

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

The Role of Vaccination in Prevention of VZV Disease in the Immunocompromised Child

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H&O Is varicella vaccine protective against varicella in immunocompromised children?

SH There are 2 scenarios here—the first is that a child becomes immunosuppressed at some point long after varicella vaccination. Since the vaccine is immunogenic and lastingly effective in the majority of healthy children,^{1,2} the child most likely will enter their period of immunosuppression with existing vaccine-induced immunity against varicella. Depending on the duration and intensity of immunosuppression, this immunity may wane over time, as is known to occur for other vaccine antigens and even naturally-induced varicella-zoster virus (VZV) immunity.^{3,4} This means that highly immunosuppressed children with a history of prior varicella vaccination (or disease) should not be presumed to be protected.⁵

A second scenario involves the possible administration of the vaccine in the immunocompromised state, to children who lack pre-existing immunity to VZV.^{6,7} Here, the potential to develop useful vaccine-induced immunity must be balanced against the risks of giving a live vaccine (which will be discussed later). Clearly, children with primary combined immunodeficiency are incapable of mounting protective vaccine responses and should not be vaccinated. Another group of children that are highly susceptible to varicella is one that receives maintenance therapy for leukemia.⁸ Trials have indicated that the vaccine can be both immunogenic

and efficacious in this group, although somewhat less so than in healthy children; after 2 doses of vaccine, more than 90% showed a VZV-specific immune response, and 75% remained seropositive in long-term follow-up.^{9,10} Vaccinated leukemic children were protected from varicella as judged by a significantly lower attack rate following household exposure. Those that did become infected mostly experienced modified (milder) disease. There also appeared to be a benefit in significantly lower rates of herpes zoster than obtained after natural varicella.¹¹ These findings in leukemic children were echoed in more recent studies of HIV-positive children.¹²

H&O Is it safe to give live attenuated varicella vaccine to immunocompromised children?

SH The answer to this question is: yes and no. Although the vaccine contains highly attenuated (weakened) virus, it is still live. When cellular immunity is severely depressed, it is easier for the vaccine strain virus to replicate and spread within the body, causing local or even systemic disease. The children who are at greatest risk from natural varicella are also the most vulnerable to the vaccine-strain virus.

This risk is more than theoretical: vaccination of children with leukemia in remission led to vaccine-associated rash in approximately 40% (15% if maintenance chemotherapy was suspended for a week before and after vaccination).¹⁰ In approximately 1%, the rash was severe

(>500 skin lesions) and associated with constitutional symptoms such as high-grade fever, abdominal and back pain, or pneumonia (ie, features of disseminated varicella infection); all cases recovered with acyclovir therapy. Children who developed rash could transmit vaccine-strain virus to others,¹³ and were themselves at greater risk of later zoster than vaccinees who did not get a rash.¹¹ There is one published case report of a child with leukemia, vaccinated in remission, who developed fatal disseminated vaccine strain varicella some weeks later while receiving reinduction chemotherapy.¹⁴ Other cases of disseminated vaccine strain varicella have occurred rarely, for example in children with unrecognized primary immunodeficiency or iatrogenic immunosuppression.¹⁵

H&O What is the recommended vaccine use in this patient population?

SH As a result of these safety concerns, neither of the commercially available varicella vaccine preparations is licensed for use in immunosuppressed individuals or those with malignant disease or blood dyscrasias. However, there clearly are some groups who can benefit from vaccination despite some degree of immunosuppression. In particular, the vaccine appears to be safe and well-tolerated in HIV-positive children with a CD4 percentage of over 15% and an absolute CD4 count of more than 200/ μ L.¹² This favorable experience is reflected in the current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccine use in the United States, which also point out the safety of varicella vaccination in those with purely humoral immunodeficiency.¹⁶

A recent publication proposed deferring varicella vaccination for at least 9 months after the completion of chemotherapy for malignancy, and maintaining a high index of suspicion for vaccine-associated disease over the ensuing weeks.¹⁴ Consideration should be given to revaccinating children who have undergone prolonged immunosuppressive chemotherapy if serologic testing suggests the waning of prior immunity.³ Recipients of allogeneic hemopoietic stem cell transplants should be considered VZV-naïve unless they have experienced an episode of VZV disease since the transplant; vaccination may therefore be appropriate following immune reconstitution.

H&O How else can immunocompromised patients be protected against varicella?

SH The mainstays of prevention are the recognition of risks posed by VZV in immunocompromised seronegative individuals and the avoidance of exposure.¹⁷ In countries with universal varicella vaccination, children obtain pro-

tection both by personal vaccination and by herd immunity. Regardless of the setting, VZV-susceptible household contacts of any immunocompromised person should be identified and offered immunization (as should susceptible healthcare workers). In the event of exposure to varicella or zoster, the VZV-susceptible immunosuppressed individual must come forward urgently for medical attention. Post-exposure prophylaxis can be offered to seronegatives in the form of VZV-immune globulin (VariZig/VZIG) if within a few days of exposure. The use of antiviral drugs as post-exposure prophylaxis in the immunocompromised has not yet been studied, but should be considered if passive immunization is not possible.¹⁸

H&O What about zoster in immunocompromised patients?

SH Cellular immunosuppression dramatically increases the risk of VZV reactivation, as well as worsening zoster severity. The greatest risk occurs in the wake of primary varicella acquired during immunocompromise, presumably reflecting the viral load during primary disease and/or the inadequate primary immune response to infection. Experience in stem cell transplant recipients suggests that low-dose acyclovir prophylaxis is highly effective in preventing zoster over the first 6–12 months post-transplant.¹⁹ Continuous prophylaxis is generally reserved for such patients and for those with recurrent zoster, for example in the context of AIDS.

There is currently no place for the live attenuated zoster vaccine in the immunocompromised, since it is a higher potency form of the varicella vaccine. However, strategies for exploring a possible future role are under evaluation.²⁰ A killed VZV vaccine showed some promise in offering additional protection against zoster in adults undergoing autologous stem cell transplantation.²¹ In the long term, public health strategies centering on varicella and zoster vaccination will impact zoster incidence in all groups, including the immunocompromised. For the foreseeable future, however, VZV is here to stay.

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