VARICELLA IN IMMUNOCOMPROMISED CHILDREN AT THE PHILIPPINE GENERAL HOSPITAL : A SIX-YEAR REVIEW

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KEYWORDS
Varicella, Chickenpox, Immunocompromised, Pediatric Cancer, Acyclovir

ABSTRACT

Objective: This research aims to describe the profile, clinical course, treatment and outcome of varicella in immunocompromised children at the Philippine General Hospital from January 1999 to December 2004

Study Population: All immunocompromised patients less than 19 years of age with a clinical diagnosis of varicella admitted at the Philippine General Hospital during the study period were included.

Method: A review of medical records and monthly census reports of the Pediatric Infectious Disease and Hematology-Oncology Services was conducted.

Results: Out of 26 immunocompromised patients who developed varicella during the study period, only 22 charts were available for review. Of these patients, 13 were male and 9 were female. The highest incidence occurred from 0 to 5 years old (41%). Twenty patients had an underlying malignancy in the form of leukemia (14%) and solid organ tumors (6%). Two patients were on chronic steroid therapy (Prednisone) for more than a month due to Nephrotic Syndrome and Myelodysplastic Syndrome with Stevens-Johnson Syndrome. The most common presenting symptom was a rash (68%), with an associated fever seen in 54% of the cases. Majority were treated with acyclovir for an average of 7 days with good response. Nine patients developed complications: mainly, pneumonia and sepsis. Recovery rate was 82%; however, fatality rate was 13.6%.

Conclusion: Varicella in immunocompromised children is associated with increased morbidity and mortality. Our patients responded well to sequential intravenous and oral acyclovir. Vaccination of targeted populations such as close household contacts of immunocompromised patients, as well as, healthcare workers may be a good strategy to protect high-risk children from developing the disease and its complications.

INTRODUCTION

Varicella in the immunocompromised child or adult is a cause of significant morbidity and mortality. Individuals with impaired cell-mediated immunity are slow to develop immunity and are prone to severe disease—with dissemination of the virus to the lungs, liver, and brain.[2, 12] Children with acute leukemia and lymphoma, as well as, those with AIDS or on prolonged corticosteroid treatment, are at greatest risk of developing serious disease.[3] Early diagnosis, together with more intense chemotherapy and radiotherapy of children with malignancies, has greatly increased their survival rate. As a result, varicella has also become a more common problem for them. Moreover, exposure to varicella often results in suspension or delay of scheduled chemotherapy in susceptible persons with malignant disorders and transplant recipients; thus, increasing the risk of progression of their underlying disease or graft rejection.[4]

The standard management of varicella in immunocompromised children is hospitalization and treatment with intravenous acyclovir for 7 to 10 days.[5] Post-exposure prophylaxis with varicella-zoster immune globulin (VZIG) has also been recommended when significant exposure has occurred. Without active or passive immunization, disseminated disease develops in about 30% of immunocompromised children, with a case fatality rate of at least 7%.[6] Thus, unlike in healthy children, management of varicella in immunocompromised patients is more expensive, inconvenient, and with greater medical and socioeconomic consequences.

In the Philippines, varicella has been one of the ten leading causes of morbidity, since 1989. The Philippine Health Statistics of 2001 reported 35,306 cases or a rate of 45.3 per 100,000 population.[8]

The epidemiology of primary varicella infection is said to differ between tropical and temperate countries. In temperate countries such as Japan and the United States, seropositivity was achieved between the ages of 10 – 13 years; where 98% – 100% of the population have been found to be already serologically immune to VZV infection. In contrast, in a study done in 1994 by Barzaga, et. al. among Metro Manila residents, prevalence rate in the age group 5 years and below was 30%; and only 55% of 10 to 15 year olds were found to be seropositive.[9] This approximates that of other Asian countries like India. The same study noted that 95% of varicella occurred by the age of 35, which was consistent with observations that in tropical areas such as the Philippines, primary VZV infection is usually delayed compared to countries in temperate regions. In another local study by Yason, out of 50 children admitted for varicella over a five-year period, children 5 years old and below comprised 64% of the population.[10] 88% of admissions were children without underlying disease prior to varicella infection; with only one case of chickenpox seen in a child with rhabdomyosarcoma.

Locally, there have been no studies done on varicella in immunocompromised children. Thus, this study was undertaken to come up with local data regarding the clinical features, laboratory profile, treatment and outcome of varicella in this population of Filipino children. The information obtained from this study could also provide added impetus to recommend routine varicella immunization to healthy children, as a strategy for protecting the more vulnerable segment of the pediatric population through vaccine-induced herd immunity. At the very least, it could highlight the value of immunizing close household contacts, as well as, healthcare workers who are in constant contact with these patients in a hospital setting.

Case Definitions:

The diagnosis of varicella (chickenpox) was based on the characteristic generalized papulovesicular rash. For purposes of this study, the attending physician's clinical diagnosis of varicella was accepted since no viral cultures or serologic tests were done to confirm the diagnosis.

Immunocompromising condition was defined as any congenital or acquired immunodeficiency, malignancy, or receipt of corticosteroids or chemotherapy within 30 days before the onset of varicella.

Varicella-associated complication was defined as a condition or event occurring within 14 days of onset of varicella, and to which varicella-zoster virus infection may have contributed in some measure.

MATERIALS AND METHODS

Study Population:

All immunocompromised Filipino patients aged 0 month to less than 19 years, who fulfilled the criteria described below and admitted at the Philippine General Hospital from January 1, 1999 to December 31, 2005 were included in this retrospective study. The patients studied were

those who were diagnosed to have varicella and with the following immunocompromised state/s:

a. Malignancies undergoing chemotherapy and/or radiotherapy;
b. Congenital or acquired T-cell immunodeficiency;
c. Up to one year after bone marrow transplantation;
d. After solid organ transplants and on immunosuppressive drugs;
e. On chronic high dose steroids (>2 mg/kg/day or 20 mg/day of Prednisone or its equivalent if weight >10 kg) for 14 days or more.

Patients were excluded if they had herpes zoster, or had with incomplete medical records, patients with chronic illnesses or immunocompromised states, other than those mentioned above or were immunocompetent pediatric patients admitted due to complications of varicella.

Data Collection:

The data for this study was initially gathered from entries in the logbooks and monthly census reports of the Pediatric Infectious Disease and the Pediatric Hematology-Oncology services from January 1, 1999 to December 31, 2004.

Cases were likewise identified through a computerized search of hospital discharge records with the International Classification of Diseases, 10th revision (ICD-10), code of B01 (Varicella).

A chart review of all cases was then done to fulfill the inclusion criteria. The following information were taken and recorded in a data case form:

1. demographic variables (name, age, sex, nutritional status, exposure);
2. clinical features (onset of symptoms, presenting sign or symptom, extent of skin lesions, associated signs and symptoms);
3. underlying disease or immunocompromised state (type of malignancy, phase of anticancer treatment, interval between last treatment and development of varicella, indication, dose and duration of steroid treatment);
4. laboratory findings (WBC count, absolute neutrophil count, absolute lymphocyte count, other laboratory results);
5. treatment given (dose, route and duration of antiviral therapy, prophylaxis with varicella-zoster immune globulin, other medications);
6. outcome (complications, length of hospital stay, case fatality rate).

STATISTICAL ANALYSIS

Data were summarized using frequency tables and percentages. Differences in frequencies or rates were assessed with Fisher's Exact Test or Chi-square analysis. A p value of < 0.05 was considered statistically significant.

Scope and Limitation of the Study

The study only involved admitted patients based on the medical records and monthly census reports of the Pediatric Infectious Disease and Hematology-Oncology Services of the Philippine General Hospital from January 1999 to December 2004. No cases of varicella that fulfilled the inclusion criteria were recorded from 1998 and earlier, limiting the study to only six years.

RESULTS

Out of a total of 4,534 pediatric patients with cancer and admitted to the Philippine General Hospital pediatric wards and Cancer Institute from January 1, 1999 to December 31, 2004, varicella occurred in 24 patients: giving an incidence rate of 0.53%. Yearly incidence over the six-year study period varied from 0 to 1.14%.

The study population consisted of 26 immunocompromised hospitalized patients on whom a clinical diagnosis of varicella was made, but only 22 charts were available for review (84.6% retrieval rate). The charts of the 4 other patients could not be located, while the study was being done. These included 3 patients with acute leukemia and a 3-year old boy with Wilm's tumor. Notably, the 2 patients with Acute Lymphoblastic Leukemia (ALL) were recorded as mortalities due to sepsis.

Demographic Profile

There were 13 males and 9 females with a male to female ratio of 1.4:1. The mean age was 8.85 $\pm$ 4.91 years (mean $\pm$ SD) (range of 1.7 to 17.4 years). Nine patients were aged 0 – 5 years comprising 41% of the cases (Table 1).

Only 4 of the 22 children had a known exposure to chickenpox. 2 of these children were exposed to siblings at home, while the other two were nosocomial transmissions from index cases in adjacent hospital beds. (Table 2). There was one case of recurrence of varicella, wherein the patient claimed to have had the first episode, 7 years prior to the present admission. None of the patients had ever received a varicella vaccine.

Underlying Disease or Immunocompromised State

20 children or 90.9% had an underlying malignancy, while 2 patients or 9.1% were receiving corticosteroids: one for Nephrotic Syndrome; and one for Myelodysplastic Syndrome complicated with Stevens-Johnson Syndrome. The former was also on his third month of treatment for pulmonary tuberculosis. Both patients were being maintained on Prednisone at 1 to 1.3 mg/kg/day, for more than a month prior to the development of varicella.

The primary disease in 14 or 64% of the patients was Leukemia—the most common type being Acute Lymphoblastic Leukemia (ALL) which occurred in 8 subjects. Solid organ tumors (rhabdomyosarcoma, yolk sac tumor, nasopharyngeal carcinoma and brainstem glioma) were seen in 6 or 27% of the patients (Table 3).

Eleven patients were on the maintenance phase of anti-cancer treatment. In 16 children, chemotherapy was administered 17.5 + 11.6 days (range 3 to 40 days) before the onset of infection (Table 4).

Clinical Features

Majority of patients (18/22) were admitted within a week or less from the onset of symptoms of varicella, with a mean of 2.95 $\pm$ 1.84 days. 3 patients developed the typical vesicular rash during the first three days of their confinement. 1 patient was apparently exposed to a case of varicella in an adjacent bed and had developed a rash on his 82nd hospital day. Unfortunately, there was no data indicating when the exposure occurred. Symptoms often lasted for more than a week, with a mean of 9.64 $\pm$ 3.4 days (Table 5).

The most common presenting symptom was a rash in 68.2% of the subjects, frequently accompanied by fever. The rash was described as generalized, vesicular and pruritic: starting from the scalp and trunk, then spreading to the

Table 1. Distribution of Subjects as to Age and Sex

Age and Sex	No.	%
Sex		
Male	13	59.1
Female	9	40.9
Age in Years	8.85 ± 4.91	
0 - 5	9	40.9
6 - 10	4	18.2
11 – 15	6	27.3
16 – 19	3	13.6

Table 2. Distribution of Subjects as to Exposure, and Relationship to Source

Exposure, Source and Relationship	No.	%
Exposure and Source		
Yes	**4**	**18.2**
Home	2	9.1
Hospital	2	9.1
Unknown	**18**	**81.8**
Relationship		
Siblings	2	9.1
Adjacent hospital bed	2	9.1
Unknown	18	81.8

Table 3. Distribution of Subjects as to Type of Malignancy

Type of Malignancy	No.	%
No Cancer (Chronic steroid use)	2	9.1
Acute Lymphoblastic Leukemia (ALL)	8	36.4
Acute Myelogenous Leukemia (AML)	5	22.7
Chronic Myelogenous Leukemia (CML)	1	4.5
Rhabdomyosarcoma	3	13.6
Nasopharyngeal Carcinoma	1	4.5
Yolk Sac Tumor	1	4.5
Brainstem Glioma	1	4.5

extremities, face, head and neck. Some patients had vesicular lesions on their oral/buccal mucosa, as well as, in the anogenital region.

Table 4. Distribution of Subjects as to Phase of Anti-Cancer Treatment and Interval between Last Treatment and Development of Varicella

Phase of Treatment and Interval	No.	%
Phase of Anti-Cancer Treatment		
Induction	6	27.3
Maintenance	11	50.0
Re-intensification	1	4.5
No information	2	9.1
Not applicable (no cancer)	2	9.1
Interval between last treatment and development of varicella	17.5 ± 11.62 days	
1 week or less	5	22.7
more than 1 week	11	50.0
No information	4	18.2
Not applicable (no cancer)	2	9.1

Table 5. Onset of Symptoms Prior to Admission and Duration of Symptoms of Varicella

Onset and Duration of Symptoms	No.	%
Onset of Symptoms Prior to Admission	2.95 ± 1.84 days	
1 week or less	18	81.8
more than 1 week	1	4.5
In the hospital when varicella developed	3	13.6
Duration of Symptoms	9.64 ± 3.40 days	
1 week or less	4	18.2
more than 1 week	18	81.8

One patient was described to have ocular lesions. The size and approximate number of lesions were not described, except in one patient whose lesions were noted to be 5 to 10 mm in diameter. Crusting was observed in about 10 days. Fever ranged from 37.8° C to 40° C, and lasted between 1 to 7 days. Other associated symptoms included anorexia, abdominal pain, cough and colds, body malaise, vomiting and odynophagia (Table 6).

Table 6. Distribution of Subjects as to Signs and Symptoms

Signs and Symptoms	No.	%
Presenting Signs and Symptoms		
Fever only	3	13.6
Rash only	15	68.2
Fever and Rash	4	18.2
Associated Signs and Symptoms		
Fever	12	54.5
Anorexia	3	13.6
Epigastric/Abdominal pain	3	13.6
Body malaise	1	4.5
Vomiting	1	4.5
Odynophagia	1	4.5
Cough and colds	3	13.6

Laboratory Features

The mean WBC count was 10.63 + 16.82 x 10^9/L. 9 patients or 40.9% had neutropenia, while 1 patient had lymphopenia (lymphocyte count < 0.2 x 10^9/L). 6 patients (27.3%) had severe lymphopenia (absolute lymphocyte count <500 cells/µl) (Table 7). The lowest lymphocyte count was noted at 25 cells/µL, in a 5 year old boy with ALL and who manifested seizures and developed nosocomial pneumonia. CSF studies done on this patient were normal.

Blood culture was done in 13 patients, one of whom was found to be positive for *Klebsiella pneumoniae* and two, for *Alkaligenes faecalis*. Urine culture was negative in 5 out of 7 patients as well.

Chest x-rays done showed evidence of pneumonia in 4 patients, one of whom also had a pleural effusion, which required thoracentesis and chest tube thoracotomy. This patient eventually died of septic shock, but no organism was isolated from the blood or pleural fluid. 1 patient grew *Pseudomonas aeruginosa* and *Acinetobacter* from culture of endotracheal aspirate. This was a patient who had been intubated for 2 months due to dysautonomia, secondary to brainstem glioma. Blood and urine cultures from this patient yielded *Alkaligenes faecalis* and *Klebsiella*, and *Proteus* respectively (Table 8).

A Tzanck smear was done in one patient, who developed infected skin lesions; but it was negative for multinucleated giant cells.

No viral cultures, serologic tests or antigen testing was done for any of the patients in this study.

Table 7. Distribution of subjects as to WBC and Differential Count

	No.	%
WBC Count	10.63 ± 16.82 x 10^9/L	
< 5 x 10^9/L	9	40.9
5 - 10 x 10^9/L	8	36.4
> 10 x 10^9/L	5	22.7
Differential Count		
PMN	0.53 ± 0.29 x 10^9/L	
< 0.50	9	40.9
0.50 - 0.70	5	22.7
> 0.70	8	36.4
Lymphocytes	0.29 ± 0.23 x 10^9/L	
< 0.20	11	50.0
0.20 - 0.40	6	27.3
> 0.40	5	22.7
Absolute Neutrophil Count	7369.85 ± 14617.47 cells/µl	
0 - 500	4	18.2
501 - 1000	1	4.5
> 1000	17	77.3
Absolute Lymphocyte Count	1955.17± 2129.48 cells/µl	
0 - 500	6	27.3
501 – 1000	3	13.6
> 1000	13	59.1

Treatment

Specific antiviral therapy in the form of acyclovir was administered to 21 out of 22 patients. 1 patient, upon diagnosis of varicella,

was not given any treatment because his parents decided to bring him home against medical advice. This was an 11-year old boy with brainstem glioma and dysautonomia, who developed varicella on his 82nd hospital day. He was also treated with multiple antibiotics for two bouts of gram negative nosocomial sepsis.

Table 8. Distribution of subjects as to Laboratory Tests done

Laboratory Tests	No.	%
Blood Culture	13	59.1
Negative / no growth	9	40.9
Klebsiella pneumoniae	1	4.5
Alkaligenes *faecalis*	2	9.1
No information	1	4.5
Urine Culture	7	31.8
Negative / no growth	5	22.7
Candida albicans, *Haffnia alvei*	1	4.5
Klebsiella, *Proteus*	1	4.5
Other Laboratory Tests		
Chest x-ray (pneumonia)	4	18.2
Tzanck smear – negative	1	4.5
ETA CS (+) *Pseudomonas, Acinetobacter*	1	4.5
CSF (-)	1	4.5

Three patients were given intravenous (IV) acyclovir at 500 mg/m^2/dose given as a one-hour infusion every 8 hours; but only one patient completed the 7- day IV therapy.

3 patients were given oral acyclovir at 60-100 mg/kg/day, 4 to 5 times a day, for 7 days. These patients were started on the oral form due to financial constraints. Of these 3 patients, one developed a varicella-associated complication, i.e. an 11-year old boy with Acute Myelogenous Leukemia, who developed infected skin lesions. He was treated with intravenous Oxacillin for 7 days and was discharged in improved condition after 8 hospital days.

15 patients received, both intravenous and oral Acyclovir, at the same dosages mentioned earlier for an average total duration of 7 days; with the exception of 1 patient who completed 14 days of therapy (2 doses IV and the rest oral) because she still had fresh lesions upon discharge. IV Acyclovir was given for an average of 3.6 days (range, 1 dose to 5 days) before switching to the oral form to complete 7 days. Prophylaxis with varicella-zoster immune globulin (VZIG) was not administered to any patient. Other medications given included an oral antihistamine for pruritus, as well as, IV antibiotics and antifungal agents to treat complications that may or may not be associated with varicella.

Of the 22 children hospitalized for varicella, 13 or 59% of them received both Acyclovir and antibiotic therapy, while 2 or 9.1% received antifungal agents as well. The antibiotics prescribed most frequently were β-lactams (12 children), aminoglycosides (8 children) and Ciprofloxacin (3 children). The mean duration of antimicrobial therapy in hospitalized patients was 6.9 days.

Outcome

Nine patients (40.9%) developed complications, mainly pneumonia (18.2%) and sepsis (9.1%). Secondary bacterial infection of the skin and cellulitis was noted in one patient each. Disseminated disease with multiple complications was seen in 3 patients (13.6%), 2 of whom were mortalities: a 9-year old boy with ALL who developed pneumonia, oral thrush, sepsis, and a bleeding diatheses—which led to his demise; and a 6-year old boy with embryonal rhabdomyosarcoma and pulmonary tuberculosis, who developed pneumonia with pleural effusion and cellulitis of the right neck, and eventually died of septic shock. The third patient was a 16-year old male with ALL, who developed pneumonia and hepatitis but recovered from these complications and was sent home improved after 11 hospital days.

Patients who developed pneumonia were diagnosed clinically and radiographically. Sepsis with systemic inflammatory response occurred in 2 children—both of whom had negative blood culture results.

There was no significant association among age, sex, and underlying immunocompromised state of a patient and the development of complications. Neither could a relationship between laboratory features and the development of varicella-associated complications be established, given the small sample size (Table 9).

Duration of hospitalization due to varicella alone was 7.96 ± 3.57 days (range, 2 to 20 days), but the total duration of hospital stay was 18.36 ± 19.25 days (range, 2 to 83 days). Majority of patients were confined for more than a week, after resolution of varicella: either for continuation of chemotherapy or treatment of a nosocomial infection.

Three patients died with a case fatality rate of 13.6%. Recovery rate was 81.8%. (Table 10)

DISCUSSION

From 1999 to 2004, 26 immunocompromised children were hospitalized for varicella at the Philippine General Hospital. 24 of these patients had underlying malignancies—giving an incidence rate of 0.53% (range, 0 to 1.14%). This approximates that of Feldman and Lott in a study of 288 American children with cancer covering a 24-year period, where the annual incidence of chickenpox was noted to vary from <0.5% to 2%.[6]

The most common primary disease or immunocompromised state was Acute Lymphoblastic Leukemia (ALL); and 30% (6/20) had solid organ tumors. It has long been presumed that cell-mediated immunity (CMI) plays a greater role both for limiting the extent of primary infection with varicella-zoster virus and for preventing reactivation of virus with herpes zoster.[11, 12] Children with impaired CMI, such as those with leukemias and solid tumors are, thus, more likely to develop disseminated chickenpox and zoster than those with B-cell abnormalities. These children are also, more likely, to be hospitalized for antiviral treatment and observation.

Table 9. Association of variables with the development of complications

Variable	With Complications No. (%)		Without Complications No. (%		p-value
Age in years					**0.439**
0 - 5	4	44.4	5	55.6	**(NS)**
6 - 10	2	50.0	2	50.0	
11 - 15	2	33.3	4	66.7	
16 - 19	1	33.3	2	66.7	
Sex					**0.439**
Male	6	46.2	7	53.8	**(NS)**
Female	3	33.3	6	66.7	
Underlying Disease or Immunocompromised State					**0.338 (NS)**
Cancer	9	45.0	11	55.0	
Chronic Steroid Therapy	0	0.0	2	100.0	
WBC Count*(10^9/L)					
< 5	**4**	**44.4**	**5**	**55.6**	
5 - 10 x	**2**	**25.0**	**6**	**75.0**	
> 10 x	**3**	**60.0**	**2**	**40.0**	
Differential Count					
PMN *					
< 0.50	**3**	**33.3**	**6**	**66.7**	
0.50 - 0.70	**3**	**60.0**	**2**	**40.0**	
> 0.70	**3**	**37.5**	**5**	**62.5**	
Lymphocytes *					
< 0.20	**6**	**54.5**	**5**	**45.5**	
0.20 - 0.40	**2**	**33.3**	**4**	**66.7**	
> 0.40	**1**	**20.0**	**4**	**80.0**	
Absolute Lymphocyte Count *					
0 - 500	**4**	**66.7**	**2**	**33.3**	
501 – 1000	**1**	**33.3**	**2**	**66.7**	
> 1000	**4**	**30.8**	**9**	**69.2**	

p value < .05 – statistically significant
NS – not significant
* Statistical test cannot be performed due to very low frequencies

Table 10. Duration of Hospital Stay and Outcomes of Treatment of Varicella

Duration of Hospital Stay	No.	%
Hospital Stay Due to Varicella	7.96 ± 3.57	
1 week or less	9	40.9
more than 1 week	13	59.1
Total Duration of Hospital Stay	18.36 ± 19.25	
1 week or less	4	18.2
more than 1 week	18	81.8
Outcome of Treatment	**No.**	**%**
Recovered	18	81.8
Home against advice/per request	1	4.5
Died	3	13.6
Intracranial hemorrhage	1	4.5
Disseminated intravascular coagulopathy 2° to sepsis	1	4.5
Septic shock	1	4.5

In this study, 18 children (90%) were on immunosuppressive chemotherapy (methotrexate, mercaptopurine, prednisone, etc.) for 2 weeks (mean 17.5 ± 11.62 days) before the development of varicella; and were mostly on the maintenance phase. 4 out of 6 children in the induction phase and 5 out of 11 children in the maintenance phase of anticancer treatment developed complications. This implies that the more severe the immunosuppression, the greater the risk of developing varicella-associated complications. Indeed, Feldman and Lott noted that children who had successfully completed chemotherapy for cancer, but developed varicella, had a clinical course that was uncomplicated and similar to otherwise normal healthy children. None of these children had received chemotherapy or irradiation for 30 days to 9 years. In contrast, VZV pneumonitis was noted to develop in 29 out of 103 children who received chemotherapy 3.3 ± 5.0 days (range, 0 to 15 days) before the infection.[6] Unfortunately, in our study, too few subjects with the infection—during different phases of anticancer treatment, were available for assessment of outcome.

2 patients were receiving corticosteroids for more than a month, prior to the development of varicella. Foreign studies have shown that severe varicella infections with fatal complications were noted in children receiving corticosteroids despite the administration of varicella-zoster immune globulin (VZIG).[25] Systemic corticosteroid therapy is said to increase morbidity, even in patients without other conditions, especially when administered during the incubation period of varicella.[12] Although these 2 patients were receiving oral prednisone at dosages of less than 2 mg per kg body weight per day—the dose which has been thought to be safe, some studies have suggested that even smaller dosages may place patients at increased risk for severe varicella.[13] Fortunately, neither of the 2 patients in this study developed varicella-associated complications.

Children less than 5 years of age comprised the bulk of admissions. They were likewise observed to develop complications more than any other age group, which was similar to the local study of Yason. This is not surprising because in general, children who belong to this age group are said to be the most vulnerable to infectious diseases in terms of morbidity and mortality.

Varicella is highly contagious. Secondary attack rates among susceptible household contacts of persons with varicella are as high as 90% (i.e., 9 out of 10 susceptible household contacts will become infected).[15] In this study, only 2 children had a known exposure to siblings in the household who developed chickenpox. No subjects were exposed to varicella in the schools perhaps because none of them were currently attending school due to their immunocompromised state. Majority (18/22) had no known exposures; similar to a study done by Buda and colleagues among children with ALL, who developed varicella infection, but with half of the cases occurring without a known exposure.[16] This implies the likelihood of community-acquired varicella as the major source of infection for

immunocompromised children. Although no seasonal trends were observed among our study population, a clustering of cases was noted during the months of December 2003 to January 2004 when 11 immunocompromised patients were admitted within a few days from each other. 9 of these patients had underlying malignancies and had no known exposures. Whether these children had a common exposure to an index case of varicella during out-patient consults at the cancer clinic could not be ascertained due to lack of information in the charts.

Nosocomial transmission is well-documented in pediatric units. In our study, there were two cases of nosocomial transmission from patients occupying adjacent hospital beds in the emergency room and in the ward. The period of infectivity of varicella is generally considered to be between 2 days before the onset of rash, through the first 4 to 5 days, and until lesions have formed crusts. However, immunocompromised patients with progressive varicella are probably contagious during the entire period, when new lesions are appearing.[15] Since most patients already had the typical skin lesions of varicella, isolation precautions were immediately instituted upon admission. In the two cases, the exposures probably occurred prior to the onset of rash in the index case, hence was unrecognized. The spread of infectious VZV from a person with chickenpox is by air droplets from nasopharyngeal secretions, which usually requires face-to-face exposure. However, varicella has reportedly occurred in hospitalized patients who had only indirect contact via air currents from hospitalized rooms of patients with varicella and localized zoster.[12]

Recurrences of varicella are uncommon events but may be seen more frequently in the immunocompromised than in immunologically normal individuals.[11] In this study, 1 patient developed a recurrence of varicella compared to 7 children reported in the study of Feldman and Lott. Recurrent varicella is defined as new episodes of disseminated skin lesions in the absence of exposure, with its onset occurring at least one month after a previous attack.[12] In most instances, the initial episode was prior to organ transplantation or treatment of cancer. This was true for the patient in our study, whose first episode of varicella occurred 7 years before he was diagnosed and treated for leukemia. It has been suggested that although the clinical findings were those of chickenpox, the recurrent episodes could represent atypical generalized zoster with no apparent dermatome localization.[6] This could be differentiated by restriction endonuclease analysis—a technology that is not currently available in the country.

In general, the presenting manifestations of chickenpox are a rash, low-grade fever, and malaise. These symptoms were seen in our patients. The rash of varicella is described as generalized, pruritic, typically consisting of 250 to 500 lesions, and rapidly progressing from macules to papules to vesicular lesions before crusting. The hallmark of the infection is the appearance of lesions at all stages. In contrast, immunocompromised children, particularly those with leukemia, have more numerous lesions—often with a hemorrhagic base, and healing takes nearly three times longer in this population.[17.] These patients may be susceptible to progressive, severe varicella characterized by continuing eruption of lesions and high fever persisting into the second week of illness.[5, 11] In this study, most of the patients developed the typical clinical features of chickenpox in normal, healthy children, with an average duration of symptoms of 10 days. Only one patient was described to have fresh lesions persisting up to 14 days from onset of symptoms. In some immunocompromised patients, an acute form of varicella with disseminated intravascular coagulopathy (DIC) develops and is rapidly fatal, at times before antiviral therapy can be instituted.[11] This was seen in two patients in our study, who developed severe skin eruptions and died within 48 hours of admission due to DIC.

Another important problem among immunocompromised patients who develop varicella is the progressive involvement of visceral organs. In the classic study done at St. Jude's Hospital by Feldman and colleagues, approximately 1/3 of children developed progressive disease involving multiple organs, including the lungs, liver, and central nervous system.[17] As seen in our study, 9 patients (41%) developed complications, 3 of whom had multiple complications with dissemination to the lungs, circulatory system and liver. Prior health status was predictive of the type of complications experienced by children with varicella requiring hospitalization.[14] Children with skin/soft tissue and neurologic complications were, more often, previously healthy, whereas those with respiratory complications were more often previously ill. This was consistent with our study, which established that pneumonia was indeed the most frequent complication, and could explain the absence of neurologic complications among our patients. Pneumonia following varicella is usually viral, but may be bacterial, and is associated with a 25% mortality rate.[6] It generally appears 3 to 5 days in the course of illness and is associated with tachypnea, cough, dyspnea and fever.[17] In our study, there was no death among our patients who had pneumonia as the only complication.

Patients with lymphopenia or poor cell-mediated immune responses during varicella infection are said to be at risk for persistent, severe or even fatal varicella.[3] Lymphopenia (lymphocyte count <2 x 10^9/L) was seen in 11 subjects in this study, 6 of whom had severe lymphopenia (absolute lymphocyte count < 500/µl). Notably, 4 out of these 6 cases developed a varicella-associated complication but no mortality was seen. Feldman and Lott noted that lymphopenia was significantly associated with VZV pneumonitis and the fatality rate more than doubled when the absolute lymphocyte count decreased to <300/µl.[6] Unfortunately, no definite conclusion can be made from this study with reference to the relationship between absolute lymphocyte count and the development of complications due to the small sample size.

All patients in this study were diagnosed clinically since laboratory confirmation is not necessary for most cases of varicella. Because of the lability of the virus, only 30% to 60% of viral cultures are positive.[12] A Tzanck smear was, however, performed on one patient who developed secondary bacterial infection of skin lesions but, with negative results. Other bacteria and fungi isolated from the blood, urine, or endotracheal aspirates of some patients in this study are reflective of nosocomial infections acquired at least 2 weeks before or after recovering from varicella, rather than pathogens associated with varicella itself.

In immunocompromised hosts, management of varicella is mainly symptomatic and/or supportive. It is also directed toward reduction of the risk of complications. In these patients, hospitalization and intravenous antiviral therapy using acyclovir is recommended.[5] Acyclovir is a DNA nucleoside analogue, which inhibits herpes virus replication with minimal adverse effects on mammalian cellular functions.[2] The oral route is not recommended because only 15% to 20% of oral acyclovir dose is absorbed from the gastrointestinal tract and is, thus, bioavailable. Numerous studies have demonstrated that acyclovir shortens the duration of viral shedding and new lesion formation; hastens lesion healing; and protects against the development of disseminated disease.[12, 19-21] All patients in our study were prescribed intravenous acyclovir. However, due to financial constraints or problems with its availability at the hospital pharmacy, oral forms were used. As observed in our study, 2 patients who did not receive intravenous therapy immediately upon admission developed a fulminant course leading to their demise. In 15 patients, intravenous acyclovir was given for a mean of 3.6 days before shifting to an oral form to complete the recommended 7 days of therapy. This approach was proven to be effective in a study done by Carcao et al. In

that study, 25 out of 26 episodes of varicella in immunocompromised children were successfully treated sequentially with intravenous acyclovir for a mean of 4.1 days, followed by oral acyclovir for a mean of 5.4 days.[2] In our study, one third of the patients (1/3) who were on oral acyclovir alone, as well as, those who received sequential intravenous and oral acyclovir (5/15), developed a varicella-associated complication. However, given our small sample size, we could not draw definite conclusions regarding the route of acyclovir therapy as a prognostic indicator.

Majority (82%) of our patients recovered from the disease but 3 patients died giving a case fatality rate of 13.6%. This number is twice that of Feldman and Lott who recorded an overall mortality rate of 7% in untreated patients during the pre-vaccine era.[6] Bleeding disorders can occur during varicella, and are due to disseminated intravascular coagulation, vasculitis, or idiopathic thrombocytopenic purpura.[1] This was observed in 2 of the mortalities who both developed a fulminant and hemorrhagic course.

Varicella is a vaccine-preventable disease. The World Health Organization recommends considering routine childhood immunization against varicella in countries where the disease is an important public health and socio-economic issue; where the vaccine is affordable; and where high (from 85-95%) and sustained coverage can be achieved. [27] However, in resource-poor countries such as the Philippines, where the incidence of varicella is high and routine administration of the varicella vaccine for all children is not feasible, targeted vaccination may be a strategy to protect high-risk individuals from severe disease, even though impact on the epidemiology of the infection is not expected. Administering the vaccine to the healthy susceptible siblings of immunosuppressed children has been proven to be a safe and effective strategy to indirectly protect high-risk children by decreasing their household exposure to the virus.[4, 23] In a study of varicella vaccine administered to healthy siblings of children with malignancies, no clinical or serologic evidence of spread of vaccine virus to the immunocompromised children was found.[24] Aside from close household contacts, immunocompromised individuals can also be protected indirectly by immunization of healthcare workers.[26] This would address the problem of nosocomial VZV transmission, as well. Susceptible people at high-risk of developing severe varicella should also be given VZIG as soon as possible after exposure or within 96 hours. However, due to its cost and unavailability in the country, passive immunization with VZIG is currently not a feasible option in the management of the disease.

CONCLUSIONS

The incidence rate of varicella among immunocompromised children admitted at the Philippine General Hospital from January 1, 1999 to December 31, 2004, was 0.53%. The most common underlying immuno-compromised state was Acute Lymphoblastic Leukemia (ALL), followed by solid organ tumors. The highest incidence of varicella-associated complications was seen in children less than 5 years of age. 41% of the patients developed complications, mainly: pneumonia, sepsis and bleeding diatheses. Disseminated disease was likewise noted, with an over-all case fatality rate of 13.6%.

Our patients responded well to sequential intravenous and oral acyclovir. Vaccination of targeted populations such as close household contacts of immunocompromised patients, as well as, healthcare workers may be a good strategy to protect high-risk children from developing the disease and its complications.

A limitation of this study is its small sample size, making it difficult to draw any definitive conclusions. Hence, a multicenter study is suggested in order to come up with a larger sample that would possibly be more informative and reflective of the general population of immunocompromised children.

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