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# Post-exposure prophylaxis to prevent varicella in immunocompromised children

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SUMMARY

***Background:*** Varicella-zoster virus (VZV) infection can cause life-threatening events in immunocompromised patients. Post-exposure prophylaxis (PEP) is required to prevent secondary VZV infection. Limited evidence is available for the use of acyclovir (ACV)/valacyclovir (VCV) as PEP.

***Methods:*** Herein, we retrospectively analyzed immunocompromised paediatric patients with significant exposure to VZV. Patients administered PEP were categorized into four groups: 1) ACV/VCV group; 2) intravenous immunoglobulin (IVIG) group; 3) ACV/VCV/IVIG group; 4) vaccine group.

***Results:*** Among 69 exposure events, 107 patients were administered PEP (91, ACV/VCV; 16, ACV/VCV/IVIG) and 10 patients did not receive PEP (non-PEP group). The index case was diagnosed based on clinical symptoms in 55 cases (79.7%). Fourteen cases (20.3%) were confirmed using direct virological diagnostic procedures. In the PEP group, only 2 patients (2.2%) developed secondary VZV infections. Additionally, 2 patients in the non-PEP group (20.0%) developed secondary VZV infection. The incidence of secondary VZV infection was significantly lower in the PEP group than in the non-PEP group ($P$=0.036). Among patients administered PEP, no antiviral drug-induced side effects were detected.

***Conclusions:*** Antiviral agents administered as PEP are effective and safe for preventing VZV infections in immunocompromised patients. Rapid virological diagnosis of index cases might allow efficient administration of PEP after significant exposure to VZV infection.



## Introduction

Varicella-zoster virus (VZV) causes varicella and zoster infections, which are typically mild in immunocompetent individuals. However, VZV can cause life-threatening infections, such as encephalitis, hepatitis, and pneumonia, in immunocompromised individuals [1]. VZV is highly contagious, and precautions are recommended to prevent airborne

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transmission [2]. In Japan, the varicella vaccine was adopted in the standard vaccine program in 2014 [3]. The proportion of children who received this vaccine was below 40% during the first half of the present investigation, and VZV outbreaks have been occasionally documented across Japan (data exclusively available in Japanese). Although the varicella vaccine has dramatically decreased the incidence of VZV infections with increased inoculation [4], few patients with VZV infection have been recorded in households, schools, kindergartens, and paediatric wards. Post-exposure prophylaxis (PEP) is needed to prevent secondary VZV infection in immunocompromised patients [1].

Typically, vaccination, intravenous varicella-zoster immunoglobulin (VZIG) (or intravenous immunoglobulin [IVIG], if VZIG is unavailable), and antiviral agents (acyclovir [ACV] and valacyclovir [VCV]) are selected as PEPs to prevent secondary VZV infection. The American Academy of Pediatrics recommends three potential interventions for individuals without evident immunity exposed to a person with varicella or herpes zoster: 1) varicella vaccine, 2) VZIG (when indicated and available), and 3) preemptive oral ACV or VCV starting on day 7 post-exposure (VZIG is not indicated or unavailable) [5]. Limited evidence is available for the use of ACV/VCV as PEP [1]. As vaccination is not indicated in several immunocompromised patients, VZIG (or IVIG) is the first choice for PEP [6]. Although VZIG can prevent the development of severe secondary VZV infection in immunocompromised patients, some issues need to be considered. First, VZIG administration imposes a burden on patients. Vascular access is often challenging in younger children. Second, VZIG is more expensive than the vaccine and oral antiviral agents. Additionally, VZIG is unavailable in some countries. IVIG is alternatively administered, but titers of any specific immunoglobulin remain uncertain, as immunoglobulin testing for anti-varicella antibodies is not routinely performed. Clinical data demonstrating the effectiveness of IVIG for PEP of VZV are limited [1]. Oral administration of antiviral agents is convenient and relatively low cost. Previous reports have demonstrated the effectiveness of oral antiviral agents in immunocompetent children exposed to VZV [7,8]. A few reports have documented the effectiveness of antiviral agents as PEP in immunocompromised hosts in a small cohort [9–12].

The present study investigated the effectiveness and safety of PEP in preventing secondary VZV infection in paediatric immunocompromised patients. Most patients were administered antiviral agents or antiviral agents with IVIG. In index cases, VZV infection in the paediatric ward was diagnosed using virological diagnostic procedures. Effectiveness and safety were compared between patients administered PEP and those who did not receive PEP.

## Methods

### Study design

We retrospectively investigated the incidence of secondary VZV infection in immunocompromised patients after significant exposure to varicella or zoster. Between April 2010 and March 2020, we identified immunocompromised patients aged <20 years in patient wards or the outpatient clinic at Nagoya University Hospital after significant exposure to varicella or zoster. In addition, medical records were collected for patients with significant exposure to varicella or zoster in terms of PEP and secondary VZV infection within 21 days of exposure. This study was approved by the Institutional Review Board of Nagoya University Hospital (2017−0404), and written informed consent was obtained from the guardians of participants.

### Patients

Diagnosis of varicella and zoster in the index case and secondary infection was based on clinical symptoms or results from direct virological diagnostic procedures, including polymerase chain reaction (PCR) and viral antigen. PCR for DNA and antigen detection was performed using fluid and/or scrapings from the base of fresh vesicles.

We defined immunocompromised patients as follows: 1) patients who had undergone hematopoietic stem cell transplantation (HSCT) or liver transplantation within 24 months; 2) patients receiving immunosuppressive therapy (such as tacrolimus, cyclosporine, mycophenolate acid mofetil, and corticosteroids), 3) patients with malignancies receiving chemotherapy or within 6 months of chemotherapy completion, and 4) patients with hypogammaglobulinemia. At our facility, airborne and contact precautions are required for immunocompromised patients with zoster for the disease duration. Significant exposure to varicella or zoster was defined as a patient who had been exposed to an index case of varicella or zoster by direct contact or had stayed in the same room for more than 30 min.

### PEP

PEP was administered as follows: 1) oral ACV, intravenous ACV, and/or oral VCV for more than 7 days, initiated from day 7 (±1) post-exposure, 2) IVIG within 96 h of exposure (VZIG is not available in Japan), or 3) vaccination within 48 h after exposure. In patients with presumed profound immunosuppression, a combination of VCV/ACV and IVIG was administered. Patients receiving PEP were categorized into four groups; 1) ACV/VCV group, 2) IVIG group, 3) ACV/VCV/IVIG group, or 4) vaccine group. Patients undergoing chemotherapy immediately after transplantation were considered severely immunocompromised, and ACV/VCV/IVIG was administered as PEP.

PEP safety data were collected every day for in-patients and at the end of the out-patient visits to the facility. We asked the out-patients to visit or call if serious adverse events were observed.

### Statistics

Data analysis was performed to compare the number of patients with secondary VZV infections in PEP and non-PEP groups, as well as to compared the antiviral agent and non-PEP groups, using Fisher's exact test. Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

## Results

Between April 2010 and March 2020, 129 immunocompromised patients exposed to VZV reported 69 exposure events. Among them, 119 patients received PEP and 10 did not receive

**Table I**
Diagnostic methods employed for the index case of VZV infection

| | Diagnostic method | Total (n, %) (n=69) | Inpatients (n, %) (n=16) | Others (n, %) (n=53) |
|---|---|---|---|---|
| Varicella (n=48) | Clinical symptoms | 42 (60.9) | 0 (0.0) | 42 (79.2) |
| | Virological tests | 6 (8.7) | 6 (37.5) | 0 (0.0) |
| Zoster (n=21) | Clinical symptoms | 13 (18.8) | 3 (18.8) | 10 (18.9) |
| | Virological tests | 8 (11.6) | 7 (43.8) | 1 (1.9) |

VZV, Varicella-Zoster virus; Others, outpatients and patients diagnosed outside Nagoya University Hospital.

PEP. (One patient received two doses of the VZV vaccine. One patient had a history of varicella. One patient was not aware of exposure to varicella before developing a secondary VZV infection. We did not find the reason for no PEP in seven patients' medical records). Twelve patients who started PEP were excluded from the analysis as appropriate measures were not followed (4, insufficient PEP duration; 2, early initiation of ACV/VCV; 4, delayed initiation of PEP; 2, unknown date of exposure to VZV infection; 2, unknown date of PEP initiation). Background data for enrolled patients were as follows: 71, under chemotherapy; 46, under immunosuppression therapy; 30, HSCT; 8, liver transplantation recipients). Accordingly, 69 VZV exposure events and 117 exposed patients were analyzed. The administered PEP doses were as follows: oral ACV or VCV, median 68 mg/kg/day (interquartile range, 41—74 mg/kg/day), and IVIG, median 148 mg/kg (interquartile range, 116—212 mg/kg).

Among 69 events, the index case occurred in the paediatric ward in 16 events (23.1%), at the outpatient clinic in 2 events (2.9%), and other places in 51 events (73.9%; 22, household; 20, in a school or kindergarten; 9, others). Regarding VZV infection in the index case, 48 cases (69.5%) were varicella and 21 cases (30.5%) were zoster. Among zoster cases, vesicular skin lesions were disseminated in 4 cases (19.0%) and localized in 9 cases (42.9%) (no records in 8 cases). The diagnosis was based on clinical symptoms in 55 cases (79.7%; 42 varicella and 13 zoster); 14 cases (20.3%; 6 varicella and 8 zoster) were confirmed using direct virological diagnostic procedures, including PCR (13 patients) and viral antigen (one patient) (Table 1). In index cases at wards, VZV infection was confirmed by virological diagnostic procedures in 13 of 16 patients (81.3%); only one case was virologically diagnosed in the outpatient clinic or outside our hospital.

As shown in Table 2, 107 patients (91.5%) received PEP, and 10 patients (8.5 %) did not receive any PEP. Among these, the history of varicella infection was unknown in 78 patients (66.7%), while information regarding varicella-zoster vaccination was unavailable in 59 patients (50.4%). Table 3 summarizes the underlying conditions of patients in PEP and non-PEP groups. Table 4 presents the efficacy of PEP. Among patients administered PEP, 91 patients (85.0%) were categorized into the ACV/VCV group (7, oral ACV; 83, VCV; 1, combination of ACV for 3 days and VCV for 4 days) and 16 patients (15.0%) were in the ACV/VCV/IVIG group; no patient was sorted into the IVIG and vaccination groups. Secondary VZV infection was diagnosed in 4 patients, 2 in the PEP group and 2 patients in the non-PEP group. Two patients were diagnosed based on typical clinical symptoms, whereas the other two were diagnosed using PCR. Two patients shared a room with index cases, and 2 other patients played with index cases. One patient received two doses of VZV vaccine. The vaccination history of three others was unknown. Two patients had varicella history while others had no records of varicella history. All patients were immunocompromised (3 patients with malignancies receiving chemotherapy, 1 patient with hypogammaglobulinemia). The incidence rate of secondary VZV infection was 1.9% (2/107) in the PEP group and 20.0% (2/10) in the non-PEP group; accordingly, a significant difference was detected between the two groups ($P$=0.036). Among patients administered PEP, no antiviral drug-induced side effects were detected. In addition, 66 patients received PEP, while 6 patients did not receive PEP after exposure to primary VZV infection confirmed by virological diagnostic testing (Table 4). Secondary VZV infection occurred in one patient in both the PEP and non-PEP groups. The secondary VZV infection rate was 1.8% (1/55) in PEP with antiviral agents and 16.7% (1/6) in the non-PEP group ($P$=0.189).

## Discussion

In the present study, we revealed the effectiveness and safety of antiviral agents as PEP for VZV in paediatric

**Table II**
Characteristics of patients exposed to VZV infection

| | | PEP | | | Non-PEP | | |
|---|---|---|---|---|---|---|---|
| | | Total (n=107) | Inpatient (n=64) | Others* (n=43) | Total (n=10) | Inpatient (n=8) | Others (n=2) |
| Sex | Male | 58 | 33 | 25 | 7 | 5 | 2 |
| | Female | 49 | 31 | 18 | 3 | 3 | 0 |
| Age (median (IQR)) | Male | 7 (4.75—10.25) | 8 (6—11.5) | 6 (4—8) | 7 (3—10) | 5 (3—10.5) | 2 (5-) |
| | Female | 6 (3—10) | 7 (4—11) | 4 (2.75—7) | 3 (4-) | 3 (4-) | - |
| Varicella history | Yes | 11 | 9 | 2 | 1 | 1 | 0 |
| | No | 25 | 9 | 16 | 2 | 1 | 1 |
| | Unknown | 71 | 46 | 25 | 7 | 6 | 1 |
| Vaccination history | 0 | 27 | 12 | 15 | 2 | 2 | 0 |
| | 1 | 9 | 5 | 4 | 0 | 0 | 0 |
| | ≥2 | 19 | 6 | 13 | 1 | 0 | 1 |
| | Unknown | 52 | 41 | 11 | 7 | 6 | 1 |

VZV, Varicella-Zoster virus, PEP, post-exposure prophylaxis, IQR, interquartile range.
* Others, outpatients and patients diagnosed outside Nagoya University Hospital.

**Table III**
Underlying conditions in patients exposed to VZV infection

| Underlying conditions | | Total (n, %) (n=117) | PEP (n, %) (n=107) | Non-PEP (n, %) (n=10) |
|---|---|---|---|---|
| Primary disorder | Hematological malignancy | 41 (35.0) | 38 (35.5) | 3 (30.0) |
| | Solid tumor | 62 (53.0) | 56 (52.3) | 6 (60.0) |
| | Primary immunodeficiency | 6 (5.1) | 6 (5.6) | 0 (0) |
| | Others | 8 (6.8) | 7 (6.5) | 1 (10.0) |
| Chemotherapy | | 71 (60.7) | 63 (58.9) | 8 (80.0) |
| Immunosuppressive therapy | | 46 (39.3) | 43 (40.2) | 3 (30.0) |
| Transplantation | Hematopoietic stem cell | 30 (25.6) | 28 (26.2) | 2 (20.0) |
| | Liver | 8 (6.8) | 8 (7.5) | 0 (0) |

VZV, Varicella-Zoster virus; PEP, post-exposure prophylaxis.

immunocompromised patients. This study was conducted in a relatively larger cohort than that previously reported [9–14]. Despite the lack of convincing evidence, some experts recommend using ACV/VCV as PEP for mildly immunocompromised patients [1]. Indeed, a few studies have reported the use of ACV/VCV as a single PEP. Ruvinsky *et al*. [12]have reported that ACV administration as PEP is effective and well-tolerated in immunocompromised children. The authors assessed 50 immunocompromised children who received oral ACV (80 mg/kg/day) on day 5 of contact/exposure for 7 days. No secondary cases were observed at 30 days, and no adverse effects were recorded. Shinjoh *et al*. [13] have investigated the incidence of secondary VZV infection following ACV administration as PEP in 65 immunocompromised patients at a pediatric ward, noting the occurrence of a single secondary case (3.1%). Our results were consistent with these findings, suggesting that PEP with antiviral agents is effective. Regarding VZIG, one recent study has analyzed more than 500 participants, including immunocompromised patients, to reveal the effectiveness of VariZIG (varicella-zoster immunoglobulin, human) in preventing secondary VZV infection [14]. The incidence of varicella was 4.5% in immunocompromised participants. Further randomized studies (antiviral agent *vs*. VZIG or IVIG) are needed to confirm the effectiveness of antiviral agents as PEP to prevent VZV infection in immunocompromised patients.

**Table IV**
Secondary incidence of VZV infection in patients exposed to VZV

| | | Patients exposed to VZV | | Patients exposed to VZV (n, %) (Diagnosis using PCR/antigen detection) | |
|---|---|---|---|---|---|
| | | n | VZV infection incidence (n, %) | n | VZV infection incidence (n, %) |
| PEP | | 107 | 2 (1.9)* | 66 | 1 (1.5)† |
| | ACV/VCV | 91 | 2 (2.2)‡ | 55 | 1 (1.8)§ |
| | ACV | 7 | 0 (0) | 3 | 0 (0) |
| | VCV | 83 | 2 (2.4)¶ | 52 | 1 (1.9)†† |
| | ACV+VCV | 1 | 0 (0) | 0 | 0 (0) |
| | IVIG | 0 | 0 (0) | 0 | 0 (0) |
| | ACV/VCV/IVIG | 16 | 0 (0) | 11 | 0 (0) |
| | ACV+IVIG | 1 | 0 (0) | 0 | 0 (0) |
| | VCV+IVIG | 15 | 0 (0) | 11 | 0 (0) |
| | ACV+VCV+IVIG | 0 | 0 (0) | 0 | 0 (0) |
| | Vaccine | 0 | 0 (0) | 0 | 0 (0) |
| Non-PEP | | 10 | 2 (20.0) | 6 | 1 (16.7) |

PEP post-exposure prophylaxis, VZV Varicella-Zoster virus, ACV acyclovir, VCV valacyclovir, IVIG intravenous immunoglobulin.

†† *P*-values refer to the comparison of incidence in the PEP group administered VCV only and non-PEP groups. *P*=0.191 Fisher's exact test.

* *P*-values refer to the comparison of incidence in the PEP and non-PEP groups. *P*=0.036 using Fisher's exact test.

† *P*-values refer to the comparison of incidence in the PEP group administered PEP and non-PEP groups. *P*=0.161 Fisher's exact test.

‡ *P*-values refer to the comparison of incidence in the PEP group administered ACV/VCV and non-PEP groups. *P*=0.048 Fisher's exact test.

§ *P*-values refer to the comparison of incidence in the PEP group administered ACV/VCV and non-PEP groups. *P*=0.189 Fisher's exact test.

¶ *P*-values refer to the comparison of incidence in the PEP group administered VCV only and non-PEP groups. *P*=0.056 Fisher's exact test.

Primary VZV infection is typically diagnosed based on clinical symptoms. In the present study, the majority of primary VZV infections were clinically diagnosed. In the current varicella-zoster vaccination era, it is sometimes difficult to differentiate varicella from other bullous lesions without virological methods, given the incidence of breakthrough (modified) varicella [15]. In immunocompromised patients, the symptoms of zoster are occasionally atypical. Accordingly, there is a growing need for diagnosis using virological methods. Direct detection of antigens or DNA in clinical samples is appropriate for rapid diagnosis when compared with serological testing. In previous reports [9–14], most primary VZV infections were exclusively diagnosed based on clinical symptoms or serological methods. However, these reports may include bullous diseases other than varicella and zoster. In the present study, we promptly diagnosed VZV using a PCR assay in suspected VZV infection to prevent an outbreak at the hospital. We then initiated treatment for VZV infection in the index case and administered PEP to exposed children as earliest. Accordingly, most patients with VZV at the hospital were diagnosed using a PCR assay. As shown in Table 4, the secondary VZV infection rate was 1.8% in the PEP group administered antiviral agents and 16.7% in the non-PEP group. Therefore, direct virological diagnosis may assess PEP more precisely.

Our study has several limitations. Firstly, half of the patients included in this study had no records of history of varicella

infection and varicella-zoster vaccination. Although data regarding sensitivity and specificity of serologic tests are unavailable for predicting the protection against varicella in immunocompromised patients, the specific antibody for VZV may influence secondary infection. Secondly, the primary disorder in patients and the degree of immunosuppression were diverse. Thirdly, 51 index cases (74%) were diagnosed based on clinical symptoms outside our hospital setting, and a few index cases of other bullous lesions, such as hand-foot-mouth disease and other herpes rashes, could have been misdiagnosed as VZV infections. Moreover, patients with relatively severe immunosuppression may regularly receive IVIG owing to temporal hypogammaglobulinemia. Indeed, 7 patients (44%) were post-HSCT in the early phase post-transplantation and received regular IVIG. Finally, the range of all administered antiviral agents and IVIG doses was extensive. However, in 2 patients who developed secondary VZV infection under PEP with VCV, the doses of VCV were not small at 75 mg/kg/day and 60 mg/kg/day. Therefore, VCV doses were unlikely to be associated with developing secondary VZV infection.

## Conclusions

Antiviral agents, such as PEP, are sufficiently effective and safe for preventing VZV infection in immunocompromised patients. The efficacy of antiviral agents may not be inferior to that of VZIG (or IVIG) in immunocompromised patients without severe immunosuppression. Rapid virological diagnosis of index cases could allow the efficient administration of PEP after significant exposure to VZV infection.

## Author contributions

MY, NT, TO, KH and TS were the primary doctors of the patients. MY, NT, and YI drafted the manuscript. YT and JK contributed to the data collection and helped to revise the manuscript. MY and YI contributed to the study conception and design. All authors read and approved the final manuscript.

## Conflict of interest

The authors declare no conflict of interest.

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