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Special Article

Varicella Zoster Virus in Solid Organ Transplantation

S. A. Pergam[a,b,c,*], A. P. Limaye[a] and the AST Infectious Diseases Community of Practice

[a] *Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, WA*
[b] *Vaccine and Infectious Disease Division and*
[c] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA*
* *Corresponding author: Steven A. Pergam, spergam@fhcrc.org*

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Abbreviations: CMV, cytomegalovirus; DFA, direct fluorescent assays; HSV, herpes simplex virus; HZ, herpes zoster; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; PCR, polymerase chain reaction; PHN, postherpetic neuralgia; SOT, solid organ transplant; VZV, varicella zoster virus.

Epidemiology and Risk Factors

Epidemiology

Varicella zoster virus (VZV) is an exclusively human virus that exposure either through direct contact with a skin lesion or through airborne spread from respiratory droplets leads to acute varicella or "chickenpox" (1,2). More than 90% of adults in the United States acquired the infection in childhood; in recent years most children and many young adults have been vaccinated with the live virus vaccine (1,3). The incubation time after primary exposure is approximately 10–21 days. Primary varicella typically presents with fever, constitutional symptoms and a vesicular, pruritic, widely disseminated rash that primarily involves the trunk and face (4); symptoms usually resolve within 7–10 days. Rates of hospitalization and mortality due to varicella have dropped with the institution of routine childhood varicella vaccination (5,6).

After initial infection, VZV establishes lifelong latency in cranial nerve and dorsal root ganglia, and can reactivate years to decades later as herpes zoster (HZ) or "shingles" (7). Nearly all patients with HZ develop an exanthem of vesicular lesions in a dermatomal distribution. The annual incidence of HZ in the general population is 1.5–3.0 cases per 1000 persons (1), and is estimated to occur in up to 20% of individuals during their lifetime (8). Secondary complications such as bacterial superinfection and postherpetic neuralgia (PHN) lead to increased morbidity (9).

All patients being considered for transplant should undergo serologic testing before transplantation to document prior exposure to VZV. Over 90% of adult solid organ transplant (SOT) recipients will be seropositive for VZV. Rates of seropositivity are lower in pediatric transplants (10,11), but may improve with increased emphasis on varicella vaccination before transplantation (3). Primary infection is rare in adult SOT recipients, but can be devastating, with visceral involvement, severe skin disease, and disseminated intravascular coagulation (12–17). HZ is a frequent infectious complication in SOT recipients with an incidence of approximately 8–11% during the first 4 years posttransplant (18–20). Dissemination similar to that seen in primary VZV infection is uncommon but has been reported in SOT and other immunocompromised populations; the level of immunosuppression may alter the risk of developing this complication (15,21,22). Rates of PHN in SOT recipients may also be higher than in immunocompetent populations (19).

Risk factors

Primary varicella: Susceptible seronegative patients are at risk for primary varicella. Studies have showed that approximately 2–3% of adult SOT recipients are seronegative for VZV (11,23). Donor transmitted VZV infection is rare but has been reported in a case where the donor had recently been treated for primary varicella (24). Breakthrough varicella can occur in vaccinated patients but is usually a milder presentation when compared to wild-type primary infection (25,26). Data on risks of breakthrough varicella in immunocompromised patients who have previously been vaccinated for varicella are unknown.

Herpes zoster: Patients with previous VZV infection or VZV vaccination are at risk for the development of HZ. Because there are no large prospective trials that have evaluated HZ in SOT, risk factors are not well defined. Similar to the general population, longitudinal studies have showed that older transplant recipients are at greater risk for the development of HZ (18,20). Heart and lung transplant patients have increased rates of HZ compared to other transplant recipients, possibly related at least in part to more intensive immunosuppression (19,20,27,28). The use of mycophenolate mofetil (MMF) has also been suggested as a potential risk factor for the development of HZ (22,29,30). It is unknown whether the development of HZ before transplant lessens the risk for posttransplant recurrence. Similar to varicella, HZ can occur in patients who have previously received varicella immunization, but the episodes are thought to be milder than in patients who acquire natural infection with wild-type virus (31).

Diagnosis

In general, both primary varicella and HZ have typical clinical presentations that allow for a presumptive clinical diagnosis. Primary varicella presents as a disseminated pruritic rash that often starts on the face and spreads down the trunk, with relative sparing of the hands and soles of the feet; mucosal involvement can occur. One distinctive feature is that new lesions appear over several days so that most patients have papules, vesicles, and crusted lesions at the same time. HZ most often presents as a painful vesicular rash that involves $\leq$2 adjacent unilateral dermatomes (1). Presentations vary as patients may present with pain as a prodrome before the development of lesions, and pain may be less frequently seen in children and young adults. Herpes zoster ophthalmicus (trigeminal ganglion), herpes zoster oticus (Ramsay-Hunt syndrome – geniculate ganglion), and other unique HZ presentations have been described elsewhere (32,33).

Immunocompromised patients with HZ may develop disseminated skin lesions that can mimic primary varicella during periods of potent immunosuppression (34,35). SOT recipients are more likely to present atypically (34–36), may present with multi-organ involvement (34,37) and can rarely develop invasive complications with delayed or absent rash (36,38). In SOT recipients, who may develop a multitude of other infectious and noninfectious rashes, laboratory testing is even more important than in the normal host, as a diagnosis may be more difficult to establish on clinical grounds alone.

Definitive laboratory testing can be used for atypical cases of VZV or HZ and should routinely be used for suspected disseminated, visceral disease or central nervous system disease. Rapid diagnostic methods, including polymerase chain reaction (PCR) and direct fluorescent assays (DFA), are the methods of choice (39). PCR testing, the most sensitive test for VZV (40), can be used for detecting visceral involvement, and detects VZV in vesicle fluid, serum, spinal fluid, and other tissues. DFA is performed on scrapings taken from the base of a skin lesion, and is a rapid and reliable method for diagnosing VZV. Viral culture is specific and can help distinguish VZV from other viral pathogens such as Herpes simplex virus (HSV). Culture provides slower results and is less sensitive for VZV (41), but remains an important diagnostic entity, particularly because other viral infections (e.g. HSV) often do grow well in culture.

The majority of patients even without a history of clinical VZV infection will be seropositive (42,43). Regardless, all patients should undergo serologic testing to document prior exposure to VZV during their pretransplant evaluation process. Serology results can be used to determine posttransplant risk as patients who are seronegative before transplant are at risk for the development of primary VZV, and seropositive patients are at risk for developing posttransplant HZ. It is important to note that in acute infections serologic testing should be interpreted with caution. False-negative serologic results are more common in immunocompromised patients and may be seen during primary infection, and false-positive results can also occur after transfusions; serology should not be used for diagnosing acute infections in this population (39).

Treatment

Treatment recommendations are listed in Table 1. It is important to note that doses given in the table are given for patients with preserved renal function. In patients with renal dysfunction dosing should be reviewed before administration, because most agents will require appropriate dose modification.

Varicella

Posttransplant patients who develop primary varicella are at risk for developing severe infection and should be treated with intravenous acyclovir (I) (Table 1; Refs. 44–46). Therapy initiated early in the course of the illness, especially within 24-hours of rash onset, maximizes efficacy (39). Reduction in immunosuppressive therapy should be considered (III) (16), but to facilitate an appropriate stress response, steroid dosing should be maintained or may need to be temporarily boosted based on clinical findings. Nonspecific intravenous immunoglobulin (IVIG) or VZV immunoglobulin are unlikely to provide additional benefits to those with established infection and are therefore not recommended (39). However, IVIG and varicella zoster immune globulin (VZIG) have been used anecdotally in those with severe infection (III) (15,47–50).

Herpes zoster

Patients with disseminated or organ invasive disease should be treated with IV acyclovir (II-2) (44,46). Localized nonsevere dermatomal HZ can be treated with oral valacyclovir or famciclovir as an outpatient in most adults with close follow-up (II-1) (51,52). Two notable exceptions for those with localized infection are those within the trigeminal ganglion (herpes zoster ophthalmicus) which may be sight-threatening, and involvement of the geniculate ganglion (herpes zoster oticus/Ramsay-Hunt syndrome) which can lead to facial palsy (53). These patients should preferably receive IV acyclovir therapy, and in cases of trigeminal involvement, prompt ophthalmologic consultation to avoid major ocular complications (III). There are no data that support adding glucocorticoids to patients on steroid-sparring regimens to prevent late PHN complications so this is not recommended (III).

Prevention/Prophylaxis

Suggestions for prevention and prophylaxis are listed in Table 2. Doses given in the table are given for patients with

Table 1: Recommendations for VZV treatment in solid organ transplant recipients

Disease	Treatment	Evidence	Comments
Outpatient treatment			
Herpes zoster localized (dermatomal)	**Acyclovir** 800 mg PO five times daily (adults and children ≥12 years) OR **Valacyclovir** 1 gram PO three times daily (adults) 20 mg/kg PO four times daily (children ≥2 and ≤18) years)[1] OR **Famciclovir** 500 mg PO three times daily (adults only)	Evidence II-1	• Oral therapy is not recommended for young children <2 years of age, or patients with evidence of dissemination, tissue invasion, HZ ophthalmicus or oticus, or those with severe symptoms. These patients should be treated with IV therapy (see below) • Antivirals are typically given for at least 7 days or until lesions have crusted over, which may be delayed in immunocompromised hosts • Valacyclovir and Famciclovir are not FDA approved for treatment of herpes zoster, but are commonly used in clinical practice • Valacyclovir is only recommended for children ≥2–18 years of age • IV acyclovir is recommended in children <2 yrs of age or those who cannot tolerate oral therapy (see below for dosing) • Careful monitoring of renal function is needed while on high-dose acyclovir therapy, and dosing should be adjusted for renal insufficiency
Inpatient treatment			
Acute varicella	**Acyclovir** 30 mg/kg IV in 3 divided doses (adults and children <1 year) OR 1500 mg/m^2 IV per day in 3 divided doses (children ≥ 1 year of age)[2]	Evidence I	• IV therapy can be changed to oral therapy once the patient has significantly improved • Careful monitoring of renal function is needed while on IV therapy, and dosing should be adjusted for renal insufficiency
Herpes zoster Disseminated or Invasive disease or Herpes zoster ophthalmicus or Ramsay-Hunt syndrome/ Herpes zoster oticus	**Acyclovir** 30 mg/kg IV in 3 divided doses (adults and children)		• In disseminated disease IV therapy should be given for at for at least 7 days, but may need to be given for longer in patients with extensive involvement or CNS disease • Ophthalmology consultation is recommended for patients with ophthalmic involvement • Consideration for switch to oral therapy dependent on patient's clinical status • Careful monitoring of renal function is needed while on IV therapy, and dosing should be adjusted for renal insufficiency

Data supporting IV therapy for herpes zoster ophthalmicus and oticus are Evidence level III.
[1]FDA approved dosing for children only in varicella not herpes zoster, maximum 3200 mg/day.
[2]Some experts recommend 30 mg/kg in 3 divided doses for this age as well Ref. (39).

preserved renal function, so patients with renal dysfunction dosing may need appropriate dose modification.

VZV prevention

Antiviral therapy: Oral acyclovir and its pro-drugs have been shown to prevent VZV reactivation in other immunosuppressed populations, but they have not been systematically studied in SOT recipients (Table 2; Ref. 54). During the early posttransplant period, many current regimens used for cytomegalovirus (CMV) prevention will likely prevent VZV reactivation, and therefore additional antiviral prophylaxis for VZV is not needed during periods of CMV prophylaxis [valganciclovir, ganciclovir, or high dose acyclovir] (55–57). In patients who do not receive CMV prophylaxis, short term antivirals [acyclovir, valganciclovir] given for herpes simplex (HSV) prophylaxis may also be effective against VZV during the period immediately posttransplant (III). Prophylactic antiviral agents for patients who are both CMV/HSV seronegative but VZV seropositive have not been studied, but it seems prudent to consider similar strategies to patients receiving HSV prophylaxis to provide at least minimal protection during the high-risk posttransplant period (III). Because the length of immunosuppression is life-long in most SOT recipients, an increased risk for HZ is continuous after transplantation (18–20). Although effective for short-term use (58), insufficient data exist to recommend routine use of long-term VZV prophylaxis in SOT recipients (III).

Table 2: Recommendations for VZV prevention in solid organ transplant recipients

Strategy	Pretransplant	Posttransplant	Dosing	Comments
Varicella/HZ prevention				
Antiviral Prophylaxis Acyclovir (and pro-drugs)	N/A	Short- term prophylaxis is recommended for patients who are HSV positive in patients not receiving CMV prophylaxis (Evidence I). Prophylaxis in VZV seropositive CMV/HSV seronegative recipients has not been studied but can be considered (Evidence III)	**Acyclovir** 600–1000 mg/day PO in 3–5 divided doses (adults and children ≥ 2 years) Max dose in children is 80 mg/kg/day not to exceed 3200 mg/day See reference 39 for dosing in children <2 yrs OR **Valacyclovir** 500 mg PO twice daily (adults only)	• Evidence in other populations for effectiveness against VZV, minimal data in SOT recipients. • IV acyclovir is recommended in children <2 yrs of age [5 mg/kg IV every 8 hours] or those who cannot tolerate oral therapy • Alternate less frequent dosing (BID) for acyclovir has been described but has not been evaluated in SOT populations • Patients receiving CMV prophylaxis generally should be protected from VZV reactivation • Valacyclovir is only recommended for children ≥2 and ≤18 years of age and has not been studied as a prophylactic agent in children post-SOT • Lifelong risk of HZ limits use of these agents for long-term prevention.
Vaccination				
Varicella Vaccine (Varivax®)	YES, if seronegative (Evidence II-1)	Consider if susceptible in select populations (Evidence III)	**Varivax®** 0.5 mL administered SQ	• Vaccination has been shown to be safe in ESRD and ESLD patients • Seroconversion rate reduced in immunosuppressed individuals • Caution should be used in posttransplant patients because live virus vaccine • 2nd dose can be given 4–8 weeks after first in adults, but must be delayed till ≥ 3 months after 1st dose in children <13 years of age (see package insert for guidelines)
Zoster Vaccine (Zostavax®)	No for most transplant recipients (Evidence III), unless patient meets label indications (Evidence I)	No (Evidence III)	N/A	• Follow label indications, as no evidence that vaccine is safe in severe organ dysfunction or posttransplant since is live virus vaccine • If patient meets label indications can be considered, but should be given at least 3–4 weeks before transplant.

Continued

Table 2: Continued

Strategy	Pretransplant	Posttransplant	Dosing	Comments
Postexposure Prophylaxis (serongative patients only)				
Immunoprophylaxis VZV immunoglobulin (VZIG, VariZIG™)	YES, if seronegative (Evidence II-1)	YES, if seronegative (Evidence II-1)	**VariZIG** 125 units/10 kg body weight in single IM dose (Max dose is 625 units, min 125 units)	• VariZIG is only available through IND protocol[1] • Must be given as soon as possible – no efficacy if given more than 10 days postexposure • Not 100% effective in clinical studies of preventing VZV, so close observation is suggested • If varicella develops, patient should be treated with antiviral therapy
IV immunoglobulin (nonspecific IVIG)	Consider, if seronegative and VZIG or VariZIG not available (Evidence III)	Consider, if seronegative and VZIG or VariZIG not available (Evidence III)	**IVIG** 400 mg/kg IV single dose	• Amount of anti-VZV antibodies in IVIG is variable, and should only be considered if VZV specific immunoglobulin therapy is not available
Antiviral Prophylaxis Acyclovir[2] (and pro-drugs)	Consider, if seronegative and VZIG or VariZIG not available or in addition to immunoprophylaxis (Evidence III)	Consider, if seronegative and VZIG or VariZIG not available or in addition to immunoprophylaxis (Evidence III)	**Acyclovir** 800 mg PO four times daily (adults) 20 mg/kg PO four times daily (maximum 800 mg four times a day, ≥ 2 yrs of age) 30 mg/kg IV per day in 3 divided doses (adults and children) OR **Valacyclovir** 1 gram PO three times daily (adults)	• Given 7–10 days after exposure for 7 days • Alternatively, some experts recommend dosing being given days 3–22 after exposure (or till day 28 if given immunoprophylaxis) • Caution with patients with underlying renal dysfunction as dosing may need to be reduced • IV acyclovir is recommended in children <2 years of age or those who cannot tolerate oral therapy • Valacyclovir is only recommended for children 2 to <18 years of age and has not been studied as a prophylactic agent in children post-SOT

ESLD = end-stage liver disease, ESRD = end-stage renal disease, HSV = herpes simplex virus, HZ = herpes zoster, SOT = solid organ transplant, VZV = varicella zoster virus.
[1]Contact information for VariZIG is available online at: (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm55e224a1.htm).
[2]Valacyclovir is preferred as oral acyclovir may have poor bioavailability and unpredictable absorption.

Pretransplant vaccination: Potential transplant patients who are susceptible to VZV, should be given varicella vaccination with the live attenuated Oka vaccine (Varivax®, Merck & Co, Inc., Whitehouse Station, NJ, USA) provided no contraindications are present (II-1). Multiple nonrandomized studies in subjects with end-stage renal disease have showed that the Oka vaccine is safe and effective before transplant (23,59–61). Although fewer data are available in subjects with end-stage liver disease, the Oka vaccine also appears to be safe if given pretransplant to these patients (II-2) (62–64). Little data exist for other pretransplant patients but the vaccine is likely safe in these populations (III) (65). Patients with end-stage organ disease have reduced seroconversion rates to varicella vaccination [~60%] (59–61,64), so two doses should be given before transplantation if practical with a minimal interval of 4–6 weeks (57,66,67). Patients should be vaccinated at least 2–4 weeks before transplant (67), but if the vaccine is given in conjunction with measles, mumps, rubella vaccine (MMR and Varicella combined vaccine [ProQuad®, Merck & Co., Inc.]) it should be administered at least 4 weeks before transplant.

The current HZ vaccine (Zostavax®, Merck & Co., Inc.) contains approximately 10–12 times more plaque forming units of live-virus then current Oka varicella vaccines. This vaccine has not been studied in patients with end-organ disease awaiting transplant, but could be considered on a case-by-case basis for those who meet current criteria for HZ vaccination (III).

Posttransplant vaccination: The Oka varicella vaccines have been shown to be safe in select children undergoing chemotherapy and small studies have showed that they can be given safely to posttransplant recipients receiving immunosuppression (68–71). Although varicella vaccination has been given safely to small numbers of susceptible SOT recipients (70,71), caution should be used with the use of this live-virus vaccine as it is currently not approved for immunocompromised patients (III). In addition, rates of seroconversion in immunocompromised patients may not be as robust as in those with intact immune systems. The HZ vaccine poses a risk of disseminated infection in immunosuppressed patients and therefore is contraindicated for posttransplant recipients (III).

Postexposure prophylaxis

Seronegative transplant recipients are at risk for developing severe primary infection after exposure and should, after a significant exposure, receive postexposure prophylaxis (II-1). In the outpatient environment significant exposure to VZV has been defined as exposure to a household contact or nontransient face-to-face contact indoors with a playmate or other contact. In the hospital significant exposure to VZV is defined as exposure in the same two to four bedroom, face-to-face contact with an infectious staff member or patient, or a visit by a person deemed contagious (39). VZV can be spread through direct contact and airborne contacts from a person with active varicella. Patients with HZ may transmit VZV to a person who has never had varicella through direct contact with the rash. There is emerging evidence that VZV may be spread through an airborne route even from localized HZ (2,72–74).

Options for postexposure prophylaxis include passive immunoprophylaxis and/or antiviral therapy. VZIG is no longer available in most centers, and a non-FDA-licensed VZV immune globulin VariZIG™ (Cangene Corporation, Winnipeg, Canada) may be the only VZV specific immunoprophylaxis available (3). In the United States it is available only through an investigational new drug application, lack of rapid access may further limit the use of VariZIG at many centers (75). If available, VZIG or VariZIG is recommended in susceptible patients exposed to VZV and should be given as soon as possible but within at least 10 days of exposure (II-1) (39,76). Immunoprophylaxis alone does not prevent all immunosuppressed patients from developing clinical varicella but lessens the severity of infection (77–79). Although not studied in clinical trials, nonspecific IVIG has been suggested as an alternate postexposure prophylaxis when VariZIG is not available (39); combination use of IVIG with antiviral therapy in immunocompromised patients can also be considered (III).

The use of antiviral agents as postexposure prophylaxis has not been evaluated in randomized clinical trials in immunocompromised patients, but should be considered as adjunctive therapy in patients receiving immunoprophylaxis or in patients who were unable to receive immunoprophylaxis before 10 days after their exposure (III) (76). The value of acyclovir as postexposure prophylaxis has been shown in a study of immunocomponent children (80) and has been suggested to be effective (in addition to VZIG) in a small study of high-risk children, which included five kidney transplant recipients (81). Because of the unpredictable absorption and low bioavailability of oral acyclovir (82,83), valacyclovir, which has improved bioavailability (84), may be preferred for prophylaxis (III). Current recommendations are for patients to receive acyclovir or valacyclovir for a 7-day course of therapy beginning 7–10 days after varicella exposure (III) (39). Alternatively, some experts believe those who are highly immunosuppressed should receive longer antiviral prophylaxis from days 3 to 22 after known exposure and from days 3 to 28 if given immunoprophylaxis (III) (85,86).

Infection Control Issues

All immunosuppressed patients admitted to the hospital with varicella or HZ should be placed on airborne and contact isolation, and close contacts who are susceptible to VZV should be immunized as soon as possible (preferably within 3 days of exposure with possible efficacy as late as 5 days postexposure) or given appropriate VZV

prophylaxis (II-2) (39). Patients should be isolated until at least all lesions are crusted, which can be delayed in immuncompromised patients (39). In addition to postexposure prophylaxis, exposed susceptible patients should remain in airborne and contact precautions from day 10 to 21 while in the hospital after exposure to the index patient, and those who receive VariZIG or IVIG should remain in precautions until day 28 (39). Patients with localized zoster lesions should also have them covered as this can potentially decrease transmission risk (74).

Because secondary cases of VZV in a household setting can be more severe due to exposure to a higher titer of virus (87), vaccination of close household members is an important part of prevention. Vaccinated individuals are at least 50% less contagious when they develop varicella and secondary attack rates are much lower (88). Close contacts and family members 12 months or older should be vaccinated for VZV if they have never received the vaccination, have no history of varicella or HZ, and have no contraindications to vaccination (I). Transplant recipients should be isolated from vaccinated contacts who develop a varicella-like rash, particularly those with >50 lesions, as vaccine associated rashes can result in transmission (88).

Future Research Issues

Studies are currently underway to evaluate the safety and efficacy of pretransplant vaccination for HZ in seropositive recipients (89,90). Large randomized trials evaluating safety and efficacy of both varicella and HZ vaccines in posttransplant patients are also needed. Inactivated VZV vaccines, which are in development, may eventually provide another option for this high-risk population (91). Additional studies to assess the use of low-dose antiviral therapy as long term postexposure prophylaxis are also needed. Finally, as new immunosuppressive agents are developed, they will need to be evaluated both in terms of altering risk for HZ posttransplant as well as their effect on vaccine efficacy.

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