

Varicella Vaccination of Immunocompromised Children

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Background. Exposure of immunocompromised children to varicella often requires postexposure prophylaxis. Exposures requiring this management are often not recognized. Varicella can be a severe disease when it occurs in immunocompromised children, in spite of antiviral therapy. Varicella exposure and varicella in these children can also disrupt scheduled therapy for their underlying illness. Both postexposure prophylaxis and treatment of varicella are likely to be expensive and use significant medical resources. Numerous trials have been undertaken to vaccinate children who are immunocompromised by a variety of conditions and therapies that depress their immune function.

Methods. Clinical trials of varicella vaccine administration to immunocompromised children that were reported since 1975 were identified in the Ovid medical database. Reports were selected for analysis and discussion on the basis of their completeness and the utility of their conclusions.

Results. Vaccination before immune compromise is discussed as a strategy for some settings. The obstacles, potential opportunities, and success in varicella vaccination for immunocompromised children are separately analyzed for (1) children with leukemia and other malignancies, (2) human immunodeficiency virus–infected children, and (3) children with hematopoietic stem cell or solid-organ transplantation.

Conclusions. Vaccination before immune compromise is often successful, and the vaccine-induced response is usually partially or fully protective. In many treatment settings, it is possible to safely vaccinate once the level of immune suppression has been reduced. Targets for future research are outlined. A consensus conference should be undertaken to develop guidelines for the use of varicella vaccine in immunocompromised children.

An excellent extensive review of the topic of varicella vaccination of immunocompromised children was published in 2004 [1]. The current review updates and selectively annotates that review. Varicella in immunocompromised children can be severe [2–6]. Even though effective antiviral therapy is available, the course of varicella in these patients can be troublesome and sometimes fatal, especially if the illness is not recognized and treated promptly. Moreover, the management of intercurrent varicella or the provision of passive immunization with varicella-zoster virus (VZV) immune

globulin (VZIG) can interfere with therapy for the underlying immunocompromising condition [7, 8]. Approximately half of varicella exposures are not recognized, thereby precluding timely VZIG administration [7].

In spite of the availability of effective anti-VZV drugs and various immunization strategies, this review remains relevant because (1) antiviral therapy sometimes fails in immunocompromised children; (2) universal immunization will not be possible in most countries; (3) immunization of close contacts of high-risk children, which is a strategy in some countries, will protect against only a small proportion of potential contacts; (4) some children may not receive scheduled varicella vaccine before they become immunocompromised; and (5) endogenous spread of varicella continues in countries with universal varicella vaccination [9].

INDIRECT PROTECTION WITH VARICELLA VACCINE

Where universal immunization is achieved, exposure to VZV will be greatly reduced, thereby protecting pa-

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tients with immunocompromising conditions [10]. In countries that do not recommend universal immunization, it is possible to indirectly protect high-risk children by immunizing siblings and susceptible providers (including medical care providers) to decrease exposure to varicella [11]. This strategy will be only partially successful, because immunocompromised children will have numerous other contacts with susceptible individuals who have not been vaccinated or who will develop “breakthrough” disease. Exposures to herpes zoster or to imported cases of varicella pose an additional risk.

OBSTACLES TO VARICELLA VACCINATION OF IMMUNOCOMPROMISED CHILDREN

Two obstacles exist to the successful varicella vaccination of immunocompromised children. The first is the concern that the current live varicella vaccine, although attenuated, could cause a significant infection akin to natural varicella and its complications. Disseminated disease has been reported in 6 immunocompromised patients ($>50 \times 10^6$ doses distributed in the United States) who were immunized before an immune defect was appreciated [12]. In addition, severe vaccine-related varicella occurred in some immunocompromised children who received VZV vaccine while receiving chemotherapy for solid tumors [13, 14]. Second, the immune response to the vaccine in these children might be suboptimal and, subsequently, non-protective. These obstacles will vary with the nature of continuing immune suppression and the interval after terminating immune suppression.

VARICELLA VACCINATION BEFORE IMMUNE COMPROMISE

This approach would ensure safety and, for most medical conditions (e.g., solid-organ transplantation), would result in good immune responses. However, this strategy will probably fail for children undergoing allogeneic hematopoietic stem cell transplantation, because immune memory is ablated by the interventions. Immune memory is also severely reduced for several months after autologous stem cell transplantation. In addition, this approach will not be practical before therapy for most solid tumors, because the interval between diagnosis and intensive chemotherapy is purposefully limited. In these situations, even when immune memory develops, protection may be inadequate during periods of intense immune suppression, such as soon after transplantation or when antitumor therapy is intensified. Determinants of the success of vaccination before immune compromise include (1) nature and stage of the underlying illness, (2) type and amount of immunosuppressive agents before vaccination, (3) vaccine dose, and (4) extent of immunosuppressive therapy at the time of exposure.

Leukemia

The Oka varicella strain was developed by Takahashi in the early 1970s [15, 16] and was studied in Japanese children with immune compromising illnesses. More than 325 children with acute leukemia received a varicella vaccine, sometimes a vaccine of lower potency than the current vaccine [16]. Most often (80%), the vaccine was administered while the patient was in remission; most chemotherapy was stopped for a week before and a week after vaccination. Before vaccination, the lymphocytes of the patients were tested for *in vitro* proliferation. With these stipulations, 15% of vaccine recipients developed mild to moderate rashes, whereas those vaccinated without stopping chemotherapy had a 40% incidence of vaccine-induced rash. Most vaccine recipients developed anti-VZV neutralizing antibody. Uncontrolled observations indicated a strong trend for prevention of varicella after exposure and attenuation in the children who developed varicella [14, 16, 17].

The Takahashi group demonstrated the relative safety and efficacy of administering varicella vaccine to leukemic children and thereby suggested inclusion and exclusion criteria for the definitive trial undertaken from 1980 to 1992 [18–20]. This involved 437 VZV-seronegative and varicella history–negative children with acute lymphocytic leukemia in remission (most for at least 1 year). Maintenance therapy was stopped for 1 week before and after vaccination; 65 children had completed therapy. Vaccine recipients had an IgG concentration of 100 mg/dL, a lymphocyte count of 700 cells/ μ L, and lymphocytes that proliferated *in vitro* to a mitogen or antigen. Vaccines containing 1000–4500 pfu/dose (made by several manufacturers and several processing methods) were used, but most children received 1000–2500 pfu/dose of a vaccine similar to the contemporary vaccine (Oka/Merck strain; 1350 pfu at expiration). Most vaccine recipients received 2 doses separated by 3 months. A mild rash occurred in 5% of children who were no longer receiving therapy and in 40% of vaccine recipients still receiving maintenance therapy. Rash was observed after the second dose in 10% of those receiving maintenance therapy. Rashes occurred at 7–40 days (mean, 28 days) after the initial vaccination. These rashes were not considered to be severe and were readily treated with acyclovir. This safety profile was judged to be acceptable and tolerable. It was subsequently determined that it was not necessary to withhold maintenance therapy before giving the second dose of vaccine.

Vaccine virus was sometimes transmitted from vaccine recipients to close contacts (14%–17%), but only from vaccine recipients who developed a rash [21]. This information on secondary spread is important for planning future studies in clinics that have large numbers of immunosuppressed patients.

Overall, >85% of vaccine recipients developed VZV antibody after 1 dose of vaccine, as measured by the fluorescent antibody to membrane antigen assay; 95% of patients not receiving ther-

apy seroconverted. Most vaccine recipients (75%) who were seronegative after 1 dose seroconverted after the second dose. This provided the rationale for the 2-dose schedule. Within 2 years ~25% of vaccine recipients lost detectable antibody [19, 20]. However, during long-term follow-up, the prevalence of antibody remained at ~75% from year 2 to year 6 after vaccination. Although some vaccine recipients lost detectable antibody, others who had been seronegative regained antibody, thus providing evidence of environmental boosting and protection [20]. VZV-specific cell-mediated immunity (CMI) could be detected in >90% of leukemic vaccine recipients after the second dose [22–24].

Thirty-six leukemic vaccine recipients developed varicella during a variable observation period that was as long as 9 years. Of the 27 who did not receive VZIG, 78% had mild disease, 18% had moderate disease, and 1 had severe disease, indicating that vaccination attenuated subsequent wild-type infection. Only 2 children subsequently received acyclovir. Eleven cases of varicella occurred after 83 household exposures for which VZIG was not administered. Compared with historical attack rates, this represented 86% protection against any diseases; none of these breakthrough cases was severe.

The vaccine efficacy in leukemic children, in terms of prevention or attenuation of clinical varicella, was not influenced by (1) duration of chemotherapy before immunization, (2) number of vaccine doses, (3) chemotherapy at the time of exposure, or (4) interval from vaccination to exposure. The attack rate was higher in seronegative than in seropositive vaccine recipients (29% vs. 8%, respectively). However, varicella did occur in some children with VZV antibody and, conversely, did not occur in many children who lacked antibody. This probably reflects the important role of immune memory, both VZV-specific antibody and CMI, which may not have been measurable but functioned to protect (or attenuate disease in) the exposed children. Such protection has been demonstrated in immunocompetent children who no longer had detectable VZV-specific antibody after being vaccinated [25]. Thus, once a VZV-specific immune response is detected, even if it is lost, it is likely that this represents a marker of protection. This mirrors clinical experience with immunocompromised children who had varicella before receiving their compromising therapy, because they are not at risk for subsequent cases of varicella, except at the extremes of immune suppression, such as immediately after bone marrow transplantation.

The rate of leukemia relapse was not altered by varicella vaccination. Subsequent studies of leukemic vaccine recipients showed that herpes zoster is at least 2.5-fold less likely in vaccine recipients than in matched control subjects who had prior natural varicella [26]. A similar effect was suggested in the Japanese studies [16].

Other Malignancies

When the time required for staging is sufficiently long, varicella vaccination should occur before starting therapy, because there is evidence that the VZV-specific immunity induced with early immunization or during the maintenance phase of treatment remains protective. However, this clinical opportunity is uncommon. The more common clinical setting of children with solid tumors was studied in >50 Japanese children with a variety of solid tumors who received the Oka strain vaccine under conditions similar to those described for lymphocytic leukemia. The clinical and immunological outcomes were similar to those described with acute leukemia [14, 16]. Cutaneous manifestations of vaccination occurred in ~10% of the children, and no severe disease was observed. Seroconversion occurred in 90%–95% of the children. An exception was noted with malignant lymphoma, in that 4 of 8 vaccine recipients developed severe vaccine-related varicella; however, these children were vaccinated without temporary cessation of their maintenance therapy. Many subsequent small studies of children with solid tumors have been reported (~150 children; >10 studies); these varied in dose, type of tumor, and measurement of VZV-specific response [27–30]. The safety, immunogenicity, and resulting protection, as determined by passive reporting of exposures, closely replicated the Japanese experience. A reasonable conclusion is that these children will benefit from varicella vaccination if maintenance therapy is stopped for at least 1 week (in some cases for >1 week) before and after vaccination and if vaccination is undertaken during the maintenance phase of therapy. One study administered vaccine at the start of chemotherapy without any serious consequences and with immunological and clinical evidence of protection; however, only 500 pfu of virus was administered, and the chemotherapy was not described [31].

HIV Infection

A 3-year open trial of varicella vaccine was undertaken in 97 HIV-infected children stratified by Centers for Disease Control and Prevention (CDC) clinical stage (74 were at stage N or A; 23 were at stage B) and CDC immunological category (43 were in category 1; 37 were in category 2; 17 had been in immunological category 3 and reconstituted to category 1 before vaccination) [32, 33]. Vaccine recipients were receiving stable antiretroviral therapy for ≥ 3 months. Vaccine recipients received 2 doses separated by 3 months. Vaccine recipients who had no VZV-specific immunity at 1 year after vaccination received a third dose of vaccine.

The vaccine had a very acceptable safety profile. Fever occurred in 40% of the children, but <5% of the fevers reached 39.4°C. Adverse experiences were similar to those seen in HIV-uninfected children and were less frequent with the second dose. CD4 cell count status and viral load were not altered by

vaccination. VZV-specific antibody was present in 59%–72% of vaccine recipients (depending on immune status) after 2 doses and was present in 43%–65% after 1 year. A similar percentage with detectable antibody was found in a comparator group of HIV-infected children who had natural varicella (instead of vaccine) in the prior year. CMI (lymphocyte proliferation and responder cell frequency) was observed in 60%–65% of vaccine recipients after dose 2 and in >70% at 1 year. This was also similar to the comparator group. At least 1 measure of VZV-specific immunity (antibody and/or CMI) was present in 83%–85% of vaccine recipients after 2 doses. The second dose of vaccine did not add significantly to the overall response at 1 year after vaccination. A third dose of vaccine induced a VZV-specific response in 11 of 18 vaccine recipients who were negative after 2 doses. The likelihood of responding to vaccination was not a function of prior or incident CD4 cell count status. Viral load at the time of vaccination was an independent determinant of response to the vaccine. There were 16 recorded exposures to varicella without a secondary case (1 vaccine recipient received VZIG). One very mild case of varicella occurred without a known exposure.

Armenian et al. [34] administered 1 dose of varicella vaccine to 10 HIV-infected children. At the time of vaccination, they were at CDC clinical stage N, and 9 children were in CDC immunological category 1. Three subjects had been in CDC immunological category 3 before antiretroviral therapy. All vaccine recipients were receiving stable antiretroviral therapy (RNA viral load, <400 copies/mL). The vaccine was well tolerated. CD4 cell count and CDC clinical stage were not affected by vaccination. Results of a VZV-specific lymphoproliferative assay were positive in all vaccine recipients at 4 weeks after vaccination; 89% remained positive at 1 year. VZV-specific antibody test results were positive in 67% of vaccine recipients at week 8 after vaccination and were positive in only 33% at 1 year.

Organ Transplantation

Hematopoietic stem cell transplantation. After allogeneic or autologous hematopoietic stem cell transplantation, the primary response to vaccination is severely depressed for an extended period. This period is generally shorter after autologous transplantation, primarily because the amount and duration of immunosuppressive therapy are less. The capacity of hematopoietic stem cell recipients to respond to VZV antigen was demonstrated with an inactivated VZV vaccine. Assuming that this was akin to a primary response, it is apparent that the capacity to respond was present at 3 months after transplantation [35, 36]. An Oka strain vaccine was administered to bone marrow transplant recipients (allogeneic and autologous) at 12–18 months after transplantation if they were not receiving immunosuppressive therapy and met criteria similar to those described for other immunosuppressed children [37]. There were

no significant adverse events. Seroconversion occurred in 8 of 9 vaccine recipients; 1 subject seroconverted after a second dose. Antibody persisted for at least 2 years in 6 responders. Future studies will be needed to determine the optimal time to vaccinate after transplantation. However, because an inactivated vaccine is safe and immunogenic in this setting [35, 36], it could be used early in the posttransplantation period, followed later by the live attenuated vaccine.

Kidney transplantation. Oka strain vaccines can be safely administered to uremic children, including those with disease severe enough to qualify for transplantation. More than 375 seronegative uremic children have received Oka strain vaccine (1000–2000 pfu) [38–41]. One or 2 doses were administered; in 1 study, the second dose was administered if there was no seroconversion after the first dose. Mild rashes were rare after vaccination, and no serious systemic events occurred. Although assays of varying sensitivity were utilized, in general, seroconversion occurred in 85%–100% of vaccine recipients. Almost all vaccine recipients seroconverted after 2 doses. After transplantation, antibody persisted in 75%–100% of vaccine recipients for ≥ 2 years, although a transient dip in antibody titer occurred in the early posttransplantation period. Although matched control subjects were lacking, the incidence of subsequent varicella in vaccine recipients was reduced by $\sim 75\%$ after transplantation, compared with unvaccinated transplant recipients; the severity of illness was generally milder in vaccine recipients who developed varicella. Infection was also significantly reduced after known exposures. In one study, only those who did not seroconvert or who lost antibody developed clinical disease. The protective effect was further indicated by the large number of late seroconversions in vaccine recipients, suggesting protection from inapparent environmental exposure. Herpes zoster appeared to be less frequent in vaccine recipients than in children who underwent transplantation and had prior natural varicella.

Administering 2 doses of varicella vaccine before transplantation is the optimal approach to the problem of varicella in renal transplant recipients. This is also a cost-saving approach [41–43].

There is limited information regarding 17 children who received varicella vaccination after renal transplantation [38]. They received 1 dose without stopping their therapy; maintenance levels of prednisone, azathioprine, and cyclosporine were carefully monitored. A lymphocyte count of >1500 cells/ μL was required. The vaccine was well tolerated. At 6–12 months, 75%–85% of the children had VZV-specific antibody. Three cases of varicella occurred during a limited follow-up period; all of the cases were attenuated. Children with nephrotic syndrome in remission can be safely immunized with the precautions described above [16], although the long-term efficacy in nephrotic children remains unknown. Children with this diagnosis often

relapse and lose significant quantities of VZV-specific antibody, although this should be compensated for by VZV-specific CMI, provided that subsequent immunosuppressive therapy is not unusually intensive.

Liver transplantation. Vaccinating before transplantation is often not an option for children who undergo transplantation for severe biliary atresia and those receiving intensive immunosuppressive therapy for autoimmune diseases. Pretransplantation vaccination was evaluated in 29 children with chronic liver disease who were not receiving immunosuppressive therapy. No serious reactions occurred after 1 dose of vaccine, and all vaccine recipients seroconverted [44], but the severity of the chronic illness did affect the persistence and magnitude of the response.

Varicella vaccine was administered to 15 children at least 6 months after transplantation (1 concomitant liver and intestinal transplant) [45]. Although they continued to receive antirejection therapy, their prednisone dose was ≤ 0.3 mg/kg, and their tacrolimus/cyclosporine A levels were monitored. Rejection episodes in the prior month were an exclusion criterion. Rash occurred in 4 subjects. These were not severe, but acyclovir was administered to 3 vaccine recipients. Low-grade fever occurred in 4 vaccine recipients. Seroconversion and VZV-specific CMI appeared in $> 85\%$ of vaccine recipients. Ten subsequent exposures to varicella occurred without the administration of VZIG; no cases of varicella resulted. Vaccination before and selectively after liver transplantation appears to be a useful approach and has been deemed cost saving [43].

DISCUSSION

Varicella vaccination can safely prevent most cases of severe varicella in immunocompromised children. This has been most successful when vaccination occurs during periods of limited immune suppression, such as before treatment with immunosuppressive therapy, when therapy is stopped temporarily, or when maintenance immune suppression is low (e.g., late after transplantation).

This protection will be very important in countries that do not routinely vaccinate all children to prevent varicella. However, even where varicella immunization rates are high, this will provide additional protection for immunocompromised children. In most settings, the protection provided will avoid the problems associated with postexposure prophylaxis.

The safety and utility of varicella vaccination in immunocompromised children is predicated on defining the level of residual immunity of the vaccine recipient and the timing of vaccination with respect to immunocompromising therapy. However, the windows of opportunity may differ (i.e., vaccination may be more or less safe) over time with significant changes in immunocompromising regimens. For example, leukemic patients continuing maintenance therapy with 6-mer-

captopurine were safely immunized and developed good VZV antibody responses [15, 19], whereas continuing to receive full therapeutic (induction) regimens resulted in unacceptable vaccine-related complications. The dose and timing of corticosteroid therapy is frequently mentioned as problematic [46, 47].

Two doses of vaccine will be optimal. This has become the recommendation for immunocompetent children [48] and produces the highest response rate in immunocompromised children without increasing toxicity.

The persistence of vaccine-induced immunity has been demonstrated for ≥ 5 years in some settings [20]. Whatever the durability of protection, it is likely to be sufficiently long for most immunocompromising regimens, presuming that children need protection primarily while receiving therapy. Once they are in remission or cured, they will have an adequate response to primary VZV infection and, thus, will not be at risk for severe varicella.

There are some clear targets for additional research:

1. Studies in some of the settings already described should be repeated, because of significant changes in management of the underlying illness or because the conclusions to date are limited by the small numbers initially studied.
2. Studies should be undertaken in immunocompromising settings not yet studied.
3. Immunocompromised children who are safely immunized and then followed for extended periods should be studied. It is unclear how to manage children who subsequently require additional induction (or “salvage”) therapy, re-enter a stage of advanced HIV infection, or require repeated transplantation. In these situations after a confirmed exposure, most physicians evaluate the immune status and may elect to provide passive immunization.
4. Conversely, for children who remain in remission or require low levels of maintenance immune suppression, it will be useful to develop guidance about the use of a booster dose.
5. Similarly, an approach is needed for children who had received a single dose of varicella vaccine before becoming immunocompromised.
6. If an inactive varicella vaccine becomes available, this will need to be studied as an adjunct to the use of the live vaccine in some clinical settings.

Many of these questions could be answered by existing collaborative trials networks that study the management of malignancies and organ transplants. Additional trials sited in these networks would benefit their study population, would provide additional data to support guidelines, and would likely be cost saving. Barring such trials, these networks, the manufacturer, and/or the CDC should maintain registries that routinely cap-

ture information on varicella vaccination of immunocompromised children, related adverse events, and subsequent varicella and herpes zoster. Databases already exist in many collaborative networks that could be updated to provide this information.

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