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Clinical report

A decade review of chickenpox among pediatric immunocompromised patients at the King Chulalongkorn Memorial Hospital, Thailand

Theparat Thanawatanatrakul, Thanyawee Puthanakit, Sasithorn Likitnukul, Chitsanu Pancharoen
Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Background: Varicella zoster virus (VZV) infection among immunocompromised patients leads to high morbidity and mortality.
Objective: Describe the natural history and treatment outcomes of chickenpox among immunocompromised children hospitalized in a tertiary care center in the era of acyclovir treatment.
Methods: We conducted a retrospective chart review of immunocompromised children hospitalized with chickenpox at King Chulalongkorn Memorial Hospital between January 1, 2000 and December 31, 2009. Demographic data, clinical manifestations, treatment, and complications were extracted from the patients' charts. Rate of complications were compared among underlying disease by using chi-square test.
Results: There were 61 admissions. Median interquartile range, (IQR) age was 79 (31 to 123) months. There were 31 (51%) children with hematologic malignancies, 20 (33%) on immununosuppressive drugs, six (10%) neonates, and four (6%) HIV positive. Index cases were from household members (23%), community (15%), and hospital (6%) whereas 56% had no information. Cases peaked during February to March. Median (IQR) duration of fever and active skin lesions were four (3 to 6) and five (4 to 7) days, respectively. All, except one, received acyclovir (50% intravenous, 48% switched from intravenous to oral, 2% oral). Median (IQR) duration of acyclovir treatment and hospitalization were 10 (7 to 14) and nine (7 to 10) days, respectively. Complications included bacterial skin infections (10%), hepatic transaminitis (8%), pneumonia (5%), and disseminated varicella (1%). Rates of complications were 18% among children with malignancies, 3% on immunosuppressive drugs, and none in neonates or HIV positives (p = 0.047). Two children (3%) died due to disseminated varicella and severe pneumonia.
Conclusion: Mortality rate of chickenpox among immunocompromised patients on acyclovir treatment is 3%. Children with hematologic malignancies have the highest rate of complications.

Keywords: Chicken pox, complications, immunocompromised host, mortality, varicella zoster virus

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Varicella zoster virus infection causes chickenpox and herpes zoster [1]. Immunocompromised patients have a higher risk of developing varicella – related complications compared to healthy individuals [1]. Common complications from varicella zoster infection include bacterial superinfection of the skin and involvement of the central nervous system (e.g. acute cerebellar ataxia, encephalitis) and varicella pneumonia [2]. According to a report from St. Jude Children Research Hospital, mortality rate among immunocompromised patients such as cancer was 7% and 28% of untreated patients developed VZV pneumonitis [3]. Patients with acute leukemia are more likely to develop pneumonitis compared to patients with other malignancies [3]. Varicella infection can be fatal for an infant if the mother develops varicella five days before or two days after delivery. The mortality rate has been reported to be as high as 31% [4].

Acyclovir is recommended for immuno-compromised patients. If therapy is initiated early in the course of the illness, especially within 24 hours after the development of rash, this will maximize the

Correspondence to: Thanyawee Puthanakit, MD, Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. E-mail: thanyawee.p@hivnat.org

treatment's efficacy. Intravenous acyclovir therapy initiated early will terminate cell-associated viremia and reduce the likelihood of acquiring progressive varicella and prevent visceral dissemination in high-risk patients [1, 5]. It has been shown that children with malignancies treated with acyclovir are less likely to develop pneumonia compared to the placebo group (45%) [6].

Live attenuated varicella vaccine is routinely recommended for children between 12 to 18 months of age [7]. However, in Thailand, varicella vaccine is not covered by the national immunization program due to the high cost of this vaccine. Therefore, varicella continues to be one of the most common childhood diseases with the reported case of 121 cases per 100,000 population [8].

This study aimed to describe the natural history and treatment outcome of chickenpox among immunocompromised children hospitalized in a tertiary care center in the era of acyclovir treatment.

Patients and methods

Patient population

We performed a retrospective chart review of immunocompromised children hospitalized with chickenpox at King Chulalongkorn Memomorial hospital between January 1, 2000 and December 31, 2009.The inclusion criteria were immunocompromised children under 15 years of age with hematologic/solid organ malignancies, HIV infection, on immuno-supressive drugs, or neonates less than one month of age. The patient medical record was searched from a hospital database using International Classification of Disease of the Tenth Revision (ICD-10) Hospital Discharge Diagnosis System. Chickenpox was diagnosed clinically based upon a classical skin manifestation of multi-stages of vesiculopapular skin lesions. Other supporting documents included were history of contact with VZV-infected patients and/or positive multinucleated giant cell from the Tzanck smear test. Demographic data, clinical manifestations, disease progression, treatment, complications, and outcomes for each patient were reviewed. The research protocol was approved by the Ethics Committee of the King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University.

Statistical analysis

Chi-square test for categorical data or unpaired Student t-test for continuous variables was used to compare clinical information between different groups of patients. P-values less than 0.05 were considered to be significant. The analysis was performed by using SPSS version 16.0.

Results

Demographics

Sixty-one children were hospitalized at the pediatric wards of the Chulalongkorn Memorial Hospital between January 1, 2000 and December 31, 2009 and were included in this study. There were 32 boys (53%). The median (Interquartile range, IQR) age was 79 (31 to 123) months. Underlying diseases of children included in the study were 31 children (51%) with hematologic malignancies/solid organ tumors and on chemotherapy, 20 children (33%) on immununosuppressive drugs, four HIV-infected children (6%), and six neonates (10%). Among children on chemotherapy, six children had mild neutropenia (absolute neutrophil count (ANC) 500-1500 cell/mm^3), one had moderate neutropenia (ANC 200-500 cell/mm3), and three had severe neutropenia (ANC <200 cell/mm^3).

Chickenpox occurred throughout the year with an incidence peak in February and March (**Figure 1**). Index cases were documented among 27 children. Fourteen children (52%) were infected from household members (including 6 perinatally VZV-infected neonates), nine (33%) from their classmates or neighbors, and four (15%) from nosocomial infection.

Clinical manifestations

All patients except for one had typical vesicular skin lesions. Twenty-two of the children (37%) had high-grade fever (body temperature (BT) >38.8°C) whereas only 21 children (35%) had low-grade fever (BT 37.8 to 38.8°C). One patient had progressive abdominal pain and after three days, developed disseminated varicella. The clinical manifestations among six neonatal cases are described in **Table 1**. Skin lesions were scraped and Tzanck smear tests were performed in 32 children of which multinucleated giant cells were documented in 23 children (72%). Median (IQR) duration of fever and active skin lesions were four (3 to 6) and five (4 to 7) days, respectively. Median (IQR) hospitalization was nine (7 to 10) days.

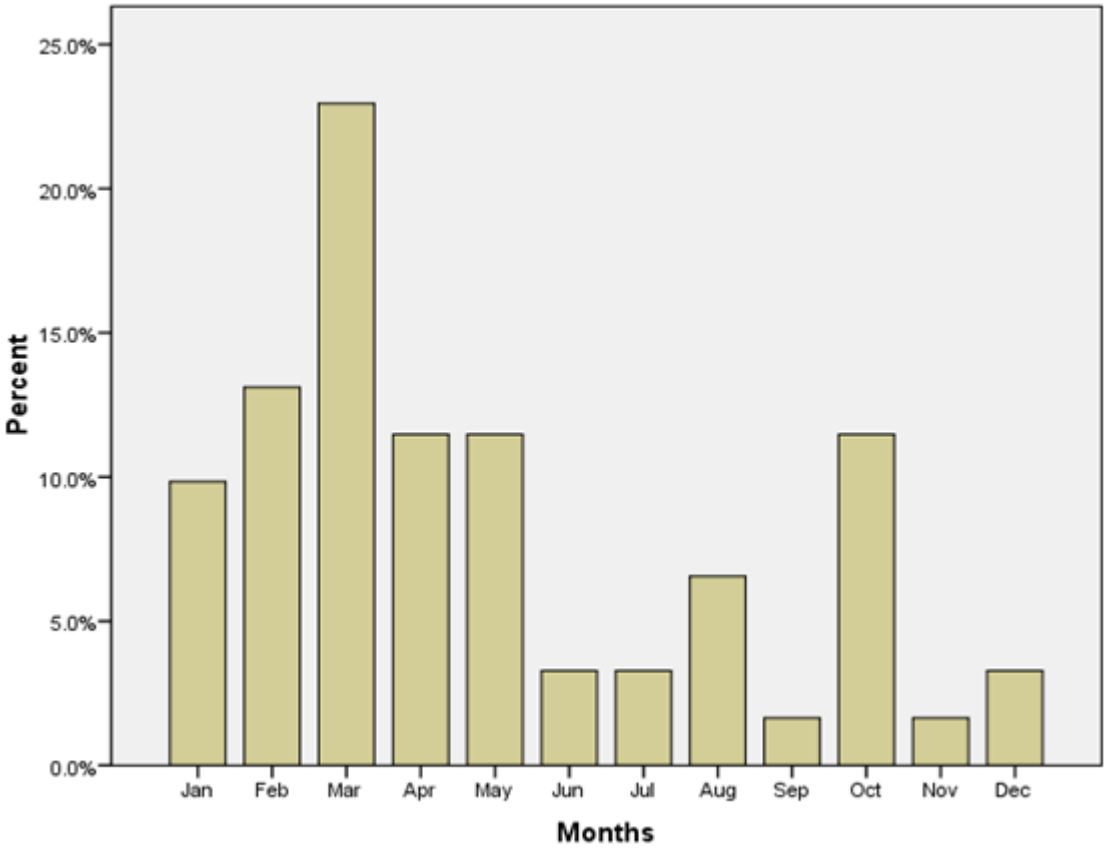

Figure 1. Seasonal distribution of chickenpox among 61 immunocompromised children

Table 1. Clinical manifestations of six neonates whose mother had varicella infection during peripartum period

Age at presentation	Onset of maternal varicella compare to delivery date	Onset of skin lesions in neonate (day of life)	Peak of body temperature (C)	Duration of active skin lesions (days)	Treatment
F, 7 days	-6	Day 6	38	3	Varicella zoster immunoglobulin on day 7 of life Acyclovir 1,500 mg/m^2/day for 7 days
F, 11 days*	-4	Day 10	38	4	Acyclovir 30 mg/kg/day for 7 days
F, 10 days*	-3	Day 9	37.5	5	Varicella zoster immunoglobulin on day 1 of life Acyclovir 1500mg/m^2/day for 7 days
M, 14 days	+5	Day 14	37.5	3	Acyclovir 30 mg/kg/day for 7 days
M, 18 days	+8	Day 16	38.2	2	Acyclovir 1500mg/m^2/day for 7 days
F, 19 days	-10	Day 17	39.3	5	Supportive symptomatic

+ = period before delivery, - = period after delivery

Treatment

All patients except one received acyclovir (50% of the children were administered acyclovir intravenously, 48% switched from intravenous to oral acyclovir, and 2% of the children were on oral acyclovir). Acyclovir was initiated at median (IQR) of 2 days (1 to 7) after the development of vesicular skin lesions. Forty-four (72%) of the children received acyclovir within 72 hours from the onset of disease. Median (IQR) duration of acyclovir treatment was 10 days (7 to 14). Two neonates were infected intrapartum. Their mothers developed chickenpox before delivery and varicella hyperimmune plasma (hyperIg) was administered but the neonates still developed mild varicella infection on days 6 and 9. Twenty-one children (34%) received concomitant antibiotics.

Complications

Thirteen children (21%) had at least one complication associated with varicella as shown in **Table 2**. There were six bacterial skin infections (10%), five hepatic transaminitis (8%), three pneumonia (5%), and one disseminated varicella (1%). Children with malignancies (18%) had more complications compared to children on immunosuppressive drugs (3%) and neonates (0%) or HIV-infected children (0%, $p = 0.047$). Two children with underlying hematologic malignancies died due to disseminated varicella and pneumonia with respiratory failure.

Discussion

In our study, the complication and mortality rates of varicella infection were 21% and 3% respectively. Children with underlying malignancies had the most complications. Bacterial skin infections, asymptomatic hepatic transaminitis, and pneumonia were the most common complications seen among immuno-compromised patients infected with varicella.

In this study, we found high incidences of varicella from February to May, which corresponds to the seasonal varicella distribution reported by the Annual Epidemiological Reports of the Thai Ministry of Public Health [9]. Median length of stay in the hospital for patients in this study was 9 days, which was longer compared to other studies. Reports from UK, Ireland [10], and Hong Kong [11] had a range of 3.7 to seven days. This difference is due to the fact that the study populations between the studies were different; this study was conducted only in immunocompromised patients whereas in the other studies, most of the patients were immunocompetent.

The mortality rate among perinatally VZV-infected children (5 days before and 2 days after delivery) not on treatment has been reported up to 30% [12]. In this study, there were no complications among the neonates less than one month old who were infected with varicella because treatment that was initiated immediately with acyclovir. Two other cases received varicella hyperimmune plasma and another two cases were considered to be infected post-delivery. The report of 44 case series of neonatal varicella between 1995 and 1997 from Australia also showed that the use of varicella zoster immunoglobulin (VZIG) in infants at exposure modified the severity of disease, 83% of cases who received VZIG presented as mild disease [13]. In another Australian case series, two (5%) neonates had severe disease because VZIG or acyclovir was not administered [13].

In this study, the complication of varicella infection among immunocompromised children was 21%. The common complications of varicella infection observed were bacterial skin infections, asymptomatic hepatic transaminitis, and pneumonia. Aside from asymptomatic hepatic transaminitis, these complications have also been well reported in immunocompetent patients. Other common causes of complicated varicella were from respiratory complications, skin infection and neurological complications [14]. In contrast, an overall rate of complications from a Hong Kong study was 47%, 598 cases hospitalized with chicken pox had complications of the skin and soft tissue, nervous system and most common was febrile seizure and pneumonia [11].

In this study, the overall mortality rate of chickenpox was 3% of which all cases had respiratory tract complications. Four patients developed pneumonia but two progressed to respiratory failure requiring assisted ventilation and subsequently died. The incidence rate of pneumonia was 6.5%. This value is much lower compared to other reports conducted in 127 immunocompromised patients not on acyclovir; the rate of varicella-zoster virus pneumonitis was reported to be as high as 28% with a mortality rate of 25% [3]. Intravenous acyclovir given within 72 hours of VZV infection can prevent progressive varicella and visceral dissemination in high-risk patients [15].

Table 2. Complications of chickenpox among immunocompromised children

Gender, Age	Underlying diseases	Neutropenia	Onset of complications	Complications	Treatment
Disseminated varicella					
M, 10 yr 3 mo	ALL	No	1	Disseminated varicella Varicella Pneumonia (**Figure 2A**) Pulmonary Hemorrhage Septic shock with acute renal failure Died on day 8 of admission	Ventilator support Hemodialysis IV antibiotics for 8 days Acyclovir for 8 days
Pneumonia					
M, 1 yr 11 mo	Neuro Blastoma	No	4	Left lobar pneumonia with pleural effusion with respiratory failure with *A.baumanii* ventilator associated pneumonia Died on day 21 of admission	Ventilator support IV antibiotics for 19 days Acyclovir for 14 days
F, 10 yr 10 mo	Systemic Lupus Erythematosis	No	5	Varicella Pneumonia: chest x-ray bilateral nodular infiltration (**Figure 2B**)	Acyclovir for 14 days IV antibiotic for 5 days
*M, 6 yr 6 mo	ALL	Mild	6	Varicella Pneumonia (bilateral peri hilar infiltration) Chest x-ray: perihilar infiltration	Acyclovir for 14 days
Liver transaminitis					
M, 6 yr 8 mo.	ALL	Severe	4	ALT 82 IU/mL, AST 188 IU/mL	Supportive
F, 8 yr	ALL	No	5	ALT 248 IU/mL, AST 174 IU/mL	Supportive
F, 7 yr 11 mo	AML	No	3	ALT 190 IU/mL, AST 174 IU/mL	Supportive
M, 10 yr 8 mo	Lymphoma	No	2	ALT 243 IU/mL, AST 158 IU/mL	Supportive
**M, 5 yr 4 mo	Medulloblastoma	Mild	7	ALT 435 IU/mL, AST 401 IU/mL	Supportive
Secondary bacterial skin infection					
M, 5 yr 7 mo	ALL	Mild	12	Abscess formation at infected skins of the trunk and extremities Pus culture was positive for *S.aureus*	Cloxacillin IV for 2 days and switched to oral dicloxacillin for 8 days
F, 3 yr 8 mo	ALL	No	8	Infection site at labia majora	Augmentin PO for 5 days
M, 9 yr 7 mo	Juvenile Rheumatiod Arthriitis	No	4	Infection site at right wrist	Dicloxacillin.PO for 5 days plus topical bactroban ointment
F, 8yr 9mo	Biliary atresia S/P Kasai operation	No	7	Infection sites at both hands	Dicloxacillin PO for 10 days plus topical bactroban ointment
*M, 6 yr 6 mo	ALL	Mild	6	Infection sites at left hand and elbow. Pus culture was positive for *S. aureus*	Cloxacillin IV for 5 days
**M, 5 yr 4 mo	Medullo blastoma	Mild	7	Infection sites were at the trunk and extremities Vesicle fluid culture was positive for *S.aureus*	Supportive No antibiotics

*The patient has 2 complications, pneumonia and secondary bacterial skin infection, **The patient has 2 complications, liver transaminitis and secondary bacterial skin infection, M = male, F = female, ALL = acute lymphoblastic leukemia, AML = acute myeloblastic leukemia, ALT = alanine transaminase, AST = aspartate transferase, PO = per oral, IV = intravenous

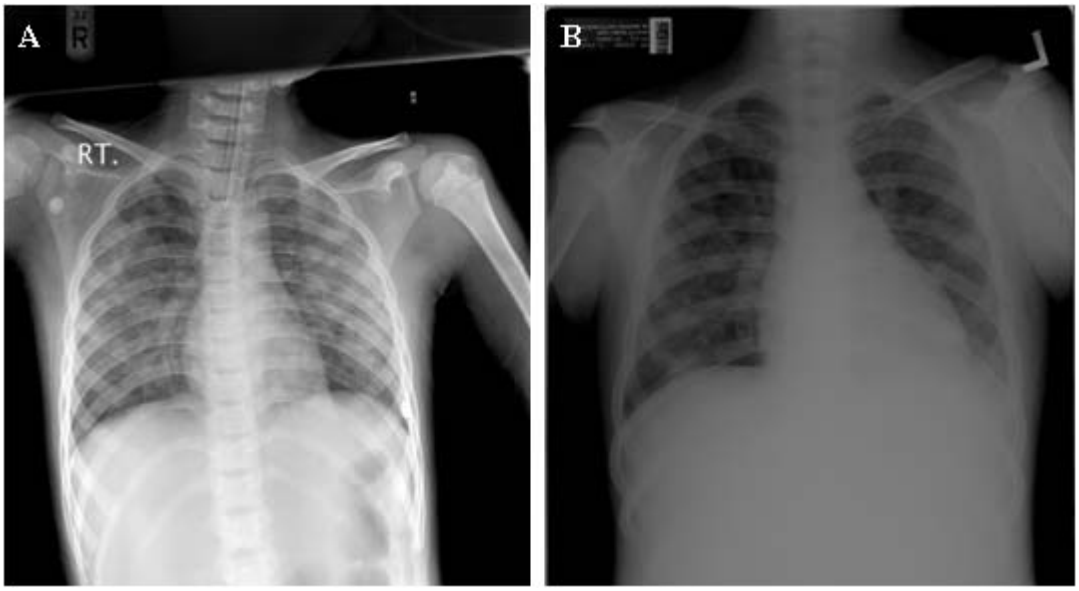

Figure 2 **A:** On day 1 of varicella rash, a 10-year-old boy with acute leukemia developed varicella pneumonia and subsequently died on day 8 due to disseminated varicella infection. **B:** On day 5 of varicella, a 10-year old girl developed bilateral nodular pulmonary infiltration.

In this study, 72% of the patients received acyclovir within 72 hours of infection. This would explain why the mortality rate in this study was lower compared to other studies. About 50% of the children switched from intravenous to oral acyclovir for a median duration of 10 days. The study by Carcao et al. showed that patients who had at least 48 hours of intravenous acyclovir, did not develop any new lesions within 24 hours, had no internal organ involvement can successfully switch from intravenous to oral therapy [16]. A VZV-infected person is the source of most transmission among household members in close contact with each other. Varicella is highly contagious and 90% of the time, other household members in close contact with the infected person will develop the disease [17]. The index cases in this study were documented in about 50% of the cases of which half were from household members. Universal vaccination is the best choice in preventing the natural infection and complications from chickenpox. However, in developing countries, this is not feasible. It is difficult to ensure that a high proportion of the population is vaccinated to provide herd immunity [18]. Another approach is to give varicella vaccine to non-immune household member of immunocompromised host. The study from Australia showed that offering varicella vaccine to 35 non-immune household members of cancer patient is safe and immunogenic, however long term follow-up is needed to prove clinical efficacy [19].The strength of this study is its large case series of chickenpox reviewed from different types of immunocompromised patients attending a tertiary care center. One of the limitations of this study is its duration. Over the span of ten years, the quality of supportive care may have varied and affected the results of the study. Regardless of this, the use of acyclovir throughout the study period should have minimized the variation effects. Another limitation of this study is its retrospective design. Some of the data from the patients' medical chart were incomplete. For example, the investigators could not determine the definite cause of pneumonia because it was not indicated whether the affliction was from varicella zoster virus or secondary bacterial infection.

In conclusion, this study showed that immunocompromised children with varicella infection experienced high rates of complications even with acyclovir treatment. High mortality rates were found in children with malignancies. A significant number of immunocompromised patients contracted chickenpox from immunocompetent non-immune household members. In the setting where universal vaccination with live attenuated varicella vaccine is not implemented, offering vaccine to non-immune household member of immunocompromised host should be considered.

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