

## Varicella-Zoster Virus (Last updated December 9, 2019; last reviewed December 9, 2019)

### Panel's Recommendations

- I. Should children with HIV without evidence of immunity to varicella receive the varicella vaccine, compared to not receiving the vaccine?
  - Vaccination with the varicella vaccine should be considered for children with HIV without evidence of immunity to varicella. Administration is considered safe for children with CD4 T lymphocyte (CD4) cell percentage  $\geq 15\%$ . Two doses of varicella vaccine should be given, starting as early as 12 months of age, with an interval of 3 months. Preferably the child will have been on effective antiretroviral therapy (ART) for  $\geq 3$  months prior to immunization. (strong, low)
- II. Should children with HIV who are without evidence of immunity to varicella and exposed to varicella or herpes zoster (HZ) receive prophylaxis with human varicella-zoster immunoglobulin, compared to not receiving varicella-zoster immunoglobulin?
  - Children with HIV who are susceptible to varicella and have had a significant exposure to varicella or HZ, and are severely immune compromised, should receive varicella zoster immune globulin (available as VariZIG) as soon as possible within the first 10 days after exposure. The extent of immune compromise should be considered in making this decision. VariZig is given intramuscularly at the recommended dose of 125 units/10 kg, up to a maximum of 625 units (i.e., 5 vials). (strong, low)
- III. Should children with HIV with varicella be treated with acyclovir, compared to not being treated with acyclovir?
  - Intravenous (IV) acyclovir therapy is recommended for children with HIV with significant immune compromise who have varicella or for any child with HIV with severe varicella. Therapy initiated early in the course of the illness, especially within 24 hours of rash onset, maximizes efficacy. For select patients with HIV perceived to be at lower risk of developing severe varicella, many experts use oral acyclovir. This decision is made for patients with relatively normal concentrations of CD4 cells, especially if they are receiving ART. (strong, moderate)
- IV. Should children with HIV with HZ be treated with acyclovir, compared to not being treated with acyclovir?
  - Oral therapy with acyclovir for 7 days to 10 days is recommended for children with HIV with HZ, although longer therapy duration should be considered when lesions are slow to resolve. Initial IV administration is recommended for children with HIV with severe immunosuppression, extensive multidermatomal HZ, disseminated infection, visceral involvement, or otherwise complicated HZ. IV acyclovir should be continued until cutaneous lesions and visceral disease are clearly resolving, after which oral administration can be considered to complete therapy. (strong, moderate)
- V. Is foscarnet the best choice for anti-varicella-zoster virus (VZV) therapy for children with HIV in whom therapy is failing because of acyclovir-resistant VZV?
  - When acyclovir resistance is considered, if possible, virus isolation should be attempted for susceptibility testing. All acyclovir-resistant VZV strains are resistant to valacyclovir, famciclovir, and ganciclovir. VZV Infections caused by acyclovir-resistant VZV strains should be treated with parenteral foscarnet. (strong, very low)

### Rating System

*Strength of Recommendation:* Strong; Weak

*Quality of Evidence:* High; Moderate; Low; or Very Low

## Epidemiology

Varicella-zoster virus (VZV) infections are endemic worldwide. Prior to the universal administration of varicella vaccine, approximately 4 million cases of varicella occurred annually in the United States. The annual incidence in children aged  $<10$  years was 9%; by adulthood  $>95\%$  of individuals had antibodies to VZV, indicating prior primary varicella infection.<sup>1</sup> In tropical and subtropical areas, varicella may be acquired later in childhood or in early adulthood, but seroprevalence among adults is high by age 30 years. In the United States, the incidence of varicella and its associated morbidity and mortality have decreased by  $\geq 88\%$  because of universal vaccination.<sup>2-4</sup>

VZV is transmitted by an airborne route.<sup>5</sup> Varicella is highly contagious; clinical infection develops in about 80% of susceptible individuals exposed to VZV within a household.<sup>6</sup> Second attacks of varicella are very uncommon.

Perinatal transmission of VZV can occur. However, because most pregnant women have varicella immunity, varicella complicating pregnancy is unusual. Perinatal transmission of VZV has not been reported in

pregnant women with HIV who develop varicella. Congenital varicella syndrome (multiple anomalies) occurs in approximately 0.4% of infants born to women who have varicella at 1 week to 12 weeks of pregnancy and in approximately 2% of infants born to women who have varicella at 13 to 20 weeks of pregnancy,<sup>7</sup> but is not seen in infants born to women who develop herpes zoster (HZ) during pregnancy.

VZV also can be transmitted to fetuses in late gestation, resulting in neonatal varicella. In mothers who develop varicella 5 days before to 2 days after delivery, the attack rate for infants is approximately 20%, and mortality, before the availability of antiviral therapy, was approximately 30%.<sup>8</sup> In comparison, if maternal varicella precedes delivery long enough to allow transfer of VZV antibodies across the placenta, infants can still develop varicella in the first 5 days of life, but the infection is rarely severe.

VZV causes both varicella (primary infection; chickenpox) and HZ (reactivation of latent infection; shingles). HZ represents reactivation of VZV that resides in a latent state in neurons in dorsal root and cranial sensory ganglia following varicella. Once established, VZV latency persists for life, but reactivation to cause HZ occurs in approximately 30% of people who had varicella. HZ is less contagious than varicella, but VZV from HZ lesions can spread by direct contact or by an airborne route to cause varicella in susceptible contacts (i.e., never had varicella or never received the varicella vaccine). HZ occurs because VZV-specific cellular immunity, which is first stimulated by primary infection (varicella) and is needed to maintain latency, declines with age. In addition, VZV-specific cellular immunity is also typically depressed by HIV infection, which explains why HZ is common in people with HIV.<sup>9-11</sup> HZ was a very common complication in children with HIV before the advent of antiretroviral therapy (ART) (approximately 10 cases/100 patient-years prior to 1996); the incidence of HZ remains at 2 to 3 cases/100 patient-years in the ART era, which is 10 to 25 times higher than in the general population.<sup>12-15</sup> Risk factors for development of HZ include low incident (i.e., coincidental with HZ reactivation) or nadir CD4 T lymphocyte (CD4) cell count/percentage; high HIV viral load; and acquisition of varicella when the CD4 percentage is <15%.<sup>14,16,17</sup> As in adults, the frequency of HZ recurrences in children correlates inversely with the CD4 count.<sup>14,18</sup> The incidence of HZ increases with age; this trend extends into adulthood, particularly in individuals aged >50 years.

In addition to ART and immune reconstitution, one reason for the declining incidence of HZ in children with HIV in countries with varicella vaccination programs is that many received the licensed varicella vaccine. Varicella vaccination is associated with a decrease in HZ in children without HIV<sup>19,20</sup> compared with those who had wild-type infection. This is also true for vaccinated children with HIV compared with those who had wild-type infection.<sup>21</sup>

## Clinical Manifestations

The incubation period for varicella ranges from 10 to 21 days (average: 14 days) in immunocompetent children. Varicella can be associated with a brief prodrome of malaise and fever, followed by the appearance of skin lesions that are more numerous on the face and trunk than on the extremities. The lesions appear in three or more successive crops over approximately 5 to 7 days. They evolve quickly (in about 24 hours) through macular, papular, vesicular, and pustular stages, culminating in crusts. Combinations of these types of lesions are present simultaneously. Varicella causes more morbidity in patients with HIV than in the general population. Initial reports of varicella in children with HIV suggested severe disease manifestations and chronic, atypical skin lesions.<sup>22,23</sup> Clinically important systemic involvement, especially in severely immune compromised children, can include neurologic manifestations such as encephalitis, cerebellar ataxia, and transverse myelitis; hepatitis; pneumonia; and multiorgan failure with intravascular coagulation. Subsequent studies suggest less complicated varicella infections in children with HIV, particularly in those receiving ART or who have higher CD4 counts at the time of infection.<sup>16,24</sup> However, the disease may last longer than normal, and the rate of complications is higher in children with HIV than in otherwise healthy children with varicella.<sup>25</sup>

Uncommonly, severely immunocompromised children with HIV can have persistent chronic varicella infection, with continued appearance of new VZV lesions for >1 month after onset of varicella.<sup>23,26</sup> The

lesions are characteristically varicelliform at onset but evolve into non-healing ulcers or necrotic, crusted, and hyperkeratotic verrucous lesions. Chronic VZV was reported in 14% of children with HIV with VZV in the pre-ART era, usually in children with low CD4 counts.<sup>18</sup>

The classical presentation of HZ is a painful or pruritic, vesicular, dermatomal rash. Typically, pain precedes the rash by 2 to 3 days. Less typical rashes, like those described for chronic varicella, including rashes that extend beyond dermatomal boundaries or are bilaterally distributed or generalized, can occur in children with HIV. These children may also have multiple recurrent episodes of HZ.<sup>14,18</sup> Disseminated HZ with multiorgan involvement can occur, with or without the typical rash of HZ. Encephalitis long after HZ, or without rash, has been reported in children with HIV.<sup>27</sup> Ruling out herpes simplex virus infection, which can be confused with VZV skin manifestations, is important in evaluating children with HIV with possible HZ infection. This can be accomplished by PCR testing of vesicular fluid.

Retinitis is a complication of VZV infection in children and adolescents with HIV<sup>28,29</sup> that can be confused with cytomegalovirus retinitis.<sup>30</sup> Progressive outer retinal necrosis is a VZV-associated entity that typically occurs in patients with CD4 counts  $<50$  cells/mm<sup>3</sup> and is often associated with HZ. Acute retinal necrosis can occur in children with HIV at any CD4 count. A rapid decrease in visual acuity, or occurrence of red eye or eye pain, should prompt an immediate consultation with an ophthalmologist for diagnosis and specific therapy.

## Diagnosis

Typical presentations of varicella and HZ are readily diagnosed clinically. Laboratory diagnostic methods are required for atypical presentations, prolonged course of disease, and non-response to therapy. VZV DNA polymerase chain reaction (PCR) is the most sensitive and specific method for diagnosing a VZV infection.<sup>31</sup> The technique can provide an etiologic diagnosis within 24 to 48 hours, and some research laboratories can differentiate between wild-type and vaccine strain VZV. In addition to lesion specimens (vesicular fluid or scabs), PCR can be applied to blood, cerebrospinal fluid, and pharyngeal and conjunctival swabs. Direct immunofluorescence for VZV antigen can be performed on cells collected from skin, conjunctiva, or mucosal lesion scrapings. Optimal sensitivity requires obtaining cells from the base of a lesion after unroofing a fresh vesicle. This method requires only a 3-hour turnaround time, but is significantly less sensitive (detecting  $<75\%$  of infections) than PCR.<sup>32,33</sup> VZV can be isolated in cell culture from vesicular fluid or ulcer swabs, but the virus is labile and specimens must be processed rapidly. Typical cytopathic effect is noted only after 5 to 7 days. The more rapid shell vial method, which combines centrifugation of samples onto tissue culture monolayers and staining with fluorescein-conjugated monoclonal antibodies to detect synthesis of early VZV proteins, requires at least 48 hours and is less sensitive than PCR.<sup>32</sup> Culture methods are most often positive when an ulcer or vesicle is sampled, especially during the early days after illness onset and before initiation of antiviral therapy. PCR results are positive if scabs are used as a sample late in the illness. PCR is critical for evaluating atypical presentations of HZ. Serologic tests are of little value in diagnosing active VZV infection in children either with or without HIV.

## Prevention Recommendations

### *Preventing Exposure*

Children with HIV without evidence of immunity to varicella (no verified history of varicella or HZ and no evidence of appropriate vaccination or varicella immunity by a sensitive, specific antibody assay) should avoid exposure to individuals with varicella or HZ. Commercially available VZV antibody assays can have false-negative and false-positive results, limiting the ability to determine varicella immunity with certainty.<sup>31,34</sup> Household contacts who lack evidence of immunity should receive varicella vaccine to reduce the possibility of transmitting wild-type VZV to their contacts who have HIV.<sup>35</sup> For the same reason, elderly household contacts should receive the HZ vaccine according to Advisory Committee on Immunization Practices (ACIP) recommendations.<sup>36</sup>

## ***Preventing Disease***

### **Active Immunization**

Children with HIV aged 1 year to 8 years without evidence of immunity to varicella who have CD4 percentages  $\geq 15\%$  should be considered for two doses of varicella vaccine, the first dose administered as soon as possible after the first birthday and the second dose 3 months later.<sup>35</sup> Limited data from a clinical trial in children with HIV with these two characteristics indicate that the vaccine was well tolerated and that  $>80\%$  of the children had detectable VZV-specific immune responses (either antibody or cell-mediated immune response or both) at 1 year after vaccination.<sup>37,38</sup> This finding has been validated by other investigators, including persistence of antibody for up to 7 years or more post-vaccination.<sup>39-42</sup> In the absence of specific safety and immunogenicity data, the combination measles-mumps-rubella-varicella vaccine should not be administered in place of the single-antigen varicella vaccine to children with HIV.

Data are limited on use of varicella vaccine in older children and adolescents with HIV. However, the safety of varicella vaccine in individuals with HIV aged  $>8$  years who have comparable levels of immune function is likely to be similar to that in younger children, although immunogenicity in individuals without HIV is lower as the age of the vaccination increases. Weighing potential risks and benefits favors administering two doses of varicella vaccine, 3 months apart, to older patients without evidence of immunity providing that they have CD4 percentages  $\geq 15\%$  and CD4 counts  $\geq 200$  cells/mm<sup>3</sup>. The response to vaccination is optimal in patients on effective ART for an extended period and in those with high CD4 counts and very low viral loads.<sup>42,43</sup> This should be considered in scheduling varicella (and other) vaccinations to elicit optimal immune responses.

Although children with HIV who are not severely immunocompromised tolerate the vaccine well, they, like healthy children, infrequently develop mild rashes around 2 to 3 weeks after vaccination. Antiviral therapy is rarely required, and skin lesions usually clear in 3 days to 5 days without treatment. Vaccine-strain VZV is susceptible to acyclovir, should antiviral treatment be necessary. Because there is still wild-type varicella circulating, albeit at low levels, VZV rashes (especially when they are extensive) that develop shortly after vaccination require virologic investigation to distinguish vaccine-associated rashes from those caused by wild-type VZV. HZ from the vaccine strain (Oka) occurs in vaccinated healthy children, although at a much lower rate than among those who had natural varicella infection.<sup>20,44</sup> Data on the frequency of HZ from vaccination in children with HIV is lacking.

Children with HIV with low CD4 percentages ( $<15\%$ ) may rarely develop systemic disease (i.e., pneumonia and neurologic manifestations) from vaccine-strain VZV and should not be vaccinated against varicella.<sup>45</sup> However, the varicella vaccine can be safely administered to children in whom stable immune reconstitution (i.e., CD4 percentage  $\geq 15\%$ ) is achieved with ART for  $\geq 3$  months.<sup>38,40</sup>

Effectiveness of the varicella vaccine in children with HIV is suggested by long-term follow-up studies of vaccinees at several institutions.<sup>13,21</sup> Vaccination (one or two doses) was 82% effective against varicella, and no cases of HZ were observed in vaccinees. This compares favorably with the efficacy of the vaccine in healthy children (after one dose) and in children with underlying leukemia (after two doses), where an efficacy of 80% to 85% was observed for prevention of clinical infection. In vaccinated children without HIV, most breakthrough varicella cases (i.e., varicella that occurs  $\geq 42$  days after receipt of varicella vaccine) are mild, with fewer lesions (commonly  $<50$ ) and less fever and a shorter duration of illness than with varicella in unvaccinated children.<sup>46,47</sup> Comprehensive information on the severity of breakthrough varicella in children with HIV is lacking.

Because HZ vaccine is licensed only for use in healthy people aged  $\geq 50$  years to prevent HZ and has not been studied in children with HIV, it should not be given to children with HIV.

### **Passive Immunization**

Published guidelines indicate that children and adolescents with HIV who lack evidence of immunity to varicella (as defined by ACIP),<sup>35</sup> and have a non-transient, significant exposure to a person with varicella or HZ should receive human VZV immunoglobulin (VariZIG) prophylaxis as soon as possible after close

contact with the person, ideally within 96 hours but potentially beneficial up to 10 days.<sup>48</sup> However, most experts limit this recommendation to varicella- or zoster-exposed children with HIV who are considered to be severely immunocompromised (i.e., CDC Immunologic Category 3 or Clinical Category C with a high HIV RNA plasma viral load and/or a Clinical Stage 3-defining opportunistic infection)<sup>48</sup> because varicella complications are not increased in such children. Some experts prefer to see these children on ART for  $\geq 3$  months and have a CD4 count  $\geq 200/\text{mm}^3$ .

Passive immunization is achieved with VariZIG, a liquid which, when properly reconstituted, is a 5% solution of hyperimmune Immunoglobulin G that can be administered intramuscularly. VariZIG is commercially available in the United States from a broad network of specialty distributors (list available on the [VariZIG website](#)). The incubation period for varicella may be prolonged up to 28 days after VariZIG administration, thus also extending the period of potential infectiousness. VariZIG may attenuate, but not prevent varicella, in which case the patient will be potentially infectious.<sup>49</sup> Subsequent active immunization, provided the vaccine is not contraindicated (and if varicella does not develop), should be delayed for 5 months. If VariZIG is not available, intravenous immune globulin (IVIG), 400 mg/kg body weight, administered once as soon as possible (ideally within 96 hours after exposure), can be used. However, the titer of anti-VZV antibodies of any specific lot of IVIG is uncertain because IVIG is not tested routinely for anti-VZV antibodies. Patients who have received the specified dose of IVIG within 3 weeks prior to varicella- or zoster-exposure should be protected. When passive immunization is not possible for severely immunocompromised patients, some experts recommend oral acyclovir for post-exposure prophylaxis (see below).

### **Post-Exposure Antiviral Prophylaxis**

Several small studies suggest that post-exposure prophylaxis with oral acyclovir often prevents or attenuates varicella in healthy children,<sup>50-52</sup> although this approach is predicated on adequate specific immune responses developing in the exposed child during the incubation period. When passive immunization is not possible, some experts recommend prophylaxis with oral acyclovir 20 mg/kg body weight (maximum dose 800 mg), administered 4 times daily for 7 days, beginning 7 days to 10 days after exposure.<sup>53</sup> The use of acyclovir for prophylaxis in VZV-exposed children with HIV has not been studied. For that reason, while some experts would recommend post-exposure prophylaxis with acyclovir beginning 7 days to 10 days after exposure, other experts consider it prudent to wait until rash appears to start acyclovir therapy in VZV-susceptible, VZV-exposed, children with HIV who were not given passive immunization.

### **Post-Exposure Prophylaxis with Varicella Vaccine**

Post-exposure prophylaxis with varicella vaccine has been successfully used in children and adults without HIV.<sup>54</sup> However, this preventive approach is predicated on a prompt and robust immune response, which is why it has not been studied in patients with HIV and is not recommended.

## **Treatment Recommendations**

### ***Treating Disease***

Based on controlled trials in children with malignancies,<sup>55,56</sup> and response to therapy in children with HIV severely ill with varicella,<sup>22</sup> acyclovir is the drug of choice for treating varicella infections. Acyclovir should be initiated as soon as possible after varicella lesions appear. In immune competent children, new lesions can continue to appear for 72 hours after initiation of acyclovir and crusting of all lesions may take 5 days to 7 days. In children with HIV, intravenous (IV) acyclovir is recommended to treat varicella in those with severe immunosuppression (CDC Immunologic Stage 3) and those who have high fever, abdominal pain, respiratory symptoms, or numerous or deep, necrotic, or hemorrhagic skin lesions. For children aged  $< 1$  year, the dose of acyclovir is 10 mg/kg body weight administered IV every 8 hours as a 1-hour infusion. Some health care providers administer the same dose to older children, while others base the dose of acyclovir in older children on body surface area (500 mg/m<sup>2</sup> IV every 8 hours as a 1-hour infusion).<sup>53</sup> Administration is for 7 days to 10 days, provided at least 48 hours have elapsed since the appearance of new lesions. The decision may be made

to complete therapy with oral acyclovir. In children with HIV, initial treatment of varicella with oral acyclovir should only be considered for patients considered mildly to moderately immune suppressed and who have mild varicella disease.

Acyclovir 20 mg/kg body weight (800 mg maximum dose) administered 4 times per day for 7 days to 10 days is the oral treatment of choice for HZ in children with HIV, although a longer duration of therapy should be considered when lesions are slow to resolve. Oral administration of acyclovir for HZ is considered safe because the risk of disseminated, life-threatening disease is lower with HZ than with varicella. However, initial IV administration of acyclovir is recommended for children with HIV with severe immunosuppression, extensive multidermatomal HZ, disseminated infection, visceral involvement, or otherwise complicated HZ and may also be considered for trigeminal nerve or sacral dermatomal involvement. IV acyclovir should be continued until cutaneous lesions and visceral disease are clearly resolving, after which oral administration can be considered to complete the course of therapy (10 days to 14 days in this situation). Doses of IV acyclovir for treating HZ are the same as those for treating varicella.

Progressive outer retinal necrosis evolves rapidly, and despite aggressive therapy, the prognosis for visual preservation is poor. Involvement of an ophthalmologist with experience in managing VZV ocular disease and its complications in children is strongly recommended when ocular involvement is evident. Optimal therapy for the retinopathy has not been defined. Regardless of specific VZV antiviral therapy, optimization of ART is recommended and monitoring for the emergence of immune reconstitution inflammatory syndrome (IRIS) is warranted, particularly among ART-naive children (see below). Most experts recommend IV anti-VZV therapy that includes combinations of systemic antivirals (acyclovir or ganciclovir plus foscarnet), frequently given in conjunction with twice-weekly intravitreal injections of ganciclovir and/or foscarnet.<sup>57-59</sup> Adjunctive retinal surgery is sometimes recommended, along with corticosteroids and/or low-dose aspirin for associated occlusive vasculopathy and optic neuropathy. In contrast to progressive outer retinal necrosis, acute retinal necrosis appears more responsive to high-dose IV acyclovir (10–15 mg/kg body weight IV every 8 hours for 10 days to 14 days), followed by prolonged (i.e., 4 weeks to 6 weeks) oral treatment with acyclovir, or valacyclovir for older patients.<sup>60,61</sup>

Alternatives to oral acyclovir for varicella and HZ in older adolescents and adults include valacyclovir and famciclovir. Valacyclovir is a prodrug of acyclovir with improved bioavailability, which is rapidly converted to acyclovir after absorption. Sufficient information exists to support the use of valacyclovir in children (especially given its improved bioavailability, which is two- to three-fold that of acyclovir) at a dose of valacyclovir 20 to 25 mg/kg body weight administered two to three times a day. Doses lower than this may be insufficient for children weighing <20 kg.<sup>62-64</sup> No pediatric formulation is available, and valacyclovir can generally only be used for children old enough to swallow the large tablets, although crushed valacyclovir tablets can be used to make an extemporaneous suspension with good bioavailability.<sup>63,65</sup> A sprinkle formulation of famciclovir is available for children who are unable to swallow the available pill formulation or are too small for available pills. A schedule for weight-adjusted dosing is available to inform dosing of small children.<sup>66</sup>

### ***Monitoring and Adverse Events, Including IRIS***

Primary toxicities of acyclovir are phlebitis (when acyclovir is administered IV), renal toxicity, nausea, vomiting, and rash. Toxicities are similar for valacyclovir and famciclovir. In infants receiving high-dose acyclovir for neonatal HSV disease, the major side effect was neutropenia (defined as absolute neutrophil count <1,000/mm<sup>3</sup>).<sup>67</sup> Among severely ill children without HIV receiving high-dose IV acyclovir, renal injury or failure was observed in >10% of patients.<sup>68</sup> Renal function should be assessed upon initiation of acyclovir treatment and at least once weekly during treatment, especially in patients with underlying renal dysfunction who are receiving prolonged therapy. If possible, avoid concomitant administration of other nephrotoxic drugs. IV acyclovir must be adequately diluted and administered slowly over 1 to 2 hours. Since acyclovir is excreted primarily by the kidneys, dose adjustment based on creatinine clearance is needed in patients with renal insufficiency or renal failure.

HZ has been considered an IRIS event in numerous reports in which the incidence of HZ was increased

transiently after institution of ART.<sup>69</sup> However, an analysis that compared the incidence of HZ in children in the 3 months before ART initiation to that in the 3 months after ART initiation indicated no difference in incidence rates.<sup>14</sup> This suggests that the high incidence occurring in the 3 months after ART is initiated represents persistence of the inability to develop a robust VZV-specific cell-mediated immune response in this early post-ART initiation period. As immune reconstitution proceeds beyond this time, the incidence of HZ declines. This relationship has been demonstrated with numerous opportunistic infections<sup>70</sup> and confirmed for HZ.<sup>13</sup>

### ***Managing Treatment Failure***

Children in whom lesions continue to develop, fail to heal, or progress after 7 days of treatment may have acyclovir-resistant VZV.<sup>71</sup> This reflects the fact that acyclovir is a virostatic drug and that, in such cases, the patient has inadequate VZV-specific cell-mediated immunity to rapidly clear the VZV infection. If possible, virus isolation should be attempted so that susceptibility testing can be performed to confirm drug resistance. As this may be difficult to arrange and will involve significant delay, the decision to change therapy is often based on clinical observations. All acyclovir-resistant VZV strains are resistant to valacyclovir, famciclovir, and ganciclovir. The therapeutic choice for acyclovir-resistant VZV is foscarnet, 40 to 60 mg/kg body weight per dose, which should be administered IV 3 times daily for 7 days or until no new lesions have appeared for at least 48 hours.<sup>60,72</sup> Foscarnet should be administered slowly IV over the course of 2 hours (no faster than 1 mg/kg/minute).

Foscarnet has significant nephrotoxic potential;  $\geq 30\%$  of patients experience increases in serum creatinine. Foscarnet also causes serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) in many patients, and secondary seizures or cardiac dysrhythmias can occur. Abnormal liver transaminases and central nervous system symptoms can occur. Infusing foscarnet with saline fluid loading can minimize renal toxicity, and infusion through a central venous catheter can prevent thrombophlebitis. Doses should be modified in patients with renal insufficiency (see package insert). For patients receiving foscarnet, CBCs, serum electrolytes, and renal function should be monitored at least 2 to 3 times per week during induction therapy and once weekly thereafter.

### ***Preventing Recurrence***

No measures are available to prevent HZ in children and adolescents with HIV. However, varicella vaccination reduces the incidence (and perhaps severity) of HZ such that the risk of HZ is lower in vaccinated children with HIV than in healthy children or children with HIV who had naturally acquired varicella.<sup>13,21,73</sup> The likelihood of initial or recurrent attacks of HZ is reduced with effective ART.<sup>14</sup> A live attenuated vaccine (Zoster Vaccine Live, ZVL) and an inactive recombinant vaccine (Recombinant Zoster Vaccine, RZV) have been approved for use in adults aged  $\geq 50$  years.<sup>36,74</sup> A large study of the recombinant vaccine in adults with HIV indicated that it was safe and induced VZV-specific antibody and cell-mediated immunity in vaccines on ART with CD4 percentage  $\geq 15$ .<sup>75</sup> Although there are no efficacy data for this vaccine in adults with HIV, it is frequently administered to adults with HIV who meet these criteria. This vaccine has not been studied in children.<sup>76</sup>

### ***Discontinuing Secondary Prophylaxis***

Not applicable.

## **Recommendations**

### ***Prevention***

#### **I. Should children with HIV without evidence of immunity to varicella receive the varicella vaccine, compared to not receiving the varicella vaccine?**

- Children with HIV without evidence of immunity to varicella should be considered for the varicella vaccine. Vaccine administration is considered safe for children with CD4 percentage  $\geq 15\%$ . Two doses

of varicella vaccine should be given, starting as early as 12 months of age, with an interval of 3 months. Preferably the child will have been on effective ART for  $\geq 3$  months prior to vaccination. **(strong, low)**

- Vaccine administration is considered safe for children with HIV with CD4 percentage  $\geq 15\%$ . Limited data from clinical trials in such children indicate that the vaccine was well-tolerated and that  $>80\%$  of the children had detectable VZV-specific immune responses (either antibody or cell-mediated immune response or both) at 1 year after vaccination.<sup>37,38</sup> Two doses of varicella vaccine should be given, starting as soon as possible after 12 months of age, with an interval of 3 months. Preferably the child will have been on ART for  $\geq 3$  months prior to immunization. In the absence of specific safety and immunogenicity data, the combination measles-mumps-rubella-varicella vaccine should not be administered in place of the single-antigen varicella vaccine to children with HIV. Effectiveness of the varicella vaccine in children with HIV is suggested by long-term follow-up studies.<sup>13,21</sup> Vaccination was 82% effective against varicella, and no cases of HZ were observed in vaccinees. Comparable efficacy was reported in vaccinated healthy children (after one dose) and in vaccinated children with underlying leukemia (after two doses), where an efficacy of 80% to 85% was observed for prevention of clinical infection.

## **II. Should children with HIV who are without evidence of immunity to varicella and exposed to varicella or HZ receive prophylaxis with human varicella-zoster immunoglobulin, compared to not receiving varicella-zoster immunoglobulin?**

- Children with HIV who are susceptible to varicella and have had a significant exposure to varicella or HZ, and are severely immune compromised, should receive varicella zoster immune globulin (available as VariZig) as soon as possible within 10 days after exposure. The extent of immune compromise should be considered in making this decision. VariZig is given intramuscularly at the recommended dose of 125 units/10 kg, up to a maximum of 625 units (i.e., 5 vials). **(strong, low)**
- Children with HIV who are susceptible to varicella and are severely immunocompromised, and have had an exposure to varicella or HZ, are likely to develop severe varicella with complications. A large observational study of immunocompromised children, without HIV infection, indicated that varicella zoster immune globulin (currently available as VariZig) given within 72 hours of exposure reduced varicella severity compared to historical controls.<sup>49</sup> Subsequent studies indicated that some protection occurred with passive immunization as long as 10 days after exposure.<sup>77</sup> Thus, varicella- or HZ-exposed children with HIV are likely to benefit from passive immunization **(strong, low)**, although most experts limit this recommendation to those who are considered to be severely immunocompromised. VariZig is given intramuscularly at the recommended dose of 125 units/10 kg, up to a maximum of 625 units (i.e., 5 vials). If VariZig is unavailable, immune globulin for IV administration can be used at the dose of 400 mg/kg. VariZIG may attenuate, but not prevent varicella, in which case the patient will be potentially infectious. If passive immunization is not possible for severely immunocompromised patients, some experts recommend oral acyclovir for post-exposure prophylaxis.

## ***Treatment***

### **III. Should children with HIV with varicella be treated with acyclovir, compared to not being treated with acyclovir?**

- IV acyclovir therapy is recommended for children with HIV with significant immune compromise who have varicella or for any child with HIV with severe varicella. Therapy initiated early in the course of the illness, especially within 24 hours of rash onset, maximizes efficacy. For select patients with HIV perceived to be at lower risk of developing severe varicella, many experts use oral acyclovir. This decision is made for patients with relatively normal concentrations of CD4 cells, especially if they are



receiving ART. (**strong, moderate**)

- On the basis of controlled trials treating severe varicella in children with malignancy<sup>55,56</sup> and of observational studies treating the disease in children with HIV,<sup>22</sup> IV acyclovir is recommended as initial therapy in children with HIV with severe immunosuppression. Treatment should be initiated as soon as possible (especially within 24 hours) after varicella lesions appear to maximize efficacy. Many experts use oral acyclovir for select children with HIV perceived to be at lower risk of developing severe varicella. However, the decision to use oral acyclovir is reserved for patients with relatively normal concentrations of CD4 cells, especially if they are receiving ART. IV administration should also be considered for children with high fever; abdominal pain; respiratory symptoms; numerous or deep, necrotic, or hemorrhagic skin lesions; disseminated infection; or visceral involvement. Administration is for 7 days to 10 days, provided that new lesions have ceased to appear for at least 48 hours. The decision may be made to complete 10 days to 14 days of therapy with oral acyclovir.

#### **IV. Should children with HIV with HZ be treated with acyclovir, compared to not being treated with acyclovir?**

- Oral therapy with acyclovir for 7 days to 10 days is recommended for children with HIV with HZ, although longer therapy duration should be considered if lesions are slow to resolve. Initial IV administration is recommended for children with HIV with severe immunosuppression, extensive multidermatomal HZ, disseminated infection, visceral involvement, or otherwise complicated HZ. IV acyclovir should be continued until cutaneous lesions and visceral disease are clearly resolving, after which oral administration can be considered to complete therapy. (**strong, moderate**)
- Oral acyclovir therapy for HZ for 7 days is established therapy in immune competent patients,<sup>78</sup> and IV therapy was demonstrably efficacious in a controlled trial in immunocompromised patients, including those with disseminated HZ.<sup>79</sup> Oral acyclovir for 7 days to 10 days is recommended for HZ in children with HIV, although longer therapy duration should be considered if lesions are slow to resolve. However, initial IV administration is recommended for children with HIV with severe immunosuppression, extensive multidermatomal HZ, disseminated infection, visceral involvement, or otherwise complicated HZ. IV acyclovir should be continued until cutaneous lesions and visceral disease are clearly resolving, after which oral administration can be considered to complete 10 to 14 days of therapy.

#### **V. Is foscarnet the best choice for anti-varicella-zoster virus (VZV) therapy for children with HIV in whom therapy is failing because of acyclovir-resistant VZV?**

- When acyclovir resistance is considered, if possible, virus isolation should be attempted for susceptibility testing. All acyclovir-resistant VZV strains are resistant to valacyclovir, famciclovir, and ganciclovir. VZV infections caused by acyclovir-resistant VZV strains should be treated with parenteral foscarnet. (**strong, very low**)
- Children in whom lesions continue to develop, fail to heal, or continue to progress after 7 days of treatment may have acyclovir-resistant VZV.<sup>71</sup> Isolation of persisting virus should be attempted so that susceptibility testing can be performed to confirm drug resistance. Since this involves considerable delay, the decision to change therapy is often based on clinical observations. All acyclovir-resistant VZV strains are resistant to valacyclovir, famciclovir, and ganciclovir. Based on this finding and three observational or open-label studies, primarily in adults, that documented responses to foscarnet, this second line drug is the therapeutic choice for acyclovir-resistant VZV.<sup>72,80,81</sup> Foscarnet (40–60 mg/kg/dose IV every 8 hours) is administered for 7 days to 10 days or until no new lesions appear.

## Dosing Recommendations for Preventing and Treating Varicella-Zoster Virus (page 1 of 2)

Indication	First Choice	Alternative	Comments/Special Issues
Pre-Exposure Prophylaxis	Varicella vaccine	N/A	See <a href="#">Figure 1</a> for detailed vaccine recommendations.
Primary (Post-Exposure) Prophylaxis	VariZIG 125 IU/10 kg body weight (maximum 625 IU) IM, administered ideally within 96 hours (potentially beneficial up to 10 days) after exposure	<p>If VariZIG is not available, IVIG 400 mg/kg body weight, administered once should be considered. IVIG should ideally be administered within 96 hours of exposure.</p> <p>When passive immunization is not possible, some experts recommend prophylaxis with acyclovir 20 mg/kg body weight/dose (maximum dose acyclovir 800 mg) by mouth, administered four times a day for 7 days, beginning 7–10 days after exposure.</p>	<p><b>Primary Post-Exposure Prophylaxis Indicated for:</b></p> <ul style="list-style-type: none"> <li>• Patients with substantial exposure to varicella or zoster who have no verified history of varicella or zoster, or who are seronegative for VZV on a sensitive, specific antibody assay, or who lack evidence of vaccination.</li> <li>• Many experts limit the recommendation for passive immunization to varicella- or zoster-exposed children with HIV considered severely immunocompromised (i.e., CDC Immunologic Category 3), especially if severely symptomatic (i.e., CDC Clinical Category C<sup>a</sup>) and experiencing a high HIV RNA plasma viral load.</li> <li>• Some experts start acyclovir at first appearance of rash in children with HIV, rather than providing acyclovir as prophylaxis.</li> </ul> <p><b>Note:</b> VariZIG is commercially available in the United States from a <a href="#">broad network of specialty distributors</a>.</p> <p><sup>a</sup> Centers for Disease Control and Prevention. Revised classification system for human immunodeficiency virus infection in children aged &lt;13 years. Official authorized addenda: human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM. <i>MMWR Morb Mortal Wkly Rep.</i> 1994;43:1-19. Available at: <a href="http://www.cdc.gov/mmwr/PDF/rr/rr4312.pdf">http://www.cdc.gov/mmwr/PDF/rr/rr4312.pdf</a>.</p>
Secondary Prophylaxis	N/A	N/A	There is no indication for secondary prophylaxis.
Treatment	<p><b>Varicella</b></p> <p><i>Children with No or Moderate Immune Suppression (CDC Immunologic Categories 1 and 2) and Mild Varicella Disease:</i></p> <ul style="list-style-type: none"> <li>• Acyclovir 20 mg/kg body weight/dose by mouth (maximum 800 mg/dose) four times a day for 7–10 days and until no new lesions for 48 hours</li> </ul> <p><i>Children with Severe Immune Suppression or Severe Varicella Disease (see text):</i></p> <ul style="list-style-type: none"> <li>• Acyclovir 10 mg/kg body weight or 500 mg/m<sup>2</sup>/dose IV every 8 hours for 7–10 days and until no new lesions for 48 hours</li> </ul>	<p><b>Patients Unresponsive to Acyclovir:</b></p> <ul style="list-style-type: none"> <li>• Foscarnet (40–60 mg/kg body weight/dose IV every 8 hours) for 7-10 days or until no new lesions have appeared for 48 hours</li> </ul>	<p>In children aged ≥1 year, some experts base IV acyclovir dosing on body surface area (500 mg/m<sup>2</sup> body surface area/dose IV every 8 hours) instead of body weight.</p> <p>Valacyclovir is approved for use in adults and adolescents with zoster at 1 g/dose by mouth three times a day for 7 days; the same dose has been used for varicella infections. Valacyclovir can be used in children at a dose of 20 to 25 mg/kg body weight administered 2 to 3 times a day. Doses lower than this may be insufficient for children weighing &lt;20 kg. There is no pediatric preparation, although 500-mg capsules can be extemporaneously compounded to make a suspension to administer valacyclovir 20 mg/kg body weight/dose (maximum dose 1 g) given three times a day (see prescribing information).</p> <p>Famciclovir is approved for use in adults and adolescents with zoster at 500 mg/dose by mouth three times a day for 7 days; the same dose has been used for varicella infections. A sprinkle formulation of famciclovir is available for children who are unable to swallow the available pill formulation. A schedule for weight-adjusted dosing is available to inform dosing of small children.</p>

## Dosing Recommendations for Preventing and Treating Varicella-Zoster Virus (page 2 of 2)

Indication	First Choice	Alternative	Comments/Special Issues
Treatment, continued	<p><u>Zoster</u></p> <p><i>Children with Uncomplicated Zoster and No or Moderate Immune Suppression:</i></p> <ul style="list-style-type: none"> <li>• Acyclovir 20 mg/kg body weight/dose (maximum 800 mg/dose) by mouth four times a day for 7–10 days</li> </ul> <p><i>Children with Severe Immunosuppression (CDC Immunologic Category 3), Trigeminal or Sacral Nerve Involvement, Extensive Multidermatomal, or Disseminated Zoster:</i></p> <ul style="list-style-type: none"> <li>• Acyclovir 10 mg/kg body weight/dose or 500 mg/m<sup>2</sup> IV every 8 hours until cutaneous lesions and visceral disease are clearly resolving, then patient can switch to oral acyclovir to complete a 10–14-day course</li> </ul> <p><i>Children with Progressive Outer Retinal Necrosis:</i></p> <ul style="list-style-type: none"> <li>• Acyclovir (10 mg/kg or 500 mg/m<sup>2</sup> every 8 hours) or ganciclovir 5 mg/kg body weight/dose IV every 12 hours, <u>plus</u></li> <li>• Foscarnet 90 mg/kg body weight/dose IV every 12 hours, <u>plus</u></li> <li>• Ganciclovir 2 mg/0.05 mL intravitreal injection twice weekly and/or foscarnet 1.2 mg/0.05 mL intravitreal injection twice weekly</li> </ul> <p><i>Children with Acute Retinal Necrosis:</i></p> <ul style="list-style-type: none"> <li>• Acyclovir 10–15 mg/kg body weight/dose IV every 8 hours daily for 10–14 days, <u>followed by</u> oral valacyclovir 1 g/dose three times a day for 4–6 weeks (for children old enough to receive adult dose).</li> <li>• Alternative to oral valacyclovir is oral acyclovir 20 mg/kg body weight/dose four times a day for 4–6 weeks</li> </ul>		<p>Involvement of an ophthalmologist with experience in managing HZ ophthalmicus and its complications in children is <u>strongly recommended</u> when ocular involvement is evident.</p> <p>Optimal management of progressive outer retinal necrosis has not been defined.</p>

Key: CDC = Centers for Disease Control and Prevention; HZ = herpes zoster; IM = intramuscular; IU = international units; IV = intravenous; IVIG = intravenous immunoglobulin; VariZIG = varicella zoster immune globulin; VZV = varicella zoster virus

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