Reliability of a History of Previous Varicella Infection in Adults

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Context.—Apparent second episodes of varicella are reported in immunocompetent hosts, but laboratory confirmation of prior immune status has rarely been possible.

Objective.—To evaluate adult patients with varicella who claimed to have had previous varicella to determine whether they had true second episodes or primary cases with inaccurate clinical histories.

Design.—Adult subjects with varicella who enrolled in an antiviral treatment trial were interviewed about a history of varicella. The clinical course of these 20 patients did not differ from those with no history of varicella. Serum samples that had been collected a mean of 12.4 months (median, 12 months; range, 3 days to 34 months) before the incident episode were available for 19 subjects. All 19 serum samples lacked IgG antibodies to varicella-zoster virus (VZV).

Participants.—Twenty military personnel with varicella and a history of the disease.

Setting.—A military hospital in San Diego, Calif.

Main Outcome Measure.—Presence or absence of antibodies to VZV.

Results.—Twenty (10.8%) of 184 adults with serologically confirmed acute varicella reported a prior history of varicella. The clinical course of these 20 patients did not differ from those with no history of varicella. Serum samples that had been collected a mean of 12.4 months (median, 12 months; range, 3 days to 34 months) before the incident episode were available for 19 subjects. All 19 serum samples lacked IgG antibodies to VZV.

Conclusion.—A history of previous varicella infection in adults with varicella may not be reliable. True second episodes of varicella are probably rare in immunocompetent adults.

VARICELLA (chickenpox) is due to primary infection with varicella-zoster virus (VZV). The characteristic vesicular exanthem occurs in most susceptible individuals who become infected.1 Sub-
Central HIV [human immunodeficiency virus] Program, Serodiagnostic Division, Bethesda, Md, from the time of military induction.

The 2 serum samples collected during the acute varicella episode, the convalescent serum sample, and the stored serum sample were tested in parallel for IgG antibodies to VZV by enzyme-linked immunosorbent assay (ELISA) (Immulon 2, Dynatech Laboratories, Chantilly, Va). Antibody titers of 1:16 or more were considered positive.11 The serum samples from the subjects who reported a prior history of varicella were additionally tested for IgG antibodies to VZV by latex agglutination and Western blot. Latex agglutination testing for IgG antibodies to VZV was performed according to the manufacturer's instructions (Becton Dickenson Immunocytemetry Systems, San Jose, Calif); antibody titers of 1:2 or more were considered positive. Control serum samples that were tested in each ELISA and latex agglutination assay included both VZV IgG-positive serum samples of high and low titer that had been stored for 10 to 16 years and known negative serum samples. All study serum samples were also tested by ELISA against an uninfected MRC-5 cell lysate as a negative control. The Western blot technique used viral lysates prepared from Vero cells infected with VZV, an uninfected cell control, and a purified VZV glycoprotein preparation as a positive control.12 Proteins were subjected to electrophoresis on a 9% polyacrylamide gel containing 0.1% sodium dodecyl sulfate, and after separation transferred to a nitrocellulose membrane (0.45 μm). Nitrocellulose strips were incubated overnight at 4°C with 5% skim milk in phosphate-buffered saline, incubated with patient serum samples (1:20 dilution) for 2 hours, washed with phosphate-buffered saline containing 0.1% Tween, and incubated with biotinylated antihuman IgG (Vector Laboratories, Burlingame, Calif) for 30 minutes. Binding of IgG to VZV proteins was detected by avidin-biotin staining. A negative Western blot result was defined as the absence of any reactivity to VZV-infected cell proteins by comparison to controls. The characteristic pattern of IgG antibodies to VZV proteins in convalescent serum samples has been described.12

Results
Varicella-zoster virus infection was proved in 184 of 186 patients, including all those with apparent second episodes, by demonstrating a 4-fold rise in VZV IgG ELISA titers between acute and convalescent serum samples. The diagnosis was also confirmed by direct immunofluorescence staining of VZV antigens in cells from cutaneous lesions in 182 of 184 subjects, including all 20 with a reported history of varicella. A total of 152 (88%) of 184 proven varicella patients had a positive VZV culture, including 18 (90%) of the 20 patients with a history of varicella.

Twenty (10.8%) of the 184 subjects with proven varicella reported a definite history of varicella. All 20 were men (only 4 of 184 subjects were women); the mean age was 21.3 years. Eight of these 20 patients reported their exact age at the time of the prior episode (mean age, 4.7 years); the other 12 subjects said they had had varicella before 6 years of age. The history was confirmed in all 11 cases in which the subject's mother could be interviewed. When recalled, clinical details of the prior episode were compatible with varicella.

The clinical course of varicella in the 20 subjects with reported second episodes did not differ from the larger group by any parameter (Table 1). Sixty-two percent of the total study group had low but detectable IgG antibody titers to VZV at the time of study entry (mean, 1.4 days after rash onset). The VZV IgG titers in acute and convalescent serum samples were equivalent in patients reporting and not reporting a history of varicella (Table 2). Sorivudine had no effect on antibody responses and a minor impact on clinical course.13 Stored serum samples were available from 19 of 20 patients who reported a prior history of varicella. The serum had been obtained from 3 days to 34 months (median, 12 months; 90% = 1 month prior to acute varicella) before enrollment in the antiviral trial. All 19 prebanked serum samples were negative for IgG antibodies to VZV by ELISA, Western blot, and latex agglutination.

Comment
Our study of antiviral therapy for adult varicella offered a unique opportunity to confirm possible second episodes of varicella in patients from whom stored serum samples were available to document prior infection. However, the complete absence of preexisting IgG antibodies to VZV in any of 19 cases of reported recurrent varicella suggests that a history of varicella is unreliable in adult patients. Although failure to develop measurable anti-VZV antibodies has been reported in occasional patients who develop varicella in the setting of HIV disease or cancer,13-16 a vigorous and sustained antibody response occurs in the normal host.17 Though we had only 19 subjects, it is very unlikely that all these healthy young adults with histories of varicella had lost preexisting anti-VZV antibodies. Detectable ELISA antibody levels are extremely durable in normal hosts after natural infection, as are latex agglutination and fluorescent antibodies to membrane antigen.17-21 The complement fixation assay, not used in this study, is less sensitive to persistent anti-VZV antibodies and is rarely used to determine VZV immunity.18 The sensitivity of the latex agglutination test has been established by comparison to the highly sensitive fluorescent antibodies to membrane antigen method.21 That the observed episodes of allegedly recurrent varicella were actually the subjects' first VZV infections is also consistent with the indistinguishable clinical courses and their similar acute and con-

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**Table 1.** Clinical Course of Varicella in 184 Subjects With and Without Reported Second Episodes of Varicella

<table>
<thead>
<tr>
<th>History of Varicella</th>
<th>No History of Varicella</th>
</tr>
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<tbody>
<tr>
<td>Days until 100% crusting</td>
<td>5.74±2.00 (5.0)</td>
</tr>
<tr>
<td>Days of new lesion formation</td>
<td>3.26±0.93 (3.0)</td>
</tr>
<tr>
<td>Days to maximum number of lesions</td>
<td>1.84±0.82 (3.0)</td>
</tr>
<tr>
<td>Days until culture negative</td>
<td>2.88±1.59 (3.0)</td>
</tr>
<tr>
<td>Days of fever</td>
<td>3.11±1.98 (3.0)</td>
</tr>
<tr>
<td>Pulmonary infiltrates, No. (%)</td>
<td>4/20 (20)</td>
</tr>
<tr>
<td>Patients With History of Varicella</td>
<td>12/14 (7)</td>
</tr>
</tbody>
</table>

*Wilcoxon rank sum test used for durations, Fisher exact test (2-tailed) for rates of pneumonia. Durations shown are means±SD (medians).

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**Table 2.** Serologic Response to Varicella-zoster Virus (VZV) in Subjects With and Without a History of Varicella

<table>
<thead>
<tr>
<th>VZV Titer</th>
<th>Patients With History of Varicella</th>
<th>Patients Without History of Varicella</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1:16</td>
<td>2 (10)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>1:16 or 1:64</td>
<td>5 (25)</td>
<td>24 (15)</td>
</tr>
<tr>
<td>&gt;1:64</td>
<td>7 (35)</td>
<td>52 (33)</td>
</tr>
</tbody>
</table>

*There were no statistically significant differences between VZV titers for the 2 groups by Pearson goodness-of-fit test (P=.81 for the acute and P=.27 for the convalescent titers). All subjects had a 4-fold or greater increase in titer. The median convalescent titer of 1:1024 was the same in both groups.

†Measured by enzyme-linked immunosorbent assay.
valescent VZV antibody titers compared with the “first time” varicella patients. This is at variance with suggestions that second episodes of varicella are milder than primary episodes. Second episodes of apparent varicella have been reported in pregnant women seropositive for VZV as in immuno-compromised hosts with cancer, with HIV disease, and following bone marrow transplantation. Some authorities believe second attacks of varicella are rare in healthy individuals, others have reported recurrences and speculated that reinfection is more common than usually assumed.

Previous attempts to document recurrent varicella in normal hosts have been hampered by methodologic limitations. Ross reported that 7% of children and less than 1% of adults with a history of varicella developed varicella after close contact with an acute case, but the histories were not confirmed serologically. Gershon et al. have reported 3 cases of varicella in healthy individuals that occurred despite preexisting IgG antibodies to VZV; these represent the most convincing evidence of recurrent varicella in normal hosts. Three clinically diagnosed cases of recurrent varicella occurred in hospital workers who were reported to have VZV antibodies in remote serum samples by an ELISA method, but the acute diagnosis of varicella was confirmed by laboratory methods and the earlier serum samples had been discarded and could not be retested. In a series of 23 children with a history of recurrent varicella, only 4 had been documented to be VZV seropositive previously, and varicella was proved by culture in only 5 children. Because of the limited clinical specimens that were available, it was not possible to demonstrate that any of the 4 patients who had preexisting antibodies to VZV had also had recurrent varicella proven by culture or direct fluorescent antibody testing.

The implications of our study is that second episodes of varicella in immunocompetent adults are rare and, as Ross had surmised, may be overreported. Episodes of vesicular rash in children are not evaluated by laboratory methods in clinical practice and may occasionally have causes other than the apparent clinical diagnosis of varicella. Prior serologic surveys of hospital employees have demonstrated a close correlation between a history of varicella, a positive VZV antibody titer, and protection from future varicella episodes. While a history of previous varicella infection may be a reasonable marker for prior infection, our study shows that 11% of young adults with varicella (and in many cases, their mothers) were mistaken about their VZV immune status. In large serosurveys of immunocompetent hosts who report prior varicella, 2% to 4% of subjects lack measurable VZV antibodies. Most cases of apparent second episodes are likely to represent primary infections.

In circumstances where exposures of immunocompromised hosts are an issue, as in the case of health care workers, serologic screening is the preferred method for establishing VZV immunity. Recurrent varicella in unvaccinated persons with IgG antibodies to VZV must be rare. Testing of health care workers to determine immune status permits selective immunization of those who are antibody negative with the live attenuated varicella vaccine.

References
