34 Varicella

34.1 Introduction

34.1.1 Varicella (chickenpox) is an acute highly infectious disease which is transmitted directly by personal contact or droplet spread, and indirectly via fomites. In the home the secondary infection rate from a case of chickenpox can be as high as 90%. It is most common in children below the age of ten in whom it is usually mild. Since chickenpox is so common in childhood, 90% of adults are immune.

34.1.2 The incidence of varicella is seasonal and reaches a peak from March to May. The incubation period is between two and three weeks.

34.1.3 Vesicles appear without prodromal illness on the face and scalp, spreading to the trunk and abdomen and eventually to the limbs; after three or four days they dry with a granular scab and are usually followed by further crops. Vesicles may be so few as to be missed or so numerous that they become confluent, covering most of the body. Virus is plentiful in the naso-pharynx in the first few days and in the vesicles before they dry up; the infectious period is therefore from one to two days before the rash appears until the vesicles are dry. This may be prolonged in immunosuppressed patients.

34.1.4 The disease can be more serious in adults, particularly pregnant women and those who smoke, as they are at risk of fulminating varicella pneumonia. For neonates and immunosuppressed individuals, the risk is greatly increased for disseminated or haemorrhagic varicella.

34.1.5 Herpes zoster is caused by the reactivation of the patient's varicella virus. It is transmissible to susceptible individuals as chickenpox but there is very little evidence that it can be acquired from another individual with chickenpox. Although more common in the elderly, it can occur in children and especially in immunosuppressed individuals. Vesicles appear in the dermatome representing cranial or spinal ganglia where the virus has been dormant. The affected area may be intensely painful with associated paraesthesiae.

■ 34.1.6 Risks to the fetus and neonate from maternal chickenpox are related to the time of infection in the mother:

a. **In the first 20 weeks of pregnancy.** Congenital (fetal) varicella syndrome which includes limb hypoplasia, microcephaly, cataracts, growth retardation and skin scarring. The mortality rate is high. From the largest available prospective study, the incidence has been estimated to be less than 1% in the first 12 weeks and around 2% between 13 and 20 weeks of pregnancy.

b. **In the 2nd and 3rd trimesters of pregnancy.** Herpes zoster in an otherwise healthy infant.

c. **A week before, to a week after delivery.** Severe and even fatal disease in the neonate. Before the introduction of VZIG in the UK, half the deaths in infants under one year occurred in those aged less than 3 weeks in whom infection would have been contracted before, during birth or during the first week of life.

■ 34.2 Varicella vaccine

Live attenuated varicella vaccine has recently been licensed in some countries, but currently no vaccine is licensed for use in the UK. It is available on a named patient basis from SmithKline Beecham and Pasteur Merieux MSD Ltd for immunocompromised individuals, particularly children with leukaemia or solid organ transplants.

■ 34.3 Human Varicella-Zoster Immunoglobulin (VZIG)

■ 34.3.1 Two licensed VZIG preparations are available in the UK. VZIG distributed in England and Wales is made by the Bio Products Laboratory (BPL), Elstree; and in Scotland and Northern Ireland it is provided by the Protein Fractionation Centre (PFC), Edinburgh. VZIG is prepared from pooled plasma of UK blood donors with a history of recent chickenpox or herpes zoster, or from those who on screening are found to have suitably high titres of V-Z antibody. The supply of VZIG is limited by the availability of suitable donors and its use is therefore restricted to those at greatest risk and for whom there is evidence that it is likely to be effective.

■ 34.3.2 VZIG is a clear, pale yellow fluid or light brown solution dispensed in vials containing 250 mg protein in a nominal 1.7ml of fluid (minimum potency 100 iu of VZ antibody per ml) with added thiomersal and sodium chloride. On keeping, a slight turbidity or occasional particles may appear.

■ 34.3.3 VZIG should be stored in a refrigerator between 2-8°C. Under these conditions it has a nominal shelf life of three years. It can be stored for short periods at room temperature and is sufficiently heat stable to be despatched by post. VZIG must NOT be frozen.

■ 34.3.4 All immunoglobulins are prepared from HIV, hepatitis B and hepatitis C negative donors.

■ 34.4 Recommendations

VZIG prophylaxis is recommended for individuals who fulfil all of the following three criteria:

(a) a clinical condition which increases the risk of severe varicella; this includes immunosuppressed patients (see 34.5), neonates (see 34.6) and pregnant women (see 34.7).

(b) no antibodies to varicella-zoster (VZ) virus (see 34.8).

(c) significant exposure to chickenpox or herpes zoster (see 34.9).

Antiviral chemotherapy may be used for patients with other clinical conditions in whom attenuation of an attack of chickenpox would be desirable.

34.5 Immunosuppressed patients

These are defined in Chapter 7 and include the following:

(a) patients currently being treated with chemotherapy or generalised radiotherapy, or within 6 months of terminating such treatment;

(b) patients who have received an organ transplant and are currently on immunosuppressive treatment;

(c) patients who within the previous 6 months have received a bone marrow transplant;

(d) children who within the previous 3 months have received prednisolone, orally or rectally, at a daily dose (or its equivalent) of 2 mg/kg/day for at least one week, or 1 mg/kg/day for one month. For adults, an equivalent dose is harder to define but immunosuppression should be considered in those who have received a dose of around 40 mg prednisolone per day for more than one week in the previous 3 months;

(e) patients on lower doses of steroids, given in combination with cytotoxic drugs (including anti-thymic globulin or other immunosuppressants);

(f) patients with evidence of impaired cell mediated immunity, for example severe combined immune deficiency syndromes, Di George syndrome and other combined immunodeficiency syndromes;

(g) patients with symptomatic HIV infection. VZIG is not indicated for asymptomatic HIV positive patients with normal CD4 counts as there is no evidence of increased risk of severe varicella in these individuals;

(h) patients with gammaglobulin deficiencies who are receiving replacement therapy with intravenous normal immunoglobulin, do not require VZIG (see 7.3.7).

Note:

For immunosuppressed patients with bleeding disorders in whom intramuscular injections are contraindicated, see 34.10.

Severe or fatal varicella can occur despite VZIG prophylaxis; varicella immunisation should therefore be considered for susceptible immunosuppressed patients at long term risk (see 34.2). About half of susceptible immunosuppressed home contacts will develop clinical chickenpox despite VZIG prophylaxis and a further 15% will be infected subclinically. There is no difference in outcome whether VZIG is given within 3 days or 4-7 days after exposure.

34.6 Neonates

VZIG is recommended for the following:

(a) Infants whose mothers develop chickenpox (but not herpes zoster) in the period 7 days before to 28 days after delivery.

(b) VZ antibody negative infants exposed to chickenpox or herpes zoster in the first 28 days of life. If supplies of VZIG are short, issues to infants with post-natal exposure may be restricted to those in contact during the first 7 days of life.

The following infants do not require VZIG since maternal antibody will be present:

Infants born **more than** seven days after the onset of maternal chickenpox.

Infants whose mothers have a positive history of chickenpox and/or a positive VZ antibody result.

Infants whose mothers develop zoster before or after delivery.

Note:

About half of neonates exposed to maternal varicella will become infected despite VZIG prophylaxis. In up to two thirds of these infants infection is mild or asymptomatic, but rare fatal cases have been reported despite VZIG prophylaxis in those with onset of maternal chickenpox in the period 4 days before to 2 days after delivery. Early treatment with intravenous acyclovir is recommended for infants in this exposure category who develop varicella despite VZIG prophylaxis.

■ 34.7 Pregnant women

VZIG is recommended for VZ antibody negative pregnant contacts exposed at any stage of pregnancy. However, when supplies of VZIG are short, issues to pregnant women may be restricted to those exposed during the first 20 weeks of pregnancy or near term (within 21 days of the estimated date of delivery).

■ Note:

VZIG does not prevent infection even when given within 72 hours of exposure. However it may attenuate disease if given up to ten days after exposure. Severe maternal varicella may still occur despite VZIG prophylaxis. There is some evidence that the likelihood of fetal infection during the first 20 weeks of gestation is reduced in women who develop chickenpox under cover of VZIG.

■ 34.8 Determination of VZ immune status

■ 34.8.1 The majority of adults and a substantial proportion of children without a definite history of chickenpox will be VZ antibody positive. One UK study found that 11% of children aged 1 to 5 years, 37% aged 6 to 16 years and 89% of adults given VZIG on the basis of a negative history of chickenpox were VZ antibody positive. To prevent wastage of VZIG, all individuals being considered for VZIG should have a serum sample tested for VZ antibody; **only those without antibody require VZIG.** In an emergency, antibody can be estimated within 24 hours; VZIG can be ordered (see 34.12) and should be returned if the test is positive. Advice on testing for VZ antibody should be obtained from the local Public Health or Hospital Laboratory.

■ 34.8.2 VZ antibody detected in patients who have been transfused or who have received intravenous immunoglobulin in the previous 3 months may have been passively acquired. Although VZIG is not indicated if antibody from other blood products is detectable, re-testing in the event of a subsequent exposure will be required as the patient may have become antibody negative.

■ 34.8.3 About 15% of patients given VZIG who remain symptom free after a home contact will have had a subclinical infection. Patients who have received VZIG in the past, following a close exposure, should therefore be re-tested in the event of another exposure, to identify those who have seroconverted asymptomatically and are antibody positive.

■ 34.8.4 The value of a clinical history of chickenpox in determining immune status varies with patient group:

(a) **Immunosuppressed contacts:** Whenever possible, contacts with a positive history of chickenpox should be tested to confirm the presence of VZ antibody. Those with a positive history in whom VZ antibody is not detected by a sensitive assay should be given VZIG.

VZIG is not indicated in immunosuppressed contacts with detectable antibody as the amount of antibody provided by VZIG will not significantly increase VZ antibody titres in those who are already positive. Second attacks of chickenpox can occasionally occur in immunosuppressed VZ antibody positive patients, but these appear be related to defects in cell-mediated immunity.

While it is recommended that immunosuppressed patients without a history of chickenpox should be tested for VZ antibody, VZIG administration should not be delayed past 7 days after initial contact while an antibody test is done. Under these circumstances VZIG should be given on the basis of a negative history of chickenpox.

(b) **Neonates:** Infants whose mothers develop chickenpox less than 8 days before delivery, or after birth, can be presumed to be VZ antibody negative. The VZ antibody status of infants whose mothers have a negative history should determined by testing a maternal blood sample before VZIG is given.

A small proportion of premature infants who are born before 28 weeks of gestation or with a birth weight less than 1000 gms may not possess maternal antibody despite a positive history in the mother.

(c) **Pregnant women:** Those with a positive history of chickenpox do not require VZIG. Those with a negative history must be tested for VZ antibody before VZIG is given. The outcome in pregnant women is not adversely affected if administration of VZIG is delayed up to 10 days after initial contact while a VZ antibody test is done.

■ 34.9 Definition of a significant exposure to varicella-zoster virus

Three aspects of the exposure are relevant:

(a) **Type of varicella-zoster infection in index case:** The risk of acquiring infection from an immunocompetant individual with non-exposed zoster lesions (e.g. thoraco-lumbar) is remote. The issue of VZIG should therefore be restricted to those in contact with chickenpox, or the following: disseminated zoster, immunocompetent individuals with exposed lesions (e.g. ophthalmic zoster) or immunosuppressed patients with localised zoster on any part of the body (in whom viral shedding may be greater).

(b) **The timing of the exposure in relation to onset of rash in index case:** VZIG should normally be restricted to patients exposed to a case of chickenpox or disseminated zoster between 48 hours before onset of rash until cropping has ceased and crusting of all lesions, or day of onset of rash until crusting for those exposed to localised zoster.

(c) **Closeness and duration of contact:** The following should be used as a guide to the type of exposure, other than maternal/neonatal and continuous home contact, that requires VZIG prophylaxis:

Contact in the same room (e.g. in a house or classroom or a 2-4 bed hospital bay) for a significant period of time (15 minutes or more).

Face-to-face contact, for example while having a conversation.

In the case of large open wards, where air-borne transmission at a distance has occasionally been reported, the necessity of giving VZIG to all susceptible high risk contacts should be considered, particularly in paediatric wards where the degree of contact may be difficult to define.

34.10 Dose of VZIG for prophylaxis

The dosage for both the BPL and PFC products are as follows:

0 - 5 years	250 mg (1 vial)
6 - 10 years	500 mg (2 vials)
11 - 14 years	750 mg (3 vials)
15 years and over	1000 mg (4 vials)

VZIG is given by **intramuscular** injection as soon as possible and not later than ten days after exposure. It must **not** be given intravenously.

If a second exposure occurs after three weeks, a further dose is required.

Contacts with bleeding disorders who cannot be given an intramuscular injection should be given intravenous normal immunoglobulin at a dose of 0.2g per kg body weight (ie. 4 mls/kg for a 5% solution) instead. This will produce serum VZ antibody levels equivalent to those achieved with VZIG.

34.11 Treatment

There is no evidence that VZIG is effective in the treatment of severe disease. Since antibody production can be delayed in immunosuppressed individuals, intravenous commercial preparations of normal human immunoglobulin may be used to provide an immediate source of antibody.

34.12 Supplies

England and Wales: Available from Public Health Laboratories and the Communicable Disease Surveillance Centre (CDSC) (Tel. 0181 200 6868).

Northern Ireland: Available from the Public Health Laboratory, Belfast City Hospital, Lisburn Road, Belfast Tel. 01232 329241.

Scotland: Available from Regional Transfusion Centres

VZIG is issued free of charge to patients who meet the criteria given in 34.4. No other licensed VZIG preparations apart from the BPL and PFC products are available in the UK.

34.13 Safety

34.13.1 VZIG is well tolerated. Very rarely anaphylactoid reactions occur in individuals with hypogammaglobulinaemia who have IgA antibodies, or those who have had an atypical reaction to blood transfusion

34.13.2 Severe reactions should be reported to the Committee on Safety of Medicines using the yellow card system.

34.13.3 No cases of blood borne infection acquired through immunoglobulin preparations designed for intramuscular use have been documented in any country.

34.14 Management of hospital outbreaks

34.17.1 Susceptible staff with a significant exposure to VZ virus (see 34.9) including those dressing localised zoster lesions on non-exposed areas of the body, should whenever possible be excluded from contact with high risk patients from eight to 21 days after exposure.

34.17.2 To simplify procedures after the admission or recognition of a case, it is recommended that hospital staff without a definite history of chickenpox should be routinely screened for V-Z antibody so that those susceptible are already identified. This is particularly important for staff in contact with high risk groups such as pregnant women and immunosuppressed patients.

34.15 Bibliography

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