir or valacyclovir is indicated as of day 7 of contact and for seven consecutive days as an alternative to gamma globulin.[1,17] The administration of acyclovir during secondary viremia (7-9 days following contact with the index case) is effective to reduce hematogenous viral spread.[1] There are limited data on prophylactic acyclovir administered to healthy children to support its indication.

In an open-label uncontrolled study conducted by Marcó del Pont, et al.[2] prophylactic acyclovir was administered to 19 susceptible patients exposed to varicella through family members or at daycare centers. The study included seven children with an underlying disease (one case of acute lymphoblastic leukemia and one of liver transplant). This measure prevented or mitigated the disease in 84% of patients. In our study, exposure took place in a different setting. Exposure occurred in a closed institution, and although it meets the definition of contact, here time and type of exposure were probably lower than in the above mentioned study. In both studies, patients were categorized as "presumably susceptible" based on questioning.

Using acyclovir as post-exposure prophylaxis was effective in both series.

A study conducted in Japan[3] assessed the effectiveness of prophylactic acyclovir in cases of nosocomial contact with varicella and herpes zoster. One hundred and seventy-four exposed children were assessed; 79 of them were immunocompromised. Acyclovir was administered to both immunocompromised patients with or without a history of varicella and immunocompetent hosts with no specific immunization or prior disease. This study reported that acyclovir was highly effective to prevent secondary cases.

A recently published review analyzed the effectiveness of different post-exposure prophylaxis measures in immunocompromised

TABLE 2. *Varicella post-exposure measure by type of host and evidence of prior immunity (clinical or through immunization)*

History and indicated prophylaxis		Immunocompetents n (%)	Immunocompromised n (%)
Total	**53 (50)**	**54 (50)**	
History of varicella			
	Referred having had varicella	25 (23)	6 (6)*
	Referred not having had varicella	19 (18)	10 (9)
	Did not know	6 (6)	38 (35)
	Previously vaccinated	3 (3)	-
Measure			
	Acyclovir	15 (14)	50 (47)
	Vaccine	10 (9)	-
	Expectant management	28 (26)	3 (3)
	Gamma globulin	-	1 (1)

* Six immunocompromised patients with a history of varicella: two patients with bone marrow transplant (one received gamma globulin, the other was taking monthly gamma globulin and did not receive chemoprophylaxis); two patients with solid tumors with no chemotherapy in the past three months, who were managed expectantly; and two patients with a recent history of myeloablative therapy, who were indicated acyclovir.

patients and reported that there are few randomized, controlled and adequately designed studies to make a recommendation for this population based on high quality evidence.[18]

In this series, acyclovir was administered to immunocompetent patients only if they could not receive the vaccine because of their age and had no history of varicella. A study conducted by Goldstein, et al. showed the same rate of seroconversion in varicella IgG of exposed patients who received post-exposure acyclovir as in those who did not receive prophylaxis and developed clinical varicella.[19] Acyclovir chemoprophylaxis is not a routine recommendation for this group given the risk of developing antiviral resistance.[20,21]

Similarly to other series that used long-term acyclovir (up to one year),[22] in this study there were no adverse events related to the administration of antiviral agents.

Specific immunoglobulin against VZV has proven to modify varicella's clinical course and prevent or mitigate the disease. Its maximum effect is achieved if administered in the first 96 hours of contact, but it has proven effective up to 10 days following exposure.[23,24] The high cost of specific gamma globulin and its limited availability restrict its use as secondary prophylaxis for immunocompromised patients with a higher risk of severe complications.

Our study's main limitation is that exposed children were categorized as susceptible only through questioning and not through serological confirmation. Given that immunocompromised patients predominated, we focused on early prophylaxis measures to prevent secondary cases and thus ensure that CG would continue functioning normally. In addition, given that this was an observational epidemiological study, patients were not randomized to receive a specific post-exposure prophylaxis measure, therefore it is not possible to compare the measures implemented in the different patient groups (immunocompetent versus immunocompromised).

This study is a record of years of epidemiological surveillance and control of a closed institution with a predominance of patients with immunosuppression and underlying diseases. Although our series has shown the effectiveness of implemented measures, adequately designed studies are required to measure their effectiveness both in immunocompetent and immunocompromised hosts.

CONCLUSIONS

The implemented post-exposure measures were effective to prevent secondary cases. Post-exposure acyclovir prophylaxis was effective and well-tolerated both in immunocompromised children and immunocompetent hosts. ■

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