Understanding the life cycle of VZV

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Varicella-zoster virus (VZV) causes two distinct diseases—namely varicella (ie, chickenpox) and herpes zoster (ie, shingles). Varicella is an extremely contagious condition that occurs seasonally and in epidemics. After varicella resolves clinically, the virus—which initially spreads from cell to cell via direct contact in virus-naive individuals—becomes latent within the dorsal root ganglia of the nervous system. Reactivation of VZV leads to herpes zoster, which in contrast to varicella, is a sporadic disease that is not associated with environmental exposure to others with active varicella or herpes zoster.

Herpes zoster does not develop in all patients who had varicella. It is more likely to occur with increasing age and with immunosenescence—the phenomenon of gradual waning of cell-mediated immunity over time. Immunosenescence allows the suppressed VZV infection to recrudesce in the form of vesicular lesions that are limited mostly to dermatomes in which the virus had been dormant. While any dermatomes in the body can be affected, those most often affected are those in the thoracic and lumbar regions and those in sites of the first or second branch of cranial nerve V—a condition known as varicella zoster ophthalmicus (VZO).

Herpes zoster can develop in individuals of any age who have histories of varicella infection, but the risk increases linearly with age, particularly among those older than age 45 years. In addition to immunosenescence, precipitators of herpes zoster include stress, viral infections, chemotherapy and other drugs and diseases that depress the cell-mediated response of the immune system, including human immunodeficiency virus infection and lymphoma.

Approximately 4% of patients may have a second episode of herpes zoster, but recurrences of dermatomal lesions are usually caused by herpes simplex virus rather than VZV.

Varicella

Before the varicella vaccine gained widespread acceptance in the United States after the Food and Drug Administration approved it in 1995, chickenpox was a ubiquitous disease that was generally considered a relatively innocuous rite of passage for youth. Often overlooked was the fact that approximately 120 children and 130 adults in the United States die annually from complications of this disease, mostly as a result of secondary staphylococcal or streptococcal cutaneous infections. With the advent of community-acquired methicillin-resistant Staphylococcus aureus, morbidity from secondary cellulitis became notably higher in individuals with varicella. Neurologic complications, in the form of acute cerebellar ataxia or encephalitis, can be life-threatening or cause long-term sequelae. Adults who become infected with varicella are at higher risk than children for...
serious complications, which usually occur as pneumonia and neurologic disorders.

Patients with varicella typically have low-grade fevers, malaise and exantheme-
tous rashes. Each rash can consist of as
many as 350 lesions in the form of macu-
lopalapules, vesicles, pustules and scabs. Un-
like virtually all other viral rashes, in which
skin lesions progress in a sequential man-
er, the varied lesions of varicella can all ap-
pear simultaneously. Most of the lesions are
small—although they can coalesce—and
they have erythematous bases. Pruritus
and, on occasion, pain are associated with
the lesions. Successive crops of lesions ap-
ppear over a period of two to four days but
generally resolve in seven to 14 days.

Patients are considered to be contagious
until all lesions have crusted over. Varicella
is nearly 100% contagious. If the disease
does not develop in exposed people, these
individuals are likely to be immune, even if
they do not recall having been previously
infected with VZV. Immunity can be con-
firmed serologically by obtaining a varicel-
la immunoglobulin G titer.

Herpes zoster
Herpes zoster is characterized by a rash of
vesicular lesions in a unilateral pattern along
a dermatomal distribution. Ophthalmolog-
ic complications with VZO can lead to
vision loss if patients are not treated aggres-
sively. Yet the prospect of enduring the
lancinating pain, protracted burning, or
pruritus associated with postherpetic neural-
gia (PHN) produces the greatest fear among
most elderly patients.

Although the discomfort associated with
the acute dermatologic condition of herpes
zoster can be substantial, it pales in compar-
sion to the neuropathic pain of PHN, which
can persist for months to years. I have seen
no other disease in which patients are so willing to pay out-of-pocket expenses to pre-
vent.

PHN occurs in as many as half of pa-
ients older than 50 who have herpes zoster,
and half of these patients will have debilitat-
ing pain that persists for more than one month.3 Pain may be worse at night or
with exposure to changes in temperature. At
its worst, PHN can be totally incapacitating.

Varicella vaccine
Since the FDA approval of the varicella vac-
cine in 1995,3 the incidence of chickenpox
has declined considerably.3 The varicella
vaccine was first administered in Japan
soon after its development in 1974, giving
US public health officials the benefit of
evaluating the vaccine’s efficacy over time.
However, many physicians in the United
States were initially hesitant about using a
vaccine for what was considered a benign
disease. In addition, concerns were ex-
pressed about the vaccine leading to lower
natural exposure rates to VZV, which
would result in more severe cases of varicel-
la in susceptible adults. This shift of varici-
ella to adults has not materialized in pop-
ulations vaccinated with the varicella
vaccine.

Concern exists that vaccine-caused herd
immunity to varicella may reduce exposure
to VZV. Previous exposures theoretically
boost cell-mediated immunity in the pop-
ulation, thereby reducing the risk for her-
pes zoster. It remains to be seen how this
change in varicella prevalence will affect the
future incidence of herpes zoster.

The Advisory Committee on Immu-
nization Practices (ACIP) from the Centers
for Disease Control and Prevention recom-
mended administering a single dose of the
varicella vaccine to children between the
ages of 12 and 15 months.6 Several years
later, however, cases were reported of vari-
cella developing in vaccinated children who
were exposed to the natural disease.6 Al-
though virtually all of these cases were mild
compared with varicella contracted by un-
vaccinated children, the virus could still be
spread. For this reason, the ACIP changed
its recommendation for varicella vaccine
administration to two doses ideally given at
age 12 to 15 months and upon entering
school.6 For children who did not receive
their first dose before entering school, the
two doses would be administered four
weeks apart.

For individuals who did not receive the
varicella vaccine in childhood, the adoles-
cent and adult populations targeted for vac-
cella are as follows:

- healthcare workers
- susceptible household contacts of
immunocompromised individuals
- individuals living or working in environ-
ments with high risk for VZV transmis-
sion (eg, daycare settings, schools)
- individuals in semiclosed populations
(eg, college dorms, military bases)
- nonpregnant women of childbearing age
- other susceptible adolescents and adults.3

Efficacy of the varicella vaccine is on the
order of 96%.5 For this reason, testing pa-
tients for antigenic response is not recom-
mended. In addition, the vaccine strain of
VZV—known as the Oka strain—is anti-
genically different from wild-type VZV,
which is used for serologic testing. As a re-
sult, serologic test results are unlikely to be
positive after vaccination.

If a patient is serologically reactive after
immunization, he or she likely had a natu-
Concern has been raised about the contagiousness of VZV resulting from vaccine-induced rash. The typical number of reported lesions that develop from the varicella vaccine is usually considerably fewer than 50, making the risk of viral transmission from vaccine-induced lesions slight. However, living in the same household as an immunocompromised person is a contraindication for receiving the varicella vaccine. Other individuals for whom the varicella vaccine is contraindicated include: immunocompromised individuals; children treated for leukemia or lymphoma; children with advanced HIV infection (CD4 cell count <200); children taking high doses of steroids; pregnant women (in whom the effect of the vaccine is not known); and children with clear history of chickenpox.

**Herpes zoster vaccine**

First marketed in the United States in 2006, the herpes zoster vaccine was initially formulated to boost cell-mediated immunity to VZV. The Oka strain of attenuated VZV used in the herpes zoster vaccine is identical to the strain used in the varicella vaccine, but its potency is 14 times higher. Hence, the two vaccines are not interchangeable for susceptible populations. The Shingles Prevention Study, which was conducted from 1999 to 2004, was a randomized, double-blinded, placebo-controlled trial of this vaccine. The trial involved approximately 38,500 subjects aged 60 or older. Forty-six percent of trial participants were at least 70 years old.

Trial results showed that herpes zoster cases among subjects who received the vaccine was 51% below that of subjects who received placebo. Individuals aged 60 to 69 who received the vaccine had a 64% decrease in incidence of herpes zoster, and vaccinated subjects aged 70 years or older had a 38% decrease.

An unforeseen benefit observed during the trial was a reduced incidence of PHN among those participants who received vaccine but nevertheless developed herpes zoster. These subjects had a 67% decrease in episodes of PHN. This benefit of the vaccine may have become the main factor driving eligible patients to get vaccinated.

The herpes zoster vaccine was initially marketed for patients older than 60 who had documented histories of varicella but no history of zoster. Since the vaccine was approved, the ACIP has reaffirmed its indications, with the recommended change that the vaccine be administered to individuals who are at least 60 years old regardless of whether they had previous episodes of herpes zoster. The ACIPs rationale for this recommendation included the following points:

- The incidence of second cases of herpes zoster is uncertain, but is believed to be in the range of 2% to 5%.
- Misdiagnosis of previous herpes zoster cases and patients’ faulty recall of past zoster infections are likely to be substantial. It is often not possible to confirm previous episodes of herpes zoster in patients. Positive results of zoster serologies cannot be distinguished from positive results of varicella titers.

The herpes zoster vaccine is a live vaccine that can be administered simultaneously with other live vaccines or at any intervals with inactivated vaccines. If a physician is considering administering another live vaccine, such as the vaccine for yellow fever or one for measles, mumps and rubella, but cannot give it at the same time as the herpes zoster vaccine, he or she must allow for a minimum four-week interval for subsequent immunization.

Individuals younger than 60 are at a defined risk for developing herpes zoster and PHN. Although the herpes zoster vaccine is not indicated for these patients—because the Shingles Prevention Study looked at subjects who were 60 or older—the vaccine would likely be effective in this younger population, with higher immunogenicity in younger populations expected. As with all vaccines, antigenic-immunogenic response is expected to be greater the younger a person is. Furthermore, the fewer exposures patients have to varicella, the greater the potential that this cell-mediated immunity will be less, which may increase their risk for getting herpes zoster at a younger age.

Unfortunately, until ongoing studies evaluating the safety and efficacy of the herpes zoster vaccine in younger age groups are completed—and until the FDA approves the vaccine for these—health insurance companies are unlikely to cover vaccinating patients younger than 60. The herpes zoster vaccine currently costs $150, which does not include administration charges.
to prevent recurrences. Currently, however, it is not known when the vaccine is most effectively given in these cases—or if it should be given at all. Some experts discourage using the vaccine in such cases because a herpes zoster outbreak late in life will result in a cell-mediated immunity memory response that would likely persist for the remainder of a patient’s life. These experts also note that recurrences of herpes zoster are rare.

For those patients who recently had herpes zoster and who insist on getting the vaccine to prevent recurrence—particularly if their initial zoster episode occurred relatively early in life or if they are recovering from particularly severe cases—waiting several months to vaccinate these patients is appropriate because cell-mediated immunity is expected to be high in the period shortly after a disease episode. At a minimum, the herpes zoster vaccine should not be administered until the acute stage of the illness is over and symptoms abate.

Remaining question
As the incidence and prevalence of chickenpox declines in the United States as a result of routine childhood vaccination schedules, one unanswered question involves the usefulness of the herpes zoster vaccine for older individuals who have never had varicella. The herpes zoster vaccine is not currently indicated for preventing varicella, although the product insert makes no reference to varicella history in its indications section.

This is currently not an important issue, because virtually everyone older than 60 has had varicella. However, once patients born after 1995—or even 1980—turn 60, that will no longer be the case.

Right now, individuals who have never had chickenpox or the childhood vaccine series and who wish to be immunized should be given the varicella vaccine—although the age cutoff for vaccination has not been defined. In addition, persons older than 60 should receive the herpes zoster vaccine regardless of zoster history. If a patient younger than 60 received only one dose of the varicella vaccine in the past, the second dose should be the varicella vaccine rather than the herpes zoster vaccine.

Patients who received one or two doses of the varicella vaccine are theoretically at risk for development of Oka-strain herpes zoster. Thus, these patients would be eligible for the herpes zoster vaccine at the targeted age level, because that vaccine contains the same Oka strain of VZV. However, it is not known whether the Oka strain in the varicella vaccine creates the same degree of risk for herpes zoster infections as does developing wild-type zoster from natural chickenpox infection.

Final notes
The pain in the acute phase of herpes zoster has a profound effect on the quality of life for many patients. For those who develop PHN, chronic pain has even more substantial effects on quality of life, with physical disability and emotional distress being common among these patients.

The effects of PHN are most noted in older patients, in part because these individuals may have more intense pain, greater frailty and more comorbidities than younger patients. These consequences can lead to a functional decline in patients that can result in dependent care and even death. In comparing the costs of morbidity as measured by quality-adjusted life years, the herpes zoster vaccine has been shown to be incrementally cost-effective in patients before age 60 years.12

References