Committee on Infectious Diseases

Expanded Guidelines for Use of Varicella-Zoster Immune Globulin

I. BACKGROUND INFORMATION

1. Zoster Immune Globulin

Zoster immune globulin (ZIG) can prevent clinical chickenpox in exposed, susceptible, *normal* children.[1] In a collaborative study[2] in which 15 susceptible children at high risk received ZIG within three days following exposure, there were no deaths and only one child developed progressive varicella. At that time, a mortality of 7% and a rate of progressive varicella of 30% were reported in similar children who failed to receive prophylaxis.[3] At the present time, varicella may be even more hazardous for children with leukemia, possibly because of the use of more intensive therapy.

2. Varicella-Zoster Immune Globulin

The use of plasma obtained from patients convalescing from zoster to prepare ZIG resulted in a limited supply of this material. The finding that plasma from normal donors with high varicella-zoster (V-Z) antibody could be used to prepare a globulin of similar potency, referred to as varicella-zoster immune globulin (VZIG),[4] now assures ample supply. The availability of this material, through the American Red Cross, permits us to recommend it for additional indications. The major deterrent to the use of VZIG is its cost, which in August 1983 was approximately $75 per 125 units (approximately 1.25 mL), the dose for a 10-kg child. The recommended adult dose of 625 units costs about $375.

3. Morbidity from Varicella in Adults

Adults suffer greater morbidity from chickenpox than do children. Although less than 2% of reported cases occur in individuals after the second decade, nearly one quarter of all the reported mortality occurs in this group.[5]

Of particular concern are pregnant women who develop chickenpox. There is a general impression that they may develop a more serious illness than other adults. In addition, two of 27 infants whose mothers had varicella during the first trimester of pregnancy had congenital malformations known to be associated with intrauterine V-Z infection in one prospective study.[6] Isolated malformations have been reported following maternal infection even later in pregnancy.[7]

4. Varicella in the Newborn

When pregnant women have chickenpox close to the time of delivery, their newborn infants may develop varicella. Varicella may occur during the neonatal period in infants whose sera contain passively acquired maternal antibody[8] or antibody from ZIG.[9] VZIG given to neonates is likely to modify varicella by providing even higher levels of antibody, but there are no objective data to support this belief. Infants whose onset of varicella is between 5 and 10 days of age or whose mothers develop varicella in the four days prior to delivery appear to be at increased risk of becoming infected suffering severe illness.[10]

5. Determination of Immune Status

Historical information obtained from adults about previous occurrence of chickenpox may be inaccurate. In one study, only 8% of adults who said they had not had chickenpox developed the infection following household exposure; 2% of those who were unsure of their past history and 0.2% of those who said they had the disease developed chickenpox under similar circumstances. The attack rate among children with a negative history in the same household was 95%.[11] It is clear, therefore, that one should not base a decision whether to give VZIG to an adult solely on past history.

A variety of techniques have been used for determining susceptibility to chickenpox. The complement fixation test, which is most easily obtainable, is too insensitive to determine immune status. The

fluorescent antibody test against membrane antigen (FAMA), enzyme-linked immunosorbent assay (ELISA), the immunoadherence hemagglutination (IAHA), and the neutralization tests can be used to determine immune status. Unfortunately, only a few laboratories perform these tests. Commercial kits are available for determining immunity, but there are no published data to judge their reliability. Serologic results of testing immunocompromised patients must be interpreted with caution. Some may be transiently misclassified as immune, presumably because of V-Z antibody emanating from blood products that they had received. Skin test material, which has been developed in Japan,[12] is now being evaluated but is not currently licensed for use.

When relying solely on historical information to assess immune status, the interview should be conducted by experienced personnel. An attempt should be made to elicit a past history of exposure to siblings or children with varicella; persons with previous household exposure to active cases are likely to be immune. Individuals who have attended an urban school or had previous occupational exposure, eg, in nursery school, kindergarten, or a pediatric health care setting, also are likely to be immune.

6. Period of Contagiousness

There are few good data on the time that individuals are capable of spreading chickenpox relative to the onset of their rash, nor is it clear when they are no longer contagious. Normal children with chickenpox are considered contagious for 24 to 48 hours prior to onset of skin lesions and for six days following the appearance of lesions.[13] Immunocompromised children with progressive varicella probably are contagious during the entire period that new lesions are appearing. Susceptible individuals who are exposed to individuals with zoster may develop chickenpox. It is not known whether patients with zoster are capable of spreading infection by the respiratory route or whether covering lesions with clothing or dressings can prevent the spread of virus.

7. Conditions of Exposure

It is well recognized that continuing household exposure to chickenpox will result in infection of almost all who are susceptible.[11] The results of other types of exposure such as in hospitals, classrooms, and car pools are not predictable. In general, there is far less risk of transmission in these situations than following household exposure. Although household contact with a playmate who is found to have a rash within the next 48 hours, occasionally has resulted in infection, the risk is far lower than following continuing household exposure as when a family member has the disease.

8. Nosocomial Spread

Cases of varicella in hospitalized patients or staff members may result in the spread of infection. This often results in disruption of routine services. Varicella can be life-threatening for some patients.[3] It is well documented that infection can spread through the air.[13-15] Children who must be hospitalized with chickenpox should be in strict isolation,[16] and in a negative pressure room if possible.[14,15]

Most cases of chickenpox in normal individuals will occur 14 to 16 days following continuous household exposure; 99% of the cases occur between 11 and 20 days.[11] All exposed children who can be discharged within ten days following exposure should be sent home. Those who must remain in the hospital and are susceptible should be kept in strict isolation from ten until 21 days following the onset of rash in the index case. Those at high risk should be given VZIG and kept in isolation for 28 days. (See II.1.a below)

Historical information should be obtained (See I.5.) from exposed personnel and, if feasible, serologic testing for susceptibility to chickenpox performed. For those who have had physical contact or face-to-face exposure to patients with chickenpox and are believed to be susceptible (see I.5.), the use of VZIG to modify the severity of chickenpox can be considered. Its administration to all suspected of being susceptible for the purpose of preventive nosocomial spread is *not* recommended because modified chickenpox may be contagious.

The use of VZIG in adults has not been carefully evaluated. It should not be assumed that VZIG will prevent, rather than modify, varicella in exposed susceptible adults. For this reason, if health care workers are permitted to continue patient contact after receiving VZIG they should be alerted to the possibility that they might develop mild chickenpox. If symptoms occur, health care workers should be notified to break patient contact immediately. *In no case should those thought to be susceptible be allowed to continue working with high-risk patients* (see I.9.), whether or not they have received VZIG.

9. Definition of High Risk

Patients receiving anticancer therapy or those with certain types of acquired or congenital immunodeficiency may incur increased morbidity if they get chickenpox. Those who are susceptible (see I.5.)

and have a significant exposure (see I.7.) should receive VZIG. Defects in cell-mediated immunity appear to be associated with greatest risk. Children receiving immunosuppressive therapy, including steroids, should receive VZIG. Recipients of low doses of steroids, eg, 5 to 10 mg/d of prednisone, do not exhibit increased morbidity when they develop varicella.[17] A dose of prednisone equivalent to 2 mg/kg of body weight per day is arbitrarily considered to confer increased risk even in those with otherwise normal immune function. The effect of inhaled steroids or steroids applied topically to large areas of the skin is unknown. Bone marrow transplant recipients should be considered at high risk regardless of their varicella history or the immune status of the donor.

II. USE OF VZIG

1. Administration

VZIG is given by intramuscular injection. It contains between 10% and 18% globulin; thimerosol 1:10,000 is included as a preservative. A vial containing 125 units is given for each 10 kg of body weight. A maximum dose of 625 units is suggested. For maximal effectiveness, VZIG should be given within 48 hours and preferably not more than 96 hours following exposure.

Use in patients with a bleeding diathesis should be avoided if possible. VZIG should never be given intravenously. Local discomfort following intramuscular injection is common.

a. High-Risk Children. High-risk (see I.9.) susceptible children (see I.5.), who have had continuing household exposure, shared a hospital room containing four or fewer beds, or played indoors for at least 1 hour with children who are in the putative contagious (see I.6.) state of chickenpox should receive VZIG. They should be discharged prior to the tenth day following exposure if possible. If not, they should be placed under strict isolation[16] until 28 days following exposure. The incubation period in these patients may be longer than in normal individuals.

b. Normal Adults. It may be desirable to give VZIG to normal adults following a close exposure (see I.7.) to VZ infection, particularly if careful history taking (see I.5.) strongly suggests that they may be susceptible. Laboratory testing should be performed whenever possible, because individuals with a negative or uncertain history of chickenpox nevertheless have a high probability of being immune.

c. Pregnant Women. Generally, the recommendations for normal adults apply to pregnant women. It is conceivable that VZIG could modify the maternal infection so that it becomes asymptomatic. In an analogous situation, some women who were passively immunized against rubella and had no clinical signs of infection gave birth to infants with rubella embryopathy. It is unknown whether the fetus will be protected against the development of malformations produced by VZ virus if this should occur. It should not be assumed, therefore, that the fetus is protected if a susceptible, exposed woman receives VZIG and does not develop signs of chickenpox.

It is unlikely that antibody administered to a pregnant woman within five days prior to delivery will be absorbed and transported across the placenta in sufficient quantities to affect significantly the outcome of the newborn. It is preferable, therefore, to administer VZIG, if necessary, directly to the newborn infant. This method is less expensive because a much smaller dose is required.

d. Indications for Use of VZIG in Newborn. VZIG (1.25 mL) should be given as soon as possible after delivery to infants whose mothers have had onset of varicella within five days prior to delivery. Approximately half of these infants can be expected to develop varicella. If they must be hospitalized beyond 10 days of age, they should be kept in strict isolation until 21 days of age.

There is no indication for the use of VZIG in normal full-term infants exposed postnatally.[8] Because of the poor transfer of antibody across the placenta early in pregnancy, infants born prior to 28 weeks of gestation who still require hospitalization for treatment of prematurity or related conditions and who are exposed to varicella in the same unit (see I.6.) should receive 125 units of VZIG.

VZIG is ineffective for the treatment of zoster[17] or varicella.

2. Follow-up of Recipients of VZIG

The administration of VZIG may cause the infection to be subclinical. It is strongly recommended that recipients be tested 2 months or later following administration of VZIG for exposure to chickenpox to ascertain their immune status. The exact duration that recipients are protected against chickenpox is unknown. If a second exposure should occur more than 3 weeks following administration of VZIG, and the immune status of the recipient is not established, another dose of VZIG should be given.

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REFERENCES

1. Brunell PA, Ross A, Miller LH, et al: Prevention of varicella zoster by immune globulin. *N Engl J Med* 1969;280:1191–1194
2. Gershon AA, Steinberg S, Brunell PA: Zoster immune globulin. *N Engl J Med* 1974;290:243–245
3. Feldman S, Hughes WT, Daniel CB: Varicella in children with cancer: 77 cases. *Pediatrics* 1975;56:388–397
4. Zaia JA, Levin MJ, Wright GG, et al: A practical method for preparation of varicella-zoster immune globulin. *J Infect Dis* 1978;137:601–604
5. Preblud SR, D'Angelo LJ: Chickenpox in the United States, 1972–77: Center for Disease Control. *J Infect Dis* 1979;140:257–259
6. Siegel M: Congenital malformations following chickenpox, measles, mumps and hepatitis. *JAMA* 1973;226:1521–1524
7. Brunell PA: Fetal and neonatal varicella-zoster infections. *Sem Perinatol* 1983;7:47–56
8. Baba K, Yabuuchi H, Takahashi M, et al: Immunologic and epidemilogical aspects of varicella infection acquired during infancy and early childhood. *J Pediatr* 1982;100:881–885
9. Evans EB, Pollock TM, Cradock-Watson JE, et al: Human anti-chickenpox immunoglobulin in the prevention of chickenpox. *Lancet* 1980;1:354–356
10. Meyers JD: Congenital varicella in term infants: Risk reconsidered. *J Infect Dis* 1974;129:215–217
11. Ross AH: Modification of chickenpox in family contact by administration of gamma globulin. *N Engl J Med* 1962; 267:369–376
12. Kamiya H, Ihara T, Hattori A, et al: Diagnostic skin test reactions with varicella virus antigen and clinical application of the test. *J Infect Dis* 1977;136:784–788
13. Thomson F: Contact infection of chickenpox, letter. *Lancet* March 8, 1919, p 397
14. Leclair JM, Zaia JA, Levin MJ, et al: Airborne transmission of chickenpox in a hospital. *N Engl J Med* 1980;302:450–453
15. Gustafson TL, Lavely GB, Brawner ER Jr, et al: An outbreak of airborne nosocomial varicella. *Pediatrics* 1982; 70:550–556
16. Dixon RE, Brachman PS, Bennett JV (eds): *Isolation Techniques for Use in Hospitals*, ed 2. Department of Health, Education and Welfare, Public Health Service. Centers for Disease Control, 1975
17. Falliers CJ, Ellis EF: Corticosteroids and varicella. *Arch Dis Child* 1965;40:593–599
18. Stevens DA, Merigan TC: Zoster immune globulin prophylaxis of disseminated zoster in compromised hosts: A randomized trial. *Arch Intern Med* 1980;140:52–54

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