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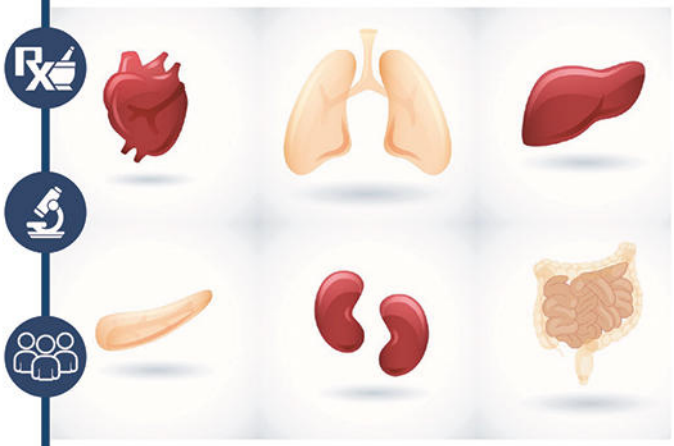

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Varicella zoster virus in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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Abstract

These updated guidelines from the American Society of Transplantation Infectious Diseases Community of Practice review the diagnosis, prevention, and management of varicella zoster virus (VZV) in the pre- and post-transplant period. Primary varicella is an uncommon complication post-solid-organ transplant (SOT), except among pediatric transplant patients and those seronegative for VZV. As the majority of SOT recipients are seropositive for VZV, herpes zoster (HZ) occurs frequently following SOT, particularly among recipients who are older (≥65 years of age) and those receiving more intensive immunosuppression. Transplant providers should aware of the increased risk for HZ-related complications such as dissemination, organ-specific involvement, and post-herpetic neuralgia. Treatment for localized zoster is primarily given as oral regimens, but those with more complicated presentations or those at risk for dissemination should be treated initially with IV therapy. Available antiviral prophylaxis regimens and vaccination strategies for varicella and HZ among these immunosuppressed patients remain a mainstay for prevention in the pre-and post-transplant periods. Finally, we discuss important approaches to addressing post-exposure prophylaxis and infection control practices for those SOT patients with documented VZV infections.

KEYWORDS
herpes zoster, transplantation, varicella

1 | EPIDEMIOLOGY AND RISK FACTORS

Primary infection with varicella zoster virus (VZV), an exclusively human herpesvirus, is acquired through direct contact with skin lesions or through airborne spread from respiratory droplets, and acquired infection can either be asymptomatic or result in clinical varicella also known as "chickenpox."[1] During childhood, more than 90% of persons in the United States acquire VZV immunity through either natural infection or by vaccination with live-attenuated VZV vaccine. Rates of hospitalization and mortality due to varicella have dropped with the institution of routine childhood varicella vaccination.[2,3]

The majority of patients undergoing evaluation for SOT even without a history of clinical VZV infection will be seropositive; pediatric recipients are more likely to be seronegative.[4-8] Since seronegative patients are at risk for primary varicella, all patients should undergo serologic testing to document prior exposure to VZV during their pre-transplant evaluation process. Studies have demonstrated that approximately 2%-3% of adult SOT candidates are seronegative for VZV, while seronegativity ranges between 7% to as high as 50% in some pediatric populations.[9-12] Seronegativity is highly dependent on age of the child, prior vaccination, history of varicella disease, and level of immunosuppression prior to

transplant. Donor-transmitted VZV infection is rare but has been reported.[11,13]

Breakthrough varicella can also occur in vaccinated patients. Although vaccine breakthrough is usually a milder presentation compared to wild-type primary infection, cases of disseminated infection have been reported.[14,15] Data in immunocompromised patients who have previously been vaccinated suggest that the risk of breakthrough varicella is low, but more likely to occur in those who did not develop immunity following vaccine or lost VZV antibodies post-transplant.[7,8]

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."[16,17] Patients with previous natural infection or prior vaccination with the live-attenuated VZV vaccine (ZVL) are at risk for the development of HZ, which is estimated to occur in up to 20% of individuals during their lifetime.[17-19] Rates of HZ among previously vaccinated persons appear to be lower than those with a history of natural varicella infection.[6,20,21] Primary infection is rare in adult SOT recipients, but is more frequent in seronegative pediatric transplant recipients.[8,22,23] Herpes zoster is a frequent infectious complication in adult SOT recipients with an incidence of approximately 8%-11% during the first 4 years post-transplant.[24-26] Since there are no large prospective trials that have evaluated HZ in SOT, risk factors are not well defined, and data among pediatric populations are not well characterized but are thought to be similar.[7] Similar to the general population, longitudinal studies have demonstrated that older transplant recipients are at greater risk for the development of HZ.[25,26] 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.[25-30] The use of mycophenolate mofetil (MMF) has also been suggested as a potential risk factor for the development of HZ.[30-32] It is unknown whether the development of HZ prior to transplant lessens the risk for post-transplant recurrence. Similar to varicella, HZ can occur in patients who have previously received varicella immunization, but the incidence and severity are thought to be milder than in patients who acquire natural infection with wild-type virus.[6]

1.1 | Recommendations—Epidemiology/risk factors

1. During the pre-transplant evaluation process, SOT candidates should be screened by serology for prior VZV infection (Grading of Recommendations Assessment, Development and Evaluation [GRADE]: strong, moderate)

1.2 | Clinical presentations

1.2.1 | Primary varicella

Solid organ transplant recipients often present with primary varicella symptoms similar to those in the general population, typically with fever, constitutional symptoms, and a vesicular, pruritic, widely disseminated rash that primarily involves the trunk and face. SOT recipients, however, are at greater risk for complications, such as pneumonia when developing primary varicella. Primary infection is rare in adult SOT recipients, but can be devastating and may present with visceral involvement, severe skin disease, and disseminated intravascular coagulation.[22,33-37] Secondary complications such as bacterial superinfection and rarely necrotizing fasciitis may also lead to increased morbidity and mortality.[38]

Immunocompromised patients with HZ may develop disseminated skin lesions that can mimic primary varicella during periods of potent immunosuppression.[39,40] Atypical presentations of primary VZV infection have been described in SOT recipients[1,39,40] and can include multi-organ visceral involvement[39,41] with delayed or absent rash.[1,38,42,43]

1.2.2 | Reactivated VZV infection (herpes zoster)

Although most commonly presenting in a classical dermatomal presentation, immunosuppressed patients are more likely to develop multi-dermatomal or disseminated zoster.[35] Disseminated HZ has been reported in SOT and other immunocompromised populations, and level of immunosuppression may increase the risk of developing this complication.[30] Rare presentations of HZ, including neurologic manifestations (eg, encephalitis) and visceral zoster (presenting as abdominal pain, elevated liver enzymes, and hyponatremia often without visible skin lesions), are rare complications in immunosuppressed patients including SOT recipients and may present with delayed or absent rash.[16,43,44] Rates of HZ complications, such as post-herpetic neuralgia are thought to be higher in SOT recipients than in immunocompetent populations.[25]

2 | DIAGNOSIS

Primary varicella and HZ have typical clinical presentations that often allow for a presumptive clinical diagnosis, but clinicians should be aware of less frequent clinical presentations such as HZ ophthalmicus (trigeminal ganglion) and HZ oticus (Ramsay-Hunt syndrome—geniculate ganglion).[1,39,45] Presentation among SOT recipients is often similar to the general population but severity, duration, and risk for complications are generally thought to be increased in immunosuppressed populations.[17,46]

Specific 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-antibody (DFA) assays, are the methods of choice for the detection of VZV.[47,48] PCR testing is the most sensitive test for VZV[49] and should be used for diagnosis of visceral and CNS involvement, and for detection of VZV in vesicle fluid, serum, spinal fluid, and other tissues. The use of saliva VZV PCR has been suggested as an alternate approach to diagnosis, particularly among those with HZ but with resolving/scabbed lesions.[50] 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). However, culture is slow and less sensitive for VZV,[4,51] but remains an important diagnostic entity for epidemiologic purposes, particularly since other viruses (eg, HSV) grow well in culture.

The majority of patients even without a history of clinical VZV infection will be seropositive.[4-6] Regardless, all patients should undergo serologic testing to document prior exposure to VZV during their pre-transplant evaluation process. Serology results can be used to determine post-transplant risk as patients who are seronegative prior to transplant are at risk for the development of primary VZV, and seropositive patients are at risk for developing post-transplant HZ. Serology should not be used to diagnose VZV-associated clinical syndromes in SOT recipients.[6,48]

2.1 | Recommendations—Diagnosis

1. Although clinical presentations often allow for a presumptive clinical diagnosis, laboratory confirmation is recommended in SOT recipients (strong, low)
2. Rapid diagnostic methods, including polymerase chain reaction (PCR) and direct fluorescent-antibody (DFA) assays, are the methods of choice for detection of VZV. PCR is the method of choice for detection of VZV in vesicle fluid, serum/blood, spinal fluid, and other tissues (strong, moderate)
3. Viral cultures while useful for epidemiologic purposes, should not be used exclusively to diagnosis primary disease (strong, low).

3 | 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 and must be reduced for patients with renal dysfunction. In patients who are allergic to acyclovir or similar agents (eg, famciclovir), or those who have documented resistant strains, other agents, such as cidofovir and foscarnet, with known efficacy against acyclovir-resistant VZV, can be considered.[52-54]

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 y of age) IV acyclovir is recommended in children <2 y of age (10 mg/kg IV every 8 h) or those who cannot tolerate oral therapy OR Valacyclovir 1 g PO three times daily (adults) 20 mg/kg PO three times daily (children ≥2 and ≤18 y of age)[a] OR Famciclovir 500 mg PO three times daily (adults only)	Strong, moderate	• Oral therapy is not recommended for young children <2 y 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 d 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 y of age • Careful monitoring of renal function is needed while on high-dose acyclovir therapy, and dosing should be adjusted for renal insufficiency
Impatient treatment			
Acute varicella	Acyclovir 30 mg/kg IV in three divided doses (adults and children <1 y) OR 1500 mg/m^2 IV per day in three divided doses (children ≥1 y of age)[b]	Strong, low	• 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 three divided doses (adults and children)	Strong, moderate	• In disseminated disease IV therapy should be given for at for at least 7 d, 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

[a]FDA approved dosing for children only in varicella not herpes zoster.
[b]Some experts recommend 30 mg/kg in three divided doses for this age as well.[39]

3.1 | Varicella

Post-transplant patients who develop primary varicella are at risk for developing severe infection and should be treated with intravenous (IV) acyclovir (Table 1).[38,55-57] Therapy initiated early in the course of the illness, especially within 24-hour of rash onset, maximizes efficacy.[48] IV therapy can be converted to oral therapy once the patient has significantly improved, or after all lesions have crusted over. Reduction in immunosuppressive therapy can be considered. Non-specific intravenous immunoglobulin (IVIG) or VZV immunoglobulin is unlikely to provide additional benefits to those with established infection and is therefore not routinely recommended[48] (weak, low), but has been used anecdotally in those with severe infection.[35,56,58-61]

3.2 | Herpes zoster

Patients with disseminated (defined as having as more than 20 vesicles outside the area of the primary and adjacent dermatomes, or affecting three or more dermatomes)[62] or organ invasive disease, including central nervous system infections, should be treated initially with IV acyclovir.[55,56] Localized non-severe dermatomal HZ can generally be treated with oral acyclovir, valacyclovir, or famciclovir as an outpatient in most adults, with close follow-up.[63-65] Antiviral therapy should be given for at least 7 days or until lesions have crusted over, which may be delayed in immunocompromised hosts. Two situations in which localized infection should be treated with IV therapy are trigeminal ganglion infection (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.[65,66] In cases of trigeminal involvement, prompt ophthalmologic consultation is recommended. In addition, IV therapy is recommended for children <2 years of age or those who cannot tolerate oral therapy. It is unknown whether routine addition of glucocorticoids to SOT patients on steroid-sparring regimens to prevent late PHN complications is effective and is not generally recommended.

3.3 | Recommendations—Treatment

1. Post-transplant patients who develop primary varicella should be treated with intravenous acyclovir, due to risk of severe complications (strong, low)
2. Intravenous immunoglobulin or VZV-specific immunoglobulin is not recommended for routine use in the treatment of VZV, except in patients with life-threatening infections (weak, low)
3. Localized non-severe dermatomal HZ should be treated with oral acyclovir, valacyclovir, or famciclovir in most adults, with close follow-up (strong, moderate)
4. Patients with severe disease (eg, those with disseminated HZ or organ invasive disease, sight-threatening HZ [HZ ophthalmicus], those with potential for invasion to the CNS [eg, HZ oticus]), or should preferentially receive IV over oral acyclovir as initial therapy (strong, moderate)
5. Patients with involvement of the eye(s) routinely assessed by ophthalmology (strong, very low)
6. Children <2 years of age or those who cannot tolerate oral therapy should preferentially receive treatment with IV acyclovir (strong, moderate)
7. Patients who are allergic to acyclovir or similar agents (eg, famciclovir), or who have documented viral-resistance, should be treated with foscarnet or cidofovir (strong, low).

4 | PREVENTION/PROPHYLAXIS

Suggestions for prevention and prophylaxis are listed in Table 2. Antiviral doses given in the table are for patients with normal renal function and need to be reduced in patients with impaired renal function, according to manufacturer recommendations.

4.1 | VZV prevention

4.1.1 | 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).[66,67] Many currently used antiviral regimens used for cytomegalovirus (CMV) prevention also prevent VZV reactivation (see comment above), and therefore additional antiviral prophylaxis for VZV is not needed during periods of CMV prophylaxis when valganciclovir, ganciclovir, letermovir, valacyclovir, or acyclovir are used.[67-69] In patients who do not receive CMV prophylaxis, short-term antivirals (acyclovir, valacyclovir) given for herpes simplex (HSV) prophylaxis may also be effective against VZV during the period immediately post-transplant. Prophylactic antivirals for patients who are both CMV/HSV seronegative but VZV seropositive have not been systematically studied. Use of antivirals specifically to prevent VZV among HSV/CMV seronegative patients during periods of intensive immunosuppression, including the immediate post-transplant period, may reduce HZ-related complications.[70] Since the length of immunosuppression is lifelong in most SOT recipients, there is a lifelong increased risk for HZ after SOT.[24-26] While effective for short-term use,[70] insufficient data exist to recommend routine use of long-term VZV prophylaxis in SOT recipients.

4.2 | Pre-transplant vaccination

4.2.1 | Varicella

Potential transplant candidates should be screened, and those who are susceptible to VZV (seronegative) should be given varicella vaccination with the live-attenuated Oka vaccine (Varivax®; Merck & Co., Inc.) provided that no contraindications are present. Multiple non-randomized studies in patients with end-stage renal disease have

TABLE 2 Recommendations for VZV prevention in solid organ transplant recipients

Strategy	Pre-transplant	Post-transplant	Dosing	Comments
Varicella/HZ prevention				
Antiviral prophylaxis				
Acyclovir (and pro-drugs)	N/A	Short-term prophylaxis is recommended for patients who are HSV seropositive and not receiving CMV prophylaxis (Strong, high). Prophylaxis in VZV seropositive CMV/HSV seronegative recipients has not been studied but can be considered (Strong, very low)	Acyclovir 600-1000 mg/d PO in 3-5 divided doses (adults and children ≥2 y) Max dose in children is 80 mg/kg/d not to exceed 3200 mg/d IV acyclovir is recommended in children <2 y of age (5 mg/kg IV every 8 h) or those who cannot tolerate oral therapy *See reference 39 for dosing in children <2 y OR Valacyclovir 500 mg PO twice daily (adults only)	• Evidence in other populations for effectiveness against VZV, minimal data in SOT recipients. 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, unless they are receiving letermovir which does not prevent VZV reactivation. • Valacyclovir is only recommended for children 2 to <18 y 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 (Strong, moderate)	Generally, contraindicated, but can be used with caution if seronegative in select populations (Weak, low)	Varivax® 0.5 mL administered SQ	• Vaccination has been shown to be safe in ESRD and ESLD patients • Minimum recommended age for vaccine is ≥6 mo of age • Do not give if <1 mo to transplant • Seroconversion rate reduced in immunosuppressed individuals • Caution should be used in post-transplant patients since live virus vaccine; education and close follow-up recommended. • Second dose can be given 4-8 wk after first dose (see package insert for guidelines)
Inactivated adjuvanted subunit herpes zoster vaccine (Shingrix®)	Yes, known seropositive and on minimal immunosuppression ≥50 y age (Strong, high), populations <50 y of age on minimal immunosuppression can be considered for vaccination (Weak, low)	Safety and efficacy studies ongoing (Weak, moderate)	Shingrix® 0.5 mL administered IM Two doses at 0 and 2-6 mo	• Currently only FDA approved for patients ≥50 y of age • Side effects are common, and frequently include pain at injection site, fever and chills/myalgias • Data demonstrate vaccine immunogenicity and safety in carefully selected renal transplant patients on immunosuppressive therapy at low risk for rejection, Efficacy data are not available to date • Patients with primary autoimmune diseases (eg, systemic lupus erythematous, etc) and or at moderate/high risk for rejection were excluded from the trial so data on safety is unknown • Prospective studies have not been done in children <18 y of age.

(Continues)

TABLE 2 (Continued)

Strategy	Pre-transplant	Post-transplant	Dosing	Comments
Live-attenuated herpes zoster vaccine (Zostavax®)	Alternative to Inactivated Adjuvanted Vaccine for >50, if not severely immunosuppressed (Strong, high)	Contraindicated (Strong, low)	Zostavax® 0.5 mL administered SQ	• Follow label indications, as no evidence that vaccine is safe in severe organ dysfunction or post-transplant • If patient meets label indications can be considered, but should be given at least 3-4 wk prior to transplant.
Post exposure prophylaxis (serongative patients only)				
Immunoprophylaxis				
VZV immunoglobulin (VZIG, VariZIG™)	Yes, if seronegative (Strong, moderate)	Yes, if seronegative (Strong, moderate)	VariZIG 125 units/10 kg body weight in single IM dose (Max dose is 625 units, min 125 units)	• Must be given as soon as possible—no efficacy if given more than 10 d post-exposure • 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 (non-specific IVIG)	Yes, if seronegative and VariZIG not available (Weak, low)	Yes, if seronegative and VariZIG not available (Weak, low)	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[a] (and pro-drugs)	Consider, if seronegative and VZIG or VariZIG not available or in addition to immunoprophylaxis (Weak, low)	Consider, if seronegative and VZIG or VariZIG not available or in addition to immunoprophylaxis (Weak, low)	Acyclovir 800 mg PO four times daily (adults) 20 mg/kg PO four times daily (maximum 800 mg four times a day, ≥2 y of age) 30 mg/kg IV per day in three divided doses (adults and children) OR Valacyclovir 1 g PO three times daily (adults)	• Given 7-10 d after exposure for 7 d • 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 y of age or those who cannot tolerate oral therapy • Valacyclovir is only recommended for children 2 to <18 y of age and has not been studied as a prophylactic agent in children post-SOT

Abbreviations: 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.
[a]Valacyclovir is preferred as oral acyclovir may have poor bioavailability and unpredictable absorption.

demonstrated that the Oka vaccine is safe and immunogenic prior to transplant.[7,9,71-73] While fewer data are available in subjects with end-stage liver disease, the Oka vaccine also appears to be safe if given pre-transplant to these patients.[73-76] Little data exist for other pre-transplant patients but the vaccine is likely safe and immunogenic in these populations, particularly if not immunosuppressed.[7,76] Since patients with end-stage organ disease have reduced response rates to varicella vaccination (~60%),[7,71,72,75,77] two doses should be given prior to transplantation if practical with a minimal interval of 4-6 weeks.[68,77-79] Patients should be vaccinated ≥4 weeks prior to transplant if possible,[78,79] 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 a minimum of 4 weeks prior to transplant. Current Infectious Diseases Society of America (IDSA) guidelines recommend completing pre-transplant vaccination in patients who are seronegative for VZV prior to initiating immunosuppression.[78]

4.2.2 | Herpes Zoster

There are two current licensed herpes zoster vaccines, a live-attenuated Oka HZ vaccine (Zostavax®; Merck & Co., Inc.), and an adjuvanted sub-unit HZ vaccine (Shingrix®; GlaxoSmithKline); both are licensed only for adults. The single-dose, live-attenuated vaccine, is similar to the varicella vaccine, but contains approximately 12-14 times more plaque forming units of live-virus then current Oka varicella vaccines. Injection site side reactions, such as erythema and soreness are the most frequent side effects seen in patients receiving the live-virus vaccine.[80] Injection site reactions are also more frequent side effects in the adjuvanted sub-unit vaccine, but systemic reactions such as fatigue, myalgias, headache, and fever, were more also more common.[81,82] Currently the IDSA and the Advisory Committee on Immunization Practice (ACIP), both recommend pre-transplant HZ vaccination, but differ in the age at which to target vaccination.[78,83] The older IDSA guidelines recommend use of the live-attenuated vaccine pre-transplant in patients ≥50 years of age (strong, moderate) who are not severely immunocompromised, at least 4 weeks prior to receiving immunosuppression; data on adjuvanted sub-unit vaccine were not available at the time of this publication. Updated ACIP and AST recommendations indicate a preference for the adjuvanted subunit vaccine over the live-attenuated vaccine due to superior efficacy for the general population >50 years of age.[84] As an alternative, the live-attenuated vaccine can be offered to patients who are eligible to receive a live virus vaccine (eg, those not immunosuppressed prior to transplant).

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. SOT recipients should be isolated from contacts vaccinated with either or the live-attenuated vaccines who develop a varicella-like rash, particularly those with >50 lesions, as vaccine-associated rashes can result in transmission.[85] Additionally, caregivers, household members, and family who are eligible to receive a HZ vaccine, should preferentially be offered the inactive adjuvanted sub-unit vaccine during the pre-transplant and/or post-transplant periods to help protect patients (strong, high).[84]

4.3 | Recommendations—Pre-transplant prevention

1. VZV seronegative transplant candidates should be given varicella vaccination with the live-attenuated vaccine provided no contraindications are present, at least 4 weeks prior to transplantation (strong, moderate)
2. For VZV seropositive pre-transplant patients >50 years of age should receive the adjuvanted HZ subunit vaccine (Shingrix®) (strong, high)
3. As a strategy to reduce VZV transmission, caregivers, household members, and family who are VZV seronegative and who do not have a contraindication should receive the live-attenuated varicella vaccine (strong, low)
4. As a strategy to reduce VZV transmission, caregivers, household members, and family who are eligible to receive a HZ vaccine, should preferentially be offered the adjuvanted sub-unit vaccine (strong, very low).

4.4 | Post-transplant vaccination

4.4.1 | Varicella

The Oka varicella vaccines have been shown to be safe in selected children undergoing chemotherapy and small studies have demonstrated that they can be given safely to post-transplant recipients receiving low-dose immunosuppression.[86-89] Post-transplant vaccine is generally discouraged, but the Infectious Diseases Society of America (IDSA), the Advisory Committee on Immunization Practice (ACIP), and the American Society of Transplantation (AST) both recommend vaccination for only selected kidney and liver transplant recipients who are seronegative post-transplant and receiving long-term, low-level immunosuppression.[78,90,91] Varicella vaccination has been given safely to susceptible SOT recipients,[88,89] but caution should be used for patients receiving high-level immunosuppression as this live-virus vaccine is currently not approved for immunocompromised patients. It is important to note that rates of seroconversion in immunocompromised patients may not be as robust as in those with intact immune systems, so documentation of seroconversion may be useful following vaccination.

4.4.2 | Herpes zoster

Live-virus vaccines are generally not recommended post-transplant, and therefore the live-attenuated herpes zoster vaccine is contraindicated for post-transplant prevention.[78] Although there are limited data suggesting that vaccination with the live-attenuated VZV vaccine among patients with low-level immunosuppression may be safe,[92,93] instances of life-threatening and fatal complications

in immunocompromised recipients have also been described.[94-96] Both IDSA and ACIP guidelines do not recommend post-transplant vaccination with the live-attenuated herpes zoster vaccine.[78,84] A randomized placebo-controlled trial of an inactivated form of the live-attenuated Oka strain HZ vaccine demonstrated an approximately 64% reduction in HZ events,[97] but this vaccine has not been studied in SOT patients and is neither FDA approved nor currently available.

Recent data from a randomized double-blind placebo-controlled study of renal transplant patients at low risk for rejection demonstrated safety and immunogenicity among carefully selected patients vaccinated with the adjuvanted subunit vaccine, but efficacy for clinical disease was not assessed.[98] This study did not appear to show any increase in rejection, which is a theoretical concern of adjuvanted vaccines. Patients at moderate or high risk for rejection were excluded from the primary study; thus, safety in these patients remains uncertain. In another immunosuppressed population, a double-blind randomized placebo-controlled study of the adjuvanted subunit vaccine in patients undergoing autologous stem cell transplantation demonstrated a 68% reduction in HZ events post-transplant.[99] Recently published herpes zoster vaccine guidelines preferentially support the use of the inactive adjuvanted subunit vaccine among patients with low-level immunosuppression (eg, <20 mg of prednisone), but recommendations for routine use in SOT recipients await final published results of both of these large randomized trials.[84] There are theoretical risks that a potently adjuvanted vaccine could increase the risk of acute or chronic allograft rejection. In addition, this vaccine has not been studied in controlled trials of other organ transplant populations.

4.5 | Recommendations—Post-transplant prevention

1. The live-virus varicella vaccine is generally contraindicated but can be given with caution in selected patients who are seronegative and receiving low-level immunosuppression in the post-transplant period (weak, low)
2. The live-virus HZ vaccine is not recommended for patients in the post-transplant period (strong, low)
3. The adjuvanted subunit HZ vaccine can be considered for HZ prevention in selected kidney transplant recipients at low-risk for rejection (weak, moderate)
4. Short-term prophylaxis with acyclovir or valacyclovir is recommended for patients who are HSV and VZV seropositive and not receiving CMV prophylaxis (or receiving letermovir prophylaxis) (strong, high)
5. Short-term prophylaxis with acyclovir or valacyclovir is recommended for patients who are VZV seropositive, seronegative for HSV and not receiving CMV prophylaxis (or receiving letermovir prophylaxis) (strong, very low).

4.6 | Post-exposure prophylaxis

Seronegative transplant recipients are at risk for developing severe primary infection after exposure and should, receive post-exposure prophylaxis after significant exposure. In the outpatient environment significant exposure to VZV has been defined as exposure to a household contact or non-transient 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 2 to 4-bed room, face-to-face contact with an infectious staff member or patient, or a visit by a person deemed contagious.[48] VZV can be spread through direct and airborne contacts from a person with active varicella. Patients with HZ may transmit VZV to a person who is varicella seronegative through direct contact with the rash. There is emerging evidence that VZV may be spread through an airborne route even from localized HZ.[83,90,100,101] Seropositive recipients are considered protected from primary varicella, but as many of those at risk are immunosuppressed (including patients who may have profound reduction in T-cell function), immunosuppressed patients with direct exposure should be closely followed to assure they do not develop symptoms or signs of varicella.

Options for post-exposure prophylaxis include passive immunoprophylaxis and/or antiviral therapy. The only VZV immune globulin currently available is VariZIG™ (Saol Therapeutics).[90,102] only through specialty distributors in the US.[102] 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.[103,104] Immunoprophylaxis alone does not prevent all immunosuppressed patients from developing clinical varicella but lessens the severity of infection.[104-106] Although not studied in clinical trials, non-specific IVIG has been suggested as an alternate post-exposure prophylaxis when VariZIG is not available[48]; combination use of IVIG with antiviral therapy in immunocompromised patients can also be considered.

The use of antiviral agents as post-exposure 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 prior to 10 days after their exposure.[102,107] The value of acyclovir as post-exposure prophylaxis has been demonstrated in a study of immunocomponent children[107] 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.[108,109] Due to the unpredictable absorption and low bioavailability of oral acyclovir,[109,110] valacyclovir, which has improved bioavailability,[111] may be preferred for prophylaxis.[48] Current recommendations are for patients to receive acyclovir or valacyclovir for a 7-day course of therapy beginning 7-10 days after varicella exposure.[17,48] 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.[112,113]

4.7 | Recommendations—Post-exposure prophylaxis

1. Seronegative transplant recipients should receive post-exposure prophylaxis after a significant exposure (strong, high)

2. VariZIG is recommended in susceptible (seronegative) patients who are exposed to VZV and should be given as soon as possible but within 10 days of exposure (strong, moderate)
3. Seronegative patients who cannot receive VariZig, should be given valacyclovir either for a 7-day course of therapy beginning 7-10 days after VZV exposure, or alternatively from day 3 to 28 following exposure (weak, low).

5 | INFECTION CONTROL ISSUES

All immunosuppressed patients admitted to the hospital with varicella or HZ should be placed on airborne and contact isolation precautions, 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 post-exposure) or given appropriate VZV prophylaxis.[48]

Patients should be isolated until at least all lesions are crusted, which can be delayed in immunocompromised patients. In addition to post-exposure 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.[17,48] Patients with localized zoster lesions should also have them covered as this can potentially decrease transmission risk.[83,114]

Since secondary cases of VZV in a household setting can be more severe due to exposure to a higher titer of virus, vaccination of close household members is an important part of prevention.[114] Vaccinated individuals are at least 50% less contagious when they develop varicella and secondary attack rates are much lower.[85]

5.1 | Recommendations—Infection control

1. All immunosuppressed patients admitted to the hospital with varicella or HZ should be placed on airborne and contact isolation precautions (strong, moderate)
2. 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 post-exposure) or given appropriate VZV prophylaxis (moderate, moderate)
3. Caregivers, household members and family who are eligible to receive a HZ vaccine, should preferentially be offered the inactive adjuvanted sub-unit vaccine during the pre-transplant and/or post-transplant periods to help protect patients (strong, low).

6 | FUTURE RESEARCH ISSUES

Data on large randomized trials evaluating safety and efficacy of both varicella and HZ vaccines in post-transplant patients are expected in the next few years, and we anticipate these studies will likely lead to updates of post-transplant recommendations. Although vaccination remains an important method for prevention, additional studies to assess the use of low-dose antiviral therapy as long-term post-exposure prophylaxis are still needed, particularly for patients not eligible to receive vaccination. Long-term studies evaluating efficacy of the adjuvanted subunit HZ vaccine are needed. Additional safety studies for the adjuvanted subunit HZ vaccine for other high-risk populations, including organ transplants, pediatric patients, patients with autoimmune diseases, and those at increased risk of rejection are needed. Novel cytomegalovirus (CMV) prevention strategies which incorporate agents that specifically target only CMV (eg, letermovir) and which do not prevent VZV reactivation,[115] may require the more frequent use of combination acyclovir/valacyclovir prophylaxis and/or vaccination among high-risk patients. Finally, as new pre-transplant conditioning agents and post-transplant immunosuppressive agents are developed, these will need to be evaluated both in terms of altering risk for HZ post-transplant as well as their effect on vaccine efficacy.

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CONFLICT OF INTEREST

SAP has served as a site investigator for Merck and serves on the CDC's Advisory Committee on Immunization Practices Zoster Working Group. APL has served as a consultant and site investigator and received an investigator-initiated grant from Merck.

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