recent Advances in varicella-Zoster Virus Infection

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Varicella-zoster virus has developed a complex strategy that allows it to remain latent in the body and avoid destruction by the immune system. Although varicella and zoster have been recognized since antiquity, several new clinical syndromes—including chronic chickenpox with persistent verrucous lesions and disseminated varicella without skin lesions—have been noted in patients with AIDS. Acyclovir has been the mainstay for treating severe varicella-zoster virus infections; however, newer antiviral agents, including valacyclovir and famciclovir, have expanded therapeutic options for treating adults with herpes zoster. The recently licensed live attenuated vaccine for varicella-zoster virus is effective in preventing chickenpox, and the vaccine's ability to stimulate immunity in seropositive adults suggests a promising strategy with which to modify the course of herpes zoster.

Molecular Biology and Immunology of Varicella-Zoster Virus

Structure and Replication

Varicella-zoster virus is a member of the herpesvirus family. The genome contains a double-stranded DNA molecule of about 125 000 base pairs (Figure 1). The genome encodes about 70 different gene products. All but five of these genes have homologues in the better-studied herpes simplex virus; therefore, the functions of many of these genes may be inferred from studies of other human herpesviruses (3).

Gene expression of varicella-zoster virus is similar to that of other herpesviruses: It is sequentially ordered into three classes. The first genes to be expressed are the immediate–early genes, which upregulate expression of early and late genes. Early gene products include proteins important for replication of viral DNA. The viral thymidine kinase phosphorylates acyclovir, which can then inhibit the viral DNA polymerase and viral replication. Other early gene products, including the viral protease and ribonucleotide reductase, are candidates for antiviral therapy. The last genes to be expressed—the late genes—encode structural components of the virion and include the viral glycoproteins and nucleocapsid proteins. These proteins are important targets for the immune system.

Pathogenesis of Varicella-Zoster Virus

Humans are infected with varicella-zoster virus when the virus comes in contact with the mucosa of the upper respiratory tract or the conjunctiva. The virus disseminates throughout the bloodstream to the skin in mononuclear cells (4), causing the generalized rash of varicella. The average incubation period for varicella is 14 days; almost all cases occur 10 to 20 days after exposure. Other organs are infected, including the central nervous system. The virus infects and becomes latent in the dorsal root and cranial nerve ganglia.

It has been difficult to verify individual steps in
viral pathogenesis because no small-animal model reproduces the signs and symptoms of chickenpox and zoster. Inoculating guinea pigs, rats, and mice with varicella-zoster virus causes a latent virus infection but does not produce lesions typical of chickenpox or zoster (5). A recent study by Arvin and colleagues (4) used severe combined immunodeficiency mice to study virus replication in human tissue. The varicella-zoster virus replicated in the T cells and skin of human fetal lymphoid tissue or skin implants in these mice that were inoculated with the virus.

We recently developed a system to “knock out” individual viral genes and study their role in pathogenesis. When tissue-culture cells are transfected with cosmids DNAs that encompass the entire genome of the varicella-zoster virus, the cosmids can recombine inside the cell and produce infectious virus. Inactivation of the open reading frame 47 (ORF47) gene of one of the cosmids led to development of a virus that does not express the ORF47 protein kinase but replicates to wild-type levels in cell culture (6). When fetal lymphocyte and skin implants in mice were inoculated with the ORF47 mutant varicella-zoster virus, the virus did not replicate in the lymphocytes or skin; wild-type virus, however, can replicate under these conditions (7). Therefore, the varicella-zoster virus ORF47 protein kinase is required for virus replication in lymphocytes and skin.

Immune Response to the Virus

Varicella-zoster virus presents many proteins to the immune system. Antibodies to the viral glycoproteins can neutralize the ability of virus to infect cells in vitro. Cellular immunity is more important than humoral immunity, both for limiting the extent of primary infection with varicella-zoster virus and for preventing reactivation of virus with herpes zoster. Children with congenital T-cell defects or AIDS are more likely to develop disseminated chickenpox and zoster than those with B-cell abnormalities. Infection with varicella-zoster virus induces production of cytotoxic T cells that recognize and destroy virus-infected cells. Cytotoxic T cells can recognize cells expressing glycoproteins gB, gC, gE, gH, and gI as well as the IE62 and IE63 tegument proteins (4). Cytotoxic T cells specific to varicella-zoster virus that are obtained from immune persons are class I or class II MHC restricted.

Immune Evasion by the Virus

Although the immune system has many ways to destroy virus-infected cells, varicella-zoster virus has evolved several mechanisms to reduce presentation of viral proteins to the immune system and thereby evade detection. The virus remains latent in the sensory ganglia for the lifetime of the host (8) and limits its expression of viral proteins during latency.

Recent studies (9–15) have investigated the cell types within human ganglia, where the virus is latent. Initial studies using in situ hybridization suggested that the virus is present in neurons or satellite cells; more recent studies have identified viral nucleic acid in both of these cell types. Studies using antibodies to varicella-zoster virus proteins (14, 15) have found certain viral proteins expressed in neurons. By using probes specific to individual viral genes (14–17), researchers have detected messenger RNAs or proteins corresponding to five

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**Figure 1.** Structure of the varicella-zoster virus genome and position of selected genes. The genome is arranged in unique long (UL), unique short (US), terminal repeat long (TRL), terminal repeat short (TRS), and internal repeat (IR) regions. Selected immediate–early (IE), early (E), late (L), and latency–associated genes are shown. ssDNA = single-stranded DNA.
genes in human ganglia (Figure 1). Therefore, although the virus encodes about 70 gene products, only a limited number of genes have been detected during latency.

Varicella-zoster virus may also evade the immune system by downregulating expression of MHC class I antigens on the surface of infected cells. When cells are infected with viruses, viral proteins are broken down inside the cell. On the surface of the infected cells, MHC class I molecules present portions of these proteins to cytotoxic T cells that can kill the virus-infected cells. Infection of human fibroblasts with varicella-zoster virus causes reduced levels of MHC class I molecules on the surface of infected cells compared with uninfected cells (18). By reducing surface expression of these proteins and limiting presentation of viral peptides to cytotoxic T cells, virus-infected cells may escape destruction by the immune system.

Transmission, Clinical Features, and Diagnosis of Varicella and Zoster

Dr. Philip A. Brunell (Medical Virology Section, Laboratory of Clinical Investigation, NIAID, NIH): Varicella is highly contagious. In a recent study (19), varicella-zoster virus DNA was demonstrated by polymerase chain reaction in air samples taken from hospital rooms of patients with varicella and patients with localized zoster. Although these findings do not necessarily indicate that infectious virus was present in these samples, varicella has reportedly occurred in hospitalized patients who had only indirect contact with patients with localized zoster (20, 21). In one case, two susceptible nurses contracted varicella from air that flowed from the room of a patient with localized zoster to the nurses’ station (22).

Although patients with varicella are probably most contagious just before the onset of rash (23), it has been difficult to demonstrate infectious virus in respiratory secretions (24, 25). Varicella-zoster virus DNA has been found by polymerase chain reaction in throat swabs of patients with varicella from whom the virus could not be isolated (26). Before the onset of varicella rash, respiratory spread is probably an important route of transmission of the virus. Patients with herpes zoster are less contagious than patients with varicella.

Clinical Features

Varicella is characterized by a generalized vesicular rash and fever. Lesions usually appear first on the face and scalp; they then spread to the trunk and later to the extremities (Figure 2A). During a period of a few days, new vesicular lesions continue...
to appear as the older ones develop a crust. The most common complication is secondary bacterial infection. In recent years, group A-β hemolytic streptococcal infections—including cellulitis, necrotizing fasciitis (Figure 2B), streptococcal toxic shock syndrome, sepsis, and skeletal infections—have increasingly complicated the course of varicella (28).

In general, adults with varicella are more severely ill than children and have a greater incidence of varicella pneumonia and death. Approximately 1 in 400 adults with varicella is hospitalized for treatment of pneumonia (29). Other complications of varicella include cerebellar ataxia, which occurs in about 1 in 4000 cases, and encephalitis, which is much less common.

Varicella is often severe in pregnant women, especially during the third trimester, and varicella pneumonia in these women may cause premature labor or death. Varicella during the first half of pregnancy is associated with the fetal varicella syndrome, which is characterized by atrophy and scarring of the skin of the affected limb (30, 31). Central nervous system damage and eye malformations are also common (32). Infants whose mothers had varicella during pregnancy often develop zoster early in life (33). The onset of varicella a few days before delivery sometimes results in varicella of the newborn. Infants between 5 and 10 days of age who develop varicella have increased morbidity (34).

Systemic corticosteroid therapy increases morbidity even in patients without other immunocompromising conditions, especially when administered during the incubation period of varicella. Although oral prednisone dosages of less than 2 mg/kg of body weight per day have been thought to be safe, recent data (35) suggest that even smaller dosages may place patients at increased risk for severe varicella. Inhaled beclomethasone may be associated with severe varicella (36).

Herpes zoster occurs when the virus reactivates from the sensory ganglia, resulting in a unilateral vesicular rash in the distribution of one to two adjacent sensory dermatomes (Figure 2C). Dermatomes innervated by the thoracic, cervical, or ophthalmic branch of the trigeminal ganglion are most frequently involved. The rash usually develops a crust within 10 days, but full healing may take 1 month. The rash is accompanied by pain that often precedes the eruption and may last for weeks or months. Postherpetic neuralgia is defined as pain that persists beyond 1 month. In a series of patients with zoster (37), the incidence of superinfection was 2.3%, the incidence of ocular complications was 1.6%, the incidence of motor neuropathy was 0.9%, the incidence of meningitis was 0.5%, and the incidence of zoster oticus was 0.2%. Other less common complications of zoster include granulomatous angiitis of the cerebral arteries, meningoencephalitis, and myelitis.

**Varicella-Zoster Virus Infections in Immunocompromised Persons**

Varicella-zoster virus infections are more severe in immunocompromised persons, particularly those with impaired cell-mediated responses. These patients are more likely to have disseminated disease with extensive skin lesions, pneumonia, hepatitis, or encephalitis.

Children infected with HIV who develop varicella have a high risk for developing zoster soon after varicella and may develop recurrent or progressive disease. Recurrent varicella is defined as new episodes of disseminated skin lesions in the absence of exposure; onset occurs at least 1 month after a previous attack. These patients usually have modest decreases in CD4 cell counts. In contrast, patients with progressive varicella, which is defined by lesions that continue to appear for at least 1 month (27), usually have very low CD4 cell counts. Verrucous skin lesions refractory to antiviral therapy have been noted in HIV-infected patients (Figure 2D). These patients have usually received antiviral therapy for long periods, and their viral isolates are often resistant to treatment (27, 38). About 30% of HIV-infected men have zoster at least once within 12 years after the diagnosis of HIV. The risk for zoster in men with HIV infection is increased about 20-fold over that in age-matched seronegative men. Second and even third attacks are common (39); in immunocompetent persons, however, the rate of second attacks is less than 5%.

Some immunocompromised persons have severe or fatal varicella-zoster virus infections with visceral or neurologic disease but have no visible skin lesions (40, 41). Progressive outer retinal necrosis with little inflammatory response may develop months after zoster in patients with HIV, who usually have very low CD4 cell counts and often respond poorly to antiviral therapy (42). Acute retinal necrosis, which induces a marked inflammatory response, occurs in otherwise normal persons. It is usually caused by reactivation of latent varicella-zoster virus in the absence of other signs of zoster (43).

**Diagnosis**

Laboratory confirmation of the diagnosis is not necessary for most cases of varicella. However, many persons who were thought to have second episodes of varicella were found to be seronegative before disease onset; this suggests that the diagnosis of the initial rash was incorrect (44).

Varicella-zoster virus can be recovered from vesicular fluid for a few days after onset of rash but rarely from other sites (for example, respiratory se-
cations). Because of the lability of the virus, only 30% to 60% of cultures are positive. Detection of varicella-zoster virus antigens in skin scrapings by fluorescence microscopy is more rapid and sensitive than culture techniques. In contrast to the Tzanck smear, detection of varicella-zoster virus antigens is more sensitive and can differentiate varicella-zoster virus from herpes simplex virus, which may also cause zosteriform lesions. Amplification of varicella-zoster virus DNA by polymerase chain reaction followed by restriction of endonuclease digestion has enabled differentiation of wild-type strains from vaccine virus. Polymerase chain reaction has also been used to detect varicella-zoster virus DNA in the cerebrospinal fluid of patients with neurologic disease or in biopsy specimens of verrucous lesions in patients with AIDS, from which cultures are often negative. Serologic testing can be used to retrospectively confirm a diagnosis and to determine the need for isolation or passive immunization with varicella-zoster immune globulin in exposed persons.

Management of Varicella, Zoster, and Postherpetic Neuralgia

Dr. Stephen E. Straus (Laboratory of Clinical Investigation, NIAID, NIH): Antiviral therapy for herpesvirus infections has evolved during the past two decades (45–51). Leukocyte interferon and vidarabine, which initially showed efficacy for treatment of varicella and zoster in clinical trials (52–55), have been replaced by acyclovir (45), valacyclovir (48), famciclovir (47), and foscarnet (56). The first three of these newer drugs are guanosine analogues that are selectively monophosphorylated by the viral thymidine kinase and are further phosphorylated by cellular kinases. All four of the newer drugs inhibit the viral DNA polymerase.

Pharmacologic factors define the route of administration and dose of these drugs (47, 48, 56, 57). Foscarnet requires intravenous administration. Because only 15% to 20% of an oral acyclovir dose is bioavailable, peak serum levels do not exceed 1 to 2 μg/mL. These levels are more than sufficient to inhibit replication of herpes simplex virus in vitro, but they are just adequate to inhibit replication of varicella-zoster virus (Figure 3). Intravenous acyclovir is required for serious varicella-zoster virus infections (55, 58).

In recent years, modifications to the acyclovir structure have resulted in development of valacyclovir, the 6-valine ester of acyclovir (48). It is well absorbed and is converted enzymatically to acyclovir in the liver. Oral valacyclovir yields fourfold greater serum levels of acyclovir than does an equimolar oral dose of acyclovir. Famciclovir is the orally bioavailable diacetyl prodrug of the poorly absorbed nucleoside analogue penciclovir, to which famciclovir is enzymatically converted (47). Penciclovir triphosphate has a more extended half-life in infected cells than does acyclovir triphosphate (59).

Antiviral drugs have a limited window of opportunity to affect the outcome of varicella or zoster. In the normal host, most virus replication (the ability to isolate virus from lesions) has ceased by 72 hours after the onset of rash; in severely immunocompromised patients, the duration of replication and virus shedding is moderately or substantially extended. Recommendations for antiviral therapy of varicella and zoster are summarized in Table 1.

Antiviral Therapy for Varicella

Controlled trials (58, 60–62) demonstrated that acyclovir shortens virus shedding and new lesion formation and speeds lesion healing in both healthy and immunocompromised patients with varicella. The degree of improvement is modest in the normal host but may be sufficient to prevent life-threatening complications in at-risk populations.

In healthy children, varicella is so often benign that the clinical benefit of treatment is too modest to justify routine therapy (63). Treatment of infected siblings should be considered because they tend to develop more lesions after a household varicella exposure. Varicella in adolescents and adults tends to be more severe, and they should be treated promptly—preferably within 24 hours of rash onset (61, 62). Valacylovir or famciclovir can be used in place of oral acyclovir in most of these cases; however, no studies have been published on
this matter. Although the risk for varicella pneumonia in late pregnancy also justifies treatment (64), acyclovir is usually not recommended early in pregnancy for uncomplicated cases because of concerns about the effect of the drug on organogenesis. These new prodrugs are not appropriate for pregnant women because their safety is untested in this setting; in addition, they are not useful for small children because no oral suspension is available.

The choice of drugs and route of administration are more problematic for varicella in the immunocompromised patient. Intravenous acyclovir, the most conservative choice, usually requires hospitalization, which imposes a risk for nosocomial transmission of the infection. High-dose oral acyclovir—or, preferably, valacyclovir or famciclovir—and careful observation for disease progression are often adequate for mildly immunocompromised patients.

In patients with advanced AIDS, intravenous foscarnet is required for varicella that persists or recurs despite treatment with acyclovir (49, 56, 65, 66). Attempts should be made to recover the virus and document its in vitro resistance to acyclovir. Isolates that are resistant to famciclovir are also resistant to acyclovir.

Treatment of Zoster

In the normal host, the primary goal of treatment is to reduce acute pain and postherpetic neuralgia (67). The acute pain of zoster is often neglected or unmet by prescribing weak analgesics, such as acetaminophen. Moderate to severe pain justifies the use of narcotics whose half-lives are long enough to afford sustained relief. The risk for acute pain and postherpetic neuralgia increases with age (68). Most persons younger than 50 years of age do not experience substantial pain, so they usually do not require antiviral drug treatment unless they have zoster involving the ophthalmic region (69) or moderate to severe pain at rash onset (70). After 50 years of age, the increased risk for prolonged pain warrants treatment in all patients within 3 days of rash onset. Although clinical trials show that treatment within the first 72 hours is beneficial (71), it might be prudent to treat persons who present after this period if new vesicular lesions are clearly continuing to appear.

Several controlled trials (69, 72, 73) verified that high-dose oral acyclovir speeds resolution of the acute lesional events and seems to reduce the risk for prolonged pain. Recent studies (74) showed valacyclovir to be more convenient than and slightly superior to acyclovir. Famciclovir is also more convenient and is comparable, if not superior, to acyclovir (75, 76). The choice among these three drugs should be based on convenience, availability, and cost.

For the immunocompromised host, no published data demonstrate that oral acyclovir, valacyclovir, or famciclovir is superior to placebo. Intravenous acyclovir has been shown to prevent disease progression in patients at high risk for dissemination (55, 77). However, for mildly to moderately immunocompromised persons, oral valacyclovir or famciclovir (with careful patient observation) may be acceptable alternatives to intravenous treatment.

The ongoing debate about the role of corticosteroids in the management of zoster has been addressed in two well-controlled trials (78, 79). Small or uncontrolled studies initially suggested that ste-

<table>
<thead>
<tr>
<th>Table 1. Therapy for Varicella and Zoster Infections</th>
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<tr>
<td><strong>Patient Group</strong></td>
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<tr>
<td><strong>Varicella</strong></td>
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<tr>
<td>Neonates</td>
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<tr>
<td>Children &lt; 12 years of age</td>
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<tr>
<td>Adolescents/adults</td>
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<tr>
<td>Women in last trimester of pregnancy</td>
</tr>
<tr>
<td>Patients with pneumonitis or other severe infection</td>
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<tr>
<td><strong>Acyclovir-resistant lesions</strong></td>
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| **Zoster** | **Immunocompetent persons** |
| Age < 50 years with mild pain | Symptomatic care only |
| Age ≥50 years or moderate to severe pain | Oral acyclovir for 7–10 days |
| **Immunocompromised persons** | **Hematologic or solid-organ malignancies or transplant recipients** |
| Corticosteroid therapy, continuous or intermittent high dose | Oral acyclovir, valacyclovir, or acyclovir for 7–10 days |
| Low-dose daily cytotoxic drug use | Oral acyclovir, valacyclovir, or acyclovir for 7–10 days |
| **HIV-infected** | Intravenous acyclovir or oral acyclovir for 7–10 days |
| **Acyclovir-resistant lesions** | Intravenous acyclovir for 10 days |

* Standard dosages are oral acyclovir, 20 mg/kg five times daily for children or 800 mg five times daily for adults; intravenous acyclovir, 500 mg/m² every 8 hours for children or 10 mg/kg every 8 hours for adults; oral valacyclovir, 1000 mg three times per day; oral famciclovir, 500 mg three times per day; intravenous foscarnet, 40 mg/kg every 8 hours.
† Not approved by the Food and Drug Administration for this indication.
‡ Examples include daily oral cyclophosphamide, methotrexate, azathioprine, and 6-mercaptopurine.
§ Oral prednisone, 30 mg twice per day for 7 days, 15 mg twice per day for 7 days, and 7.5 mg twice per day for 7 days.
steroids decreased the rate of postherpetic neuralgia. Wood and colleagues (78), however, showed that the addition of high-dose steroids to acyclovir did not protect against postherpetic neuralgia. In a more rigorous analysis, Whitley and coworkers (79) showed that adding steroids to acyclovir speeds the resolution of acute pain and the return to normal daily activities. This finding justified the use of steroids in persons older than 50 years of age who have no relative contraindications (for example, diabetes, hypertension, or glaucoma). No data are available on the combination of prednisone with famciclovir or valacyclovir; however, one of these combinations may be used in selected patients at high risk for persistent pain after zoster (80).

**Treatment of Postherpetic Neuralgia**

Postherpetic neuralgia arises from inflammatory injury to sensory nerves, ganglia, and nerve roots and from maladaptive central responses to pain signaling (67). Experimental model systems in animals suggest that aggressive, early intervention will lessen the later perpetuation of pain; this finding underscores the importance of treating pain in acute zoster. After postherpetic neuralgia has been established, however, it is difficult to treat. The only licensed treatment is a topical ointment containing capsaicin, an extract of chili peppers (81). It relieves symptoms for some persons, but for others it burns more than it benefits. Two controlled trials (82, 83) verify that low doses of tricyclic antidepressants relieve neuropathic pain processes, including postherpetic neuralgia. A recent double-blind, placebo-controlled trial documented substantial alleviation of pain when the anticonvulsant gabapentin was added to the existing regimen for postherpetic neuralgia (84). Many other approaches are available, each of which seems to benefit a certain subset of patients, but controlled trials have not been done to verify these impressions (67). Carbamazepine alleviates lancinating pain, topical lidocaine provides transient local relief, and regional nerve blocks are often performed. Transcutaneous electrical stimulation and acupuncture can alleviate chronic pain in some patients. Narcotics can be beneficial and are generally underused. Because postherpetic neuralgia is predominantly a problem of elderly persons, the choice of therapies is complicated by coexisting medical conditions, interactions with other medications, and the underlying frailty of some patients.

**Prevention of Varicella and Zoster**

Dr. Philip R. Krause (Division of Viral Products, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland): The only product licensed for postexposure prophylaxis of varicella is varicella-zoster immune globulin. In part because of its high cost, this treatment is indicated only for certain groups (Table 2). Varicella-zoster immune globulin must be given within 96 hours of exposure to be effective. It may prolong the incubation period of chickenpox by about 1 week (1).

Although further study is needed, small studies have suggested that a 1-week course of high-dose acyclovir (85) or a dose of the chickenpox vaccine (86–88) given after exposure may prevent chickenpox. To be effective, acyclovir or vaccine must be used at specific times after exposure (Table 2). Acyclovir is less expensive than varicella-zoster immune globulin; because about 20% of persons receiving acyclovir prophylaxis do not seroconvert, serologic follow-up is recommended for persons who are receiving acyclovir and do not show symptoms of varicella (85). Vaccination is the least expensive of these choices and could be used in anyone who is otherwise a candidate for varicella vaccination. Each prophylactic regimen also reduced the severity of disease in persons who subsequently became infected.

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**Table 2. Interventions Studied for Varicella Postexposure Prophylaxis**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Regimen</th>
<th>Estimated Efficacy in Immunocompetent Persons</th>
<th>Cost for Adults</th>
<th>Potential Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicella-zoster immune globulin</td>
<td>One dose up to 4 days after exposure</td>
<td>90*</td>
<td>400</td>
<td>Immunocompromised persons; pregnant women; preterm infants; neonates whose mothers had varicella within 5 days before or 2 days after delivery</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>40–80 mg/kg for 7 days, beginning 7–9 days after exposure</td>
<td>80–85</td>
<td>119</td>
<td>Persons in whom vaccine is contraindicated; persons with late presentation</td>
</tr>
<tr>
<td>Oka-strain vaccine</td>
<td>One dose, beginning 0–3 days after exposure</td>
<td>~70–90</td>
<td>39</td>
<td>Any vaccine candidate (adults should receive two doses)</td>
</tr>
</tbody>
</table>

* Based on healthy children only.
Prevention of Varicella

The Oka strain of varicella vaccine currently used in the United States and elsewhere was isolated from a healthy child with chickenpox, attenuated by repeated passage in cell culture (89, 90), and developed as a vaccine 25 years ago in Japan (91). As a live attenuated virus, the vaccine strain causes subclinical varicella-zoster virus infection in vaccinees and leads to immunity to the virus.

The vaccine currently marketed in the United States is indicated for immunocompetent persons older than 12 months of age without a history of varicella and is 70% to 90% effective in preventing symptoms of chickenpox (1, 92–94). Children who contract chickenpox after vaccination usually have a mild illness, with few lesions and a low incidence of fever (95, 96) (Figure 2E). In persons older than 12 years of age, two doses of vaccine administered 4 to 8 weeks apart are recommended.

A small percentage of recipients experience injection-site discomfort; fever; rash that appears at the injection site about 2 weeks after vaccination; or mild, disseminated, varicella-like rash (92) (Figure 2F). Because a low risk exists that the virus could be transmitted from vaccinees with rash while the rash is visible (or 1 to 2 days before the rash appears), it is advisable to avoid close contact between vaccinees and persons at high risk for complications of varicella (for example, those who are pregnant or severely immunocompromised).

As a live herpesvirus, the Oka-strain vaccine establishes latency and can reactivate, although zoster rates are lower after vaccination than after wild-type varicella in immunocompromised children (97, 98). In short-term follow-up studies of immunocompetent vaccinated children, zoster rates did not exceed those observed in naturally infected children (92). These data suggest that zoster is unlikely to be a major problem in vaccinees.

A substantial risk is associated with the administration of live vaccines in immunocompromised persons; these persons should not be vaccinated except as part of clinical trials (92). The major risk to immunocompromised children is severe vaccine-induced varicella, which may require antiviral therapy (99, 100). Although low dosages of corticosteroids have been associated with an increased severity of varicella from wild-type virus, these dosages (for example, inhaled steroids or <2 mg of prednisone per kg per day or a total of 20 mg of prednisone per day) are not considered contraindications to vaccination of persons with attenuated virus (1, 94). Because sufficient data are lacking, these patients should be carefully observed after immunization. In all cases, the risks of vaccination must be weighed against the risks for contracting wild-type varicella.

Pregnant women should not receive the vaccine because of the theoretical risk for fetal varicella syndrome in early pregnancy and the increased severity of varicella in late pregnancy. Women who receive vaccine while pregnant or within 3 months of becoming pregnant should be reported to the varicella vaccine pregnancy registry (1, 94). To date, most reported exposures have been among women who received the vaccine before realizing that they were pregnant or about to become pregnant, and as yet there is no evidence of vaccine-associated teratogenicity.

Proper use of the vaccine in health care workers can substantially reduce the risk for nosocomial varicella. Current guidelines recommend ensuring the immunity of all health care workers by history, serologic testing, or vaccination (1, 94). In addition, adults and adolescents derive great benefit from vaccination because they are at risk for more severe disease. An adaptation of this recommendation is presented in Table 3.

Oka-strain vaccine is recommended for universal immunization of U.S. children (1, 94). If vaccination eliminates most circulating wild-type virus, however, the absence of boosting with wild-type varicella-zoster virus may result in waning immunity, leaving some vaccinees susceptible to more severe infections as adults (101). Mathematical modeling suggests that universal vaccination may increase the rate of adult varicella if a large number of children become adults without getting varicella as children (102). To prevent this, it may be necessary to achieve greater vaccination rates than are traditional or to mandate subsequent boosting (as is done for measles). Postlicensure studies are being done to further evaluate the long-term efficacy of vaccine (93).

### Table 3. Use of Varicella Vaccine To Ensure Immunity of Health Care Workers

| Use history with or without serologic testing to identify vaccine candidates. Histories of varicella are considered reliable. Serologic confirmation of negative histories is cost-effective. Recent vaccinees should avoid contact with severely immunocompromised persons and nonimmune, pregnant women. Routine serologic follow-up after vaccination is not recommended. Administrative options after known exposure of a vaccinated health care worker: Place the worker on furlough. Ensure that the worker cares only for patients at low risk for severe varicella (for example, those who are not immunocompromised); observe worker for rash. Do not reassign worker; observe worker for rash. Some hospitals use antibody levels to decide among these options because seropositive persons have lower infection rates. If chickenpox occurs in a vaccinee, place him or her on furlough and trace his or her contacts. |

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Prevention of Herpes Zoster

Studies are under way to determine whether administering the live Oka-strain vaccine to elderly persons can boost immunity specific to varicella-zoster virus and modify the course of zoster. This hypothesis is based on the assumption that repeated exposure to virus, through exposure to children with varicella or through subclinical reactivation, stimulates immunity specific to varicella-zoster virus and reduces the likelihood of zoster. The observation that most persons develop zoster only once, if at all, suggests that one episode of zoster may enable immune responses to levels that are sufficient to prevent further recurrences.

Immunocompromised children who received more than one dose of vaccine or had household exposures to varicella after vaccination had a lower incidence of zoster than children who received only one dose of vaccine or did not have exposures. This finding suggests that immunologic boosting may reduce zoster (103). After a single dose of Oka-strain vaccine, cell-mediated immunity to varicella-zoster virus increased to a level similar to that of an episode of zoster by certain in vitro assays, although the immunologic correlates of protection from subsequent zoster are not known (104). The half-life of the vaccine-induced immunologic response was calculated at 4 to 5 years, which suggests that a dose of vaccine has a long-term immunologic effect that may reduce the subsequent rate of varicella-zoster virus reactivations (104).

**Glossary**

**Cosmid:** Plasmid vector used for cloning large DNA fragments.

**Cytotoxic T cells:** Lymphocytes that recognize and lyse virus-infected cells.

**MHC antigens:** Major histocompatibility complex antigens. These proteins are expressed on the surface of cells and present protein fragments of microbes to cytotoxic T cells for recognition. CD8 cells recognize protein fragments with MHC class I antigens; CD4 cells recognize protein fragments with MHC class II antigens.

**Varicella-zoster immune globulin:** A high-titer varicella-zoster virus antibody preparation derived from persons immune to varicella-zoster virus.

**Disclaimer:** The opinions expressed by Dr. Krause in this article are his own; no official endorsement by the FDA is implied or should be inferred.

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**References**


I drift off again and now they’re waking me up and pulling down the bedclothes. Father Gorey is touching me with oil and praying in Latin. I know it’s Extreme Unction, and that means I’m going to die and I don’t care. They wake me again to receive Communion. I don’t want it, I’m afraid I might get sick. I keep the wafer on my tongue and fall asleep and when I wake up again it’s gone.

It’s dark and Dr. Campbell is sitting by my bed. He’s holding my wrist and looking at his watch. He has red hair and glasses and he always smiles when he talks to me. He sits now and hums and looks out the window. His eyes close and he snores a little. He tilts over on the chair and farts and smiles to himself and I know now I’m going to get better because a doctor would never fart in the presence of a dying boy.

Frank McCourt
Angela’s Ashes
Scribner; 1996:192

Submitted by:
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