Postexposure prophylaxis against varicella-zoster virus infection among recipients of hematopoietic stem cell transplant: Unresolved issues

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

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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...
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, INFECTION DISEASES SOCIETY OF AMERICA, AND AMERICAN SOCIETY FOR BLOOD AND BONE MARROW TRANSPLANTATION

| Type of Prevention                                      | Rating
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing of recipient IgG serostatus</td>
<td>AIII</td>
</tr>
<tr>
<td>Counseling about the seriousness of wild-type VZV</td>
<td>AII</td>
</tr>
<tr>
<td>infection in HSCT recipients and strategies to prevent exposure†</td>
<td>AII</td>
</tr>
<tr>
<td>Vaccination of family members and close household</td>
<td>AII</td>
</tr>
<tr>
<td>contacts who are seronegative or have no history of VZV</td>
<td>AII</td>
</tr>
<tr>
<td>Respiratory and contact isolation of HSCT recipients</td>
<td>AII</td>
</tr>
<tr>
<td>with VZV</td>
<td></td>
</tr>
<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>
<td>EIII</td>
</tr>
<tr>
<td>after transplant from receiving VZV vaccine</td>
<td></td>
</tr>
</tbody>
</table>

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 III rating).
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.46 Comparable

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### TABLE 2

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Period</th>
<th>No. of Cases</th>
<th>Location</th>
<th>Known Exposure and Appropriate Incubation</th>
<th>Laboratory Confirmation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldhoff et al.30</td>
<td>1968-1979</td>
<td>3</td>
<td>Minneapolis, MN</td>
<td>Yes</td>
<td>Serology in 1 case</td>
<td>Pediatric renal transplant recipients</td>
</tr>
<tr>
<td>Schimpff et al.31</td>
<td>1969-1971</td>
<td>7</td>
<td>Baltimore, MD</td>
<td>4 of 7</td>
<td>None</td>
<td>All cases of “atypical disseminated varicella” among patients with prior varicella at a cancer hospital</td>
</tr>
<tr>
<td>Gershon et al.32</td>
<td>1975-1982</td>
<td>8</td>
<td>United States</td>
<td>4 of 8</td>
<td>Serology by multiple methods, VZV DNA analysis in 1 case, cell-mediated immunity in 2 cases</td>
<td>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.</td>
</tr>
<tr>
<td>Morens et al.33</td>
<td>1975-1982</td>
<td>8</td>
<td>Bethesda, MD</td>
<td>7 of 8</td>
<td>Serology in some cases</td>
<td>Eight of 22 cases of VZV during an outbreak among cancer patients</td>
</tr>
<tr>
<td>Pallett and Nichols34</td>
<td>1982</td>
<td>3</td>
<td>England</td>
<td>Yes</td>
<td>None</td>
<td>Outbreak among elderly nursing home residents</td>
</tr>
<tr>
<td>Zaia et al.35</td>
<td>1983</td>
<td>16</td>
<td>United States</td>
<td>Yes</td>
<td>Serology</td>
<td>Immunocompromised children with no history of varicella and exposed to a sibling with VZV enrolled in a study of varicella immune globulin</td>
</tr>
<tr>
<td>Talbot et al.36</td>
<td>1984</td>
<td>1</td>
<td>Philadelphia, PA</td>
<td>Yes</td>
<td>Serology</td>
<td>Nurse without a history of varicella exposed to a patient with zoster</td>
</tr>
<tr>
<td>Husstedt et al.37</td>
<td>1984</td>
<td>1</td>
<td>Germany</td>
<td>Unknown</td>
<td>Serology</td>
<td>Pregnant woman</td>
</tr>
<tr>
<td>Ljungman et al.38</td>
<td>1986</td>
<td>3</td>
<td>Sweden</td>
<td>Yes</td>
<td>None</td>
<td>Pediatric bone marrow transplant recipients</td>
</tr>
<tr>
<td>McNamara et al.39</td>
<td>1987</td>
<td>1</td>
<td>Milwaukee, WI</td>
<td>Yes</td>
<td>Serology</td>
<td>Renal transplant recipient receiving azathioprine and prednisone</td>
</tr>
<tr>
<td>Junker et al.40</td>
<td>1988</td>
<td>7</td>
<td>Denmark</td>
<td>Yes</td>
<td>None</td>
<td>Outbreak among 6 immunocompromised patients with lymphoproliferative disease and 1 immunocompromised individual all reporting childhood varicella</td>
</tr>
<tr>
<td>Marczynska41</td>
<td>1989</td>
<td>1</td>
<td>Poland</td>
<td>Unknown</td>
<td>None</td>
<td>Child with acute lymphocytic leukemia</td>
</tr>
<tr>
<td>Schoub et al.42</td>
<td>1992</td>
<td>3</td>
<td>South Africa</td>
<td>Yes</td>
<td>Serology</td>
<td>Outbreak among elderly nursing home residents</td>
</tr>
</tbody>
</table>

VZV = varicella-zoster virus.

*Cases of zoster that occurred after exposure to an index case with zoster or varicella are not included.
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/μL, 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.49,54

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.

**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**

<table>
<thead>
<tr>
<th>For</th>
<th>Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical potential for supplementing immunity against VZV</td>
<td>Cost</td>
</tr>
<tr>
<td>Previous reports of varicella in VZV-seropositive patients</td>
<td>Paucity of reports of varicella in VZV-seropositive patients</td>
</tr>
<tr>
<td>Low incidence of adverse effects associated with VZIG administration</td>
<td>Lack of proven efficacy in VZV IgG–seropositive patients</td>
</tr>
<tr>
<td>Only a single dose of VZIG required</td>
<td>Potential for adverse effects and discomfort associated with VZIG administration (ie, primum non nocere)</td>
</tr>
<tr>
<td>Prevents undertreatment of patients with false-positive antibody results</td>
<td>Extends the potential VZV incubation period to 28 days after exposure</td>
</tr>
<tr>
<td>Obliviates the need for rapid VZV antibody turnaround</td>
<td>Healthcare provider peace of mind</td>
</tr>
<tr>
<td>Extends the potential VZV incubation period to 28 days after exposure</td>
<td></td>
</tr>
</tbody>
</table>

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

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 seronegative 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 treat-
ment with agents such as fludarabine or alemtuzumab.\textsuperscript{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 (e.g., \textit{Pneumocystis carinii} pneumonia or cytomegalovirus reactiva-
tion). Further data are clearly needed to establish formal guidelines for these patients.

DISCUSSION

The guidelines\textsuperscript{20} 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 popu-
lation. 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 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.\textsuperscript{58} No two centers used the same dose of acyc-
lovir.

We have addressed six common issues in the man-
agement of VZV among recipients of hematopoietic stem cell transplant. First, a consensus definition of VZV ex-
posure remained elusive, although a highly inclusive defini-
tion 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. Filth, 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 manag-
ning VZV exposures similarly to the suggested recommen-
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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