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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

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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.¹⁻¹⁹ 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.^{20,21} 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 indi-

vidual with VZV disease.²² 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.^{23,24} 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).²² Importantly, nosocomial transmission of VZV to seronegative individuals who had no known contact with the index case-patient has occurred.²⁵⁻²⁸ 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

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TABLE 1

SUMMARY OF MAJOR RECOMMENDATIONS FOR THE PREVENTION OF INFECTION WITH VARICELLA-ZOSTER VIRUS AS OUTLINED IN THE GUIDELINES FROM THE CENTERS FOR DISEASE CONTROL AND PREVENTION, INFECTIOUS DISEASES SOCIETY OF AMERICA, AND AMERICAN SOCIETY FOR BLOOD AND BONE MARROW TRANSPLANTATION

Type of Prevention	Rating*
Testing of recipient IgG serostatus	AIII
Counseling about the seriousness of wild-type VZV infection in HSCT recipients and strategies to prevent exposure†	AII
Vaccination of family members and close household contacts who are seronegative or have no history of VZV†	AII
Respiratory and contact isolation of HSCT recipients with VZV	AII
Respiratory isolation of seronegative, susceptible HSCT recipients exposed to wild-type VZV†	AI
VZIG within 96 hours for VZV-seronegative recipients following an exposure with wild-type VZV†	AII
Exclusion of HSCT recipients < 24 months after transplant from receiving VZV vaccine	EIII

HSCT = hematopoietic stem cell transplant; VZV = varicella-zoster virus; VZIG = varicella-zoster immune globulin.

*Rating system follows the scheme developed by the Infectious Diseases Society of America and the U.S. Public Health Service for the human immunodeficiency virus opportunistic infection guidelines (Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis* 1994;18:421).

†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 were 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.^{22,29} 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).¹⁰ 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.

WHAT IS THE ROLE OF VZIG FOR POSTEXPOSURE PROPHYLAXIS AMONG VZV-SEROPOSITIVE RECIPIENTS OF HEMATOPOIETIC STEM CELL TRANSPLANT?

Given that seropositive recipients of hematopoietic stem cell transplant may be at risk for reinfection, established interventions must be considered after an exposure. 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 specificity⁴³ and have not been evaluated specifically for recipients of hematopoietic stem cell transplant. As discussed, VZV-naïve 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 reinfection, 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 2

REPORTS OF 57 IMMUNOCOMPROMISED AND 5 IMMUNOCOMPETENT PATIENTS WITH POSSIBLE REINFECTION WITH VARICELLA-ZOSTER VIRUS*

Study	Study Period	No. of Cases	Location	Known Exposure and Appropriate Incubation	Laboratory Confirmation	Description
Feldhoff et al. ³⁰	1968–1979	3	Minneapolis, MN	Yes	Serology in 1 case	Pediatric renal transplant recipients
Schimpff et al. ³¹	1969–1971	7	Baltimore, MD	4 of 7	None	All cases of “atypical disseminated varicella” among patients with prior varicella at a cancer hospital
Gershon et al. ³²	1975–1982	8	United States	4 of 8	Serology by multiple methods, VZV DNA analysis in 1 case, cell-mediated immunity in 2 cases	Three normal adults, 4 patients with leukemia, and 1 patient with lupus. One patient with leukemia developed reinfection from wild-type VZV 10 months after receiving VZV vaccine.
Morens et al. ³³	1975–1982	8	Bethesda, MD	7 of 8	Serology in some cases	Eight of 22 cases of VZV during an outbreak among cancer patients
Pallett and Nichols ³⁴	1982	3	England	Yes	None	Outbreak among elderly nursing home residents
Zaia et al. ³⁵	1983	16	United States	Yes	Serology	Immunocompromised children with no history of varicella and exposed to a sibling with VZV enrolled in a study of varicella immune globulin
Talbot et al. ³⁶	1984	1	Philadelphia, PA	Yes	Serology	Nurse without a history of varicella exposed to a patient with zoster
Husstedt et al. ³⁷	1984	1	Germany	Unknown	Serology	Pregnant woman
Ljungman et al. ¹⁰	1986	3	Sweden	Yes	None	Pediatric bone marrow transplant recipients
McNamara et al. ³⁸	1987	1	Milwaukee, WI	Yes	Serology	Renal transplant recipient receiving azathioprine and prednisone
Junker et al. ³⁹	1988	7	Denmark	Yes	None	Outbreak among 6 immunocompromised patients with lymphoproliferative disease and 1 immunocompromised individual all reporting childhood varicella
Marczynska ⁴⁰	1989	1	Poland	Unknown	None	Child with acute lymphocytic leukemia
Schoub et al. ⁴¹	1992	3	South Africa	Yes	Serology	Outbreak among elderly nursing home residents

VZV = varicella-zoster virus.

*Cases of zoster that occurred after exposure to an index case with zoster or varicella are not included.

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.^{35,44-46}

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.⁴⁸ 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/uL, 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.

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,^{20,44} 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.

WHAT TREATMENT IS APPROPRIATE FOR SUSCEPTIBLE HOUSEHOLD AND OTHER CLOSE CONTACTS WHO ARE EXPOSED TO VZV?

Considering the inordinately high risk of transmission from household and other close contacts, we recommend an aggressive treatment strategy to avoid VZV disease among this group. If a VZV-susceptible household or close contact is exposed to VZV, the contact should receive VZV vaccination. In a study of immunocompetent children vaccinated within 3 days of exposure, the protective efficacy of VZV vaccine as postexposure prophylaxis was approximately 90%.⁵⁵ If ineligible for vaccine, the exposed contact should receive the combination of VZIG and either valacyclovir or acyclovir. Because VZIG appears to be significantly less effective at preventing VZV disease than does vaccination, individuals treated with VZIG should also be offered valacyclovir or acyclovir until day 28 after exposure (as described earlier) to further reduce both their personal risk and the risk of transmitting VZV to the recipient of hematopoietic stem cell transplant. Contact between the exposed individual and the recipient of hematopoietic stem cell transplant should be minimized to whatever extent possible between days 10 and 21 (or 10 and 28 if VZIG was administered) after exposure.

ARE CANCER PATIENTS OTHER THAN THOSE RECEIVING HEMATOPOIETIC STEM CELL TRANSPLANT AT RISK FOR VZV REINFECTION?

Prophylaxis after VZV exposure is not routinely recommended in cancer patients who have not received hematopoietic stem cell transplant and are VZV seropositive or report a history of VZV disease. However, most reported cases of reinfection occurred among patients with hematologic malignancies who had not undergone hematopoietic stem cell transplant. In addition, the advent of new high-dose regimens and chemotherapies (eg, fludarabine, alemtuzumab, temozolomide, or high-dose alkylating agents) that can induce profound and prolonged T-cell immunodeficiency has raised concern over the sus-

ceptibility of some cancer patients to VZV reinfection. Reactivation of latent herpes viruses can occur after treatment with agents such as fludarabine or alemtuzumab.^{56,57} 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 reactivation). Further data are clearly needed to establish formal guidelines for these patients.

DISCUSSION

The guidelines²⁰ 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 population. Despite the potential for severe consequences, prophylactic regimens to prevent VZV infection among recipients of hematopoietic stem cell transplant are controversial and vary widely. For example, in a 1994 survey of nine pediatric centers for hematopoietic stem cell transplant in the United Kingdom, postexposure prophylaxis consisted of VZIG alone at three centers, VZIG and acyclovir at one center, and acyclovir alone at the remaining five centers.⁵⁸ No two centers used the same dose of acyclovir.

We have addressed six common issues in the management of VZV among recipients of hematopoietic stem cell transplant. First, a consensus definition of VZV exposure remained elusive, although a highly inclusive definition may be justified considering the potential for serious VZV disease in this population. Second, the literature indicates 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 consensus was reached on the extent of immune restoration necessary 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 recommendations 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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