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David M. Weinstock  
Mem. Sloan-Kettering Cancer Center

Michael Boeckh  
University of Washington - Seattle Campus

Farid Boulad  
Mem. Sloan-Kettering Cancer Center

Janet A. Eagan  
Mem. Sloan-Kettering Cancer Center

Victoria J. Fraser  
Washington University School of Medicine in St. Louis

See next page for additional authors

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Infections in Immunocompromised Patients

EDITED BY KENT A. SEPKOWITZ, MD

Postexposure Prophylaxis Against Varicella-Zoster Virus Infection Among Recipients of Hematopoietic Stem Cell Transplant: Unresolved Issues

David M. Weinstock, MD; Michael Boeckh, MD; Farid Boulad, MD; Janet A. Eagan, RN; Victoria J. Fraser, MD; David K. Henderson, MD; Trish M. Perl, MD, MSc; Deborah Yokoe, MD, MPH; Kent A. Sepkowitz, MD

ABSTRACT

Recent guidelines for the prevention of opportunistic infections have addressed a variety of issues germane to recipients of hematopoietic stem cell transplant. However, there are several issues regarding postexposure prophylaxis against varicella-zoster virus that remain unresolved. We address these questions and offer several consensus recommendations (Infect Control Hosp Epidemiol 2004;25:603-608).

Varicella-zoster virus (VZV) causes significant morbidity in recipients of hematopoietic stem cell transplant. Recent studies have reported VZV disease (ie, either varicella or zoster) in 10% to 67% of recipients of autologous and allogeneic hematopoietic stem cell transplants. Recommendations for the prevention of opportunistic infections among recipients of hematopoietic stem cell transplant were jointly published in 2000 by the Centers for Disease Control and Prevention, the Infectious Diseases Society of America, and the American Society for Blood and Bone Marrow Transplantation. Multiple guidelines for the prevention and treatment of VZV among recipients of hematopoietic stem cell transplant are included in the recommendations (Table 1). However, six common clinical issues were not specifically addressed. We discuss these issues, highlight areas of continued controversy, and make consensus recommendations when possible.

WHAT CONSTITUTES A VZV EXPOSURE AMONG RECIPIENTS OF HEMATOPOIETIC STEM CELL TRANSPLANT?

VZV can be transmitted to recipients of hematopoietic stem cell transplant through either direct contact with or inhalation of respiratory secretions from an individual with VZV disease. The risk of acquiring VZV is directly proportional to the duration and intensity of contact and inversely proportional to the exposed individual’s immunity to VZV. Varicella develops in approximately 90% of immunocompetent, susceptible household contacts who receive no prophylaxis after exposure to varicella and 25% after exposure to zoster. The risk of VZV transmission after exposure to varicella decreases to less than 20% following brief contact (eg, with playmates or exposure in the hospital). Importantly, nosocomial transmission of VZV to seronegative individuals who had no known contact with the index case-patient has occurred. The roles of air ventilation systems and intermediaries who may have harbored clinical or subclinical infection (eg, hospital staff) are poorly understood.

Because of these reports and the significant potential for complications from VZV among recipients of hematopoietic stem cell transplant, an inclusive definition for “exposure” seems appropriate. However, the literature does not support an absolute definition for exposure and the authors did not reach a consensus. Some authors consider any contact with an individual with varicella or zoster (ie, other than a single dermatome that was completely covered) to be an exposure. This includes all...
VZV antibodies prior to exposure developed clinically and were associated with an astounding 28% with detectable VZIG among immunocompromised children with no clinical history of varicella, an astounding 28% with detectable VZIG among immunocompromised children with no clinical history of varicella, an astounding 28% with detectable VZIG among immunocompromised children with no clinical history of varicella.

In contrast, at least 57 immunocompromised patients with minimal or no risk of acquiring VZV to unnecessary treatment and isolation. As with many patients who spent time on the same inpatient unit or outpatient clinic as an individual with VZV disease who was not appropriately isolated. Other authors think that this definition is overly inclusive and relegates too many seronegative or have no history of VZV.

The arguments for and against postexposure VZIG for VZV-seropositive recipients of hematopoietic stem cell transplant are listed in Table 3. There is no evidence that passive antibody prophylaxis with VZIG augments preexisting humoral response or reduces the risk of VZV reactivation among VZV-seropositive recipients of hematopoietic stem cell transplant.2,42 In addition, a dose–response relationship does not clearly exist between VZIG dose and the risk of developing varicella. In a randomized trial, doubling the dose of VZIG had no effect on the likelihood of developing clinically apparent VZV infection (adjusted risk ratio, 1.00).35

A particularly compelling point in favor of VZIG administration is the potential for false-positive VZV antibody results. Commercially available VZV antibody tests vary markedly in sensitivity and specificity44 and have not been evaluated specifically for recipients of hematopoietic stem cell transplant. As discussed, VZV-naive patients may passively acquire detectable levels of VZV antibody from transfused blood products including immune globulin.20 Many laboratories report VZV antibody results as only “positive” or “negative,” preventing any distinction between low and high positive titers. Finally, rapid turnaround of reliable VZV antibody results is not available at all centers, limiting the practitioner’s ability to make expedient decisions on the need for postexposure VZIG.

Recipients of hematopoietic stem cell transplant who are exposed to VZV should undergo antibody testing as soon as possible after exposure. Despite the potential for false-positive antibody results, the authors do not routinely recommend VZIG for recipients of hematopoietic stem cell transplant who are VZV seropositive. The low risk of reactivation, lack of evidence for a VZIG dose–response relationship, limited efficacy of VZIG, and availability of alternative prophylaxis all argue against the use of VZIG for these patients. If the VZV serostatus is unknown (eg, in settings where rapid turnaround of VZV antibody results is not available), the authors recommend that VZIG be administered. Although

### Table 1

<table>
<thead>
<tr>
<th>Type of Prevention</th>
<th>Rating*</th>
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<tbody>
<tr>
<td>Testing of recipient IgG serostatus</td>
<td>AIII</td>
</tr>
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<tr>
<td>to prevent exposure†</td>
<td></td>
</tr>
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<tr>
<td>contacts who are seronegative or have no history of VZV</td>
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</tr>
<tr>
<td>Respiratory and contact isolation of HSCT recipients</td>
<td>AII</td>
</tr>
<tr>
<td>with VZV</td>
<td></td>
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<tr>
<td>Respiratory isolation of seronegative, susceptible</td>
<td>AI</td>
</tr>
<tr>
<td>HSCT recipients exposed to wild-type VZV†</td>
<td></td>
</tr>
<tr>
<td>VZIG within 96 hours for VZV-seronegative recipients</td>
<td>AII</td>
</tr>
<tr>
<td>following an exposure with wild-type VZV†</td>
<td></td>
</tr>
<tr>
<td>Exclusion of HSCT recipients &lt; 24 months</td>
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</tr>
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HSCT = hematopoietic stem cell transplant; VZV = varicella-zoster virus; VZIG = varicella-zoster immune globulin.


†The same recommendations were also made for the VZV vaccine (with BIII rating).

### Patients who spent time on the same inpatient unit or outpatient clinic as an individual with VZV disease who was not appropriately isolated. Other authors think that this definition is overly inclusive and relegates too many patients with minimal or no risk of acquiring VZV to unnecessary treatment and isolation. As with many pathogens of concern to infection control practitioners, the institutional definitions for VZV exposure are frequently affected by the presence or absence of nosocomial transmission within recent memory.

ARE VZV-SEROPOSITIVE RECIPIENTS OF HEMATOPOIETIC STEM CELL TRANSPLANT SUSCEPTIBLE TO VZV REINFECTION (IE, SECOND ACUTE INFECTION)?

The conventional wisdom is that the risk of VZV reinfection among immunocompetent hosts is negligible.22,23 In contrast, at least 57 immunocompromised patients with possible reinfection have been described (Table 2). In a study of postexposure varicella-zoster immune globulin (VZIG) among immunocompromised children with no clinical history of varicella, an astounding 28% with detectable VZV antibodies prior to exposure developed clinically apparent VZV infection.35 At least 5 recipients of hematopoietic stem cell transplant have developed possible VZV reinfections (M. Boeckh, MD, personal communication, April 2003; F. Boulad, MD, personal communication, June 2003).35 Most of the possible reinfections were mild and manifested as an atypical, maculopapular rash without visceral involvement. In many cases, the diagnosis of reinfection was based on an appropriate temporal relationship between exposure and the onset of symptoms and supported by serologic evidence of immunity prior to reinfection. The patients frequently had no clinical history of varicella and VZV antibody titers prior to reinfection were low, potentially resulting from passive immunization through transfused blood products, immune globulin, or both.20 Together, these reports suggest a low, but not insignificant, rate of reinfection in this group of patients.

### Table 2

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this approach uses an expensive resource, prevention of VZV disease remains a high priority for transplant centers and the consequences of infection may be substantial.

WHAT IS THE ROLE OF ACYCLOVIR AND OTHER ANTIHERPETICS FOR VZV POSTEXPOSURE PROPHYLAXIS AMONG RECIPIENTS OF HEMATOPOIETIC STEM CELL TRANSPLANT?

Unfortunately, VZIG appears to be only partially effective at preventing VZV disease. In studies of VZIG prophylaxis, 25% to 45% of treated contacts (including immunocompetent individuals) developed clinically apparent varicella.33,44-46 In contrast, acyclovir has demonstrated reasonable efficacy as prophylaxis for susceptible individuals exposed to VZV. In one nonrandomized study, varicella developed in 16% of seronegative immunocompetent children treated with acyclovir during the second week after exposure compared with 100% of untreated controls.47 No data are available on acyclovir as postexposure prophylaxis for recipients of hematopoietic stem cell transplant. However, extensive clinical experience indicates that acyclovir and valacyclovir are highly effective at preventing VZV reactivation in transplant recipients.48-54 In a meta-analysis of 1,574 patients after solid organ transplantation, the risk of herpes zoster was reduced 94% among patients administered any dose of acyclovir or valacyclovir.46 Comparable
TABLE 3
ARGUMENTS FOR AND AGAINST THE ADMINISTRATION OF VARICELLA-ZOSTER IMMUNE GLOBULIN TO VARICELLA-ZOSTER VIRUS–SEROPOSITIVE RECIPIENTS OF HEMATOPOIETIC STEM CELL TRANSPLANT EXPOSED TO VARICELLA

For
- Theoretical potential for supplementing immunity against VZV
- Previous reports of varicella in VZV-seropositive patients
- Low incidence of adverse effects associated with VZIG administration
- Only a single dose of VZIG required
- Prevents undertreatment of patients with false-positive antibody results
- Obviates the need for rapid VZV antibody turnaround
- Healthcare provider peace of mind

Against
- Cost
- Paucity of reports of varicella in VZV-seropositive patients
- Lack of proven efficacy in VZV IgG–seropositive patients
- Potential for adverse effects and discomfort associated with VZIG administration (ie, primum non nocere)
- Extends the potential VZV incubation period to 28 days after exposure

VZV = varicella-zoster virus; VZIG = varicella-zoster immune globulin.

efficacy has been reported in several trials of acyclovir after hematopoietic stem cell transplant.49,54

The authors recommend that postexposure prophylaxis with valacyclovir or acyclovir be considered in addition to VZIG for all VZV-seronegative recipients of hematopoietic stem cell transplant. VZV-seropositive recipients of hematopoietic stem cell transplant should also receive valacyclovir or acyclovir if it has been less than 6 months since an autologous hematopoietic stem cell transplant, it has been less than 12 months since an allogeneic hematopoietic stem cell transplant, if they are receiving immunosuppressive therapy, if they have active graft-versus-host disease, or if they are otherwise immunodeficient (eg, CD4 count < 200/L, recent opportunistic infection). The one exception is seropositive patients who have previously experienced an episode of VZV disease after hematopoietic stem cell transplant. These patients appear to be at no risk for VZV reinfection.20,22

Some authors argued that all recipients of hematopoietic stem cell transplant who are not immunocompetent (ie, eligible to receive a live vaccination such as measles) should receive valacyclovir or acyclovir after VZV exposure, based on the limited toxicity and cost of these agents. In addition, the brief duration of therapy is highly unlikely to induce resistance among VZV.4

No standard doses of acyclovir or valacyclovir have been clearly justified for postexposure prophylaxis. Based on institutional experiences and extrapolation from the treatment of VZV disease, the authors recommend 1 g of valacyclovir orally three times daily if greater than 40 kg, or 500 mg orally three times daily if less than 40 kg. An alternative is 600 mg/m² of acyclovir four times daily from days 3 to 22 after exposure. Valacyclovir is not recommended for children younger than 12 years. All VZV-seronegative (or unknown) recipients should also receive VZIG within 96 hours after exposure. Because VZIG can prolong the incubation period of VZV,20,49 valacyclovir (or acyclovir) should be administered between days 3 and 28 after exposure in patients who also receive VZIG. Patients who are receiving prophylactic acyclovir or valacyclovir at lower doses should receive the higher dose during the period 3 to 22 days (or 3 to 28 days if VZIG was administered) after VZV exposure. Patients receiving standard induction or maintenance doses of ganciclovir, foscarnet, or cidofovir do not require a change in therapy after VZV exposure, as these agents are active against VZV.
ceptibility of some cancer patients to VZV reinfection. Reactivation of latent herpes viruses can occur after treat-
ment with agents such as fludarabine or alemtuzumab. However, no cases of VZV reinfection have been reported.
Among these patients, the authors recommend reserving postexposure prophylaxis against VZV reinfection for those
who (1) are currently receiving highly immunosuppressive therapy, (2) have a profound T-cell defect, or (3) previously
experienced a significant opportunistic infection caused by a pathogen associated with cellular immunodeficiency (eg, Pneumocystis carinii pneumonia or cytomegalovirus reacti-
vation). Further data are clearly needed to establish formal guidelines for these patients.

DISCUSSION
The guidelines of the Centers for Disease Control and Prevention, Infectious Diseases Society of America, and American Society for Blood and Bone Marrow Transplantation for prevention of opportunistic infections in recipients of hematopoietic stem cell transplant address many important issues facing transplant and infectious disease physicians who care for these patients. Infection control measures, including counseling, vaccination of close contacts, and early isolation of potential cases of VZV disease, are the primary mechanisms of preventing VZV exposures. However, exposures will continue to occur as VZV disease remains a common event in the pop-
ulation. Despite the potential for severe consequences, prophylactic regimens to prevent VZV infection among recipients of hematopoietic stem cell transplant are contro-
versial and vary widely. For example, in a 1994 survey of nine pediatric centers for hematopoietic stem cell trans-
plant in the United Kingdom, postexposure prophylaxis consisted of VZIG alone at three centers, VZIG and acyc-
lovir at one center, and acyclovir alone at the remaining five centers. No two centers used the same dose of acyc-
lovir.

We have addressed six common issues in the manage-
ment of VZV among recipients of hematopoietic stem cell transplant. First, a consensus definition of VZV expo-
sure remained elusive, although a highly inclusive defini-
tion may be justified considering the potential for serious VZV disease in this population. Second, the literature in-
dicates that recipients of hematopoietic stem cell transplant with detectable VZV antibody are at risk for VZV infection. Because of this apparent susceptibility, the third issue is whether such individuals should be given postexposure prophylaxis with VZIG. Based on our experience and our current understanding of its efficacy, we recommend VZIG only for postexposure prophylaxis of immunocompromised recipients of hematopoietic stem cell transplant who are not known to be VZV seropositive after hematopoietic stem cell transplant. Fourth, recipients of hematopoietic stem cell transplant should receive valacyclovir or acyclovir after exposure unless they both are VZV seropositive and have regained significant immunity after transplant. No consen-
sus was reached on the extent of immune restoration nec-
essary to negate the possibility of VZV reinfection. Fifth, every effort should be made to prevent varicella in VZV-
susceptible contacts who are exposed to VZV. Finally, for severely immunosuppressed oncology patients who have profound T-cell immunodeficiency but are not recipients of hematopoietic stem cell transplant, we recommend managing VZV exposures similarly to the suggested recommenda-
dations for recipients of hematopoietic stem cell transplant outlined above.

We recognize that questions remain, opinions forged in the absence of definitive evidence will vary markedly, and vaccine-related exposures were not addressed. Therefore, we hope these recommendations will stimulate further discussion and investigation.

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