Notifiable in Scotland and Northern Ireland

Chapter 34

Varicella

Introduction

Varicella (chickenpox) is an acute highly infectious disease that 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%. The infection is most common in children below the age of ten in whom it usually causes mild disease. Since chickenpox is so common in childhood, 90% of adults are immune.

The incidence of varicella is seasonal and reaches a peak from March to May. The incubation period is between 2 and 3 weeks.

Vesicles appear without prodromal illness on the face and scalp, spreading to the trunk and abdomen and eventually to the limbs; after 3 or 4 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 1 to 2 days before the rash appears until the vesicles are dry. This may be prolonged in immunosuppressed patients. Early treatment with oral/systemic aciclovir shortens the duration and severity of illness.

The disease can be more serious in adults, particularly pregnant women and those who smoke, as they are at risk of fulminating varicella pneumonia. Pregnant women appear to be at greatest risk late in the second or early third trimester; of the nine deaths due to varicella in pregnancy in England and Wales between 1985 and 1998, seven occurred between 27 and 32 weeks' gestation.[1] For neonates and immunosuppressed individuals the risk of disseminated or haemorrhagic varicella is greatly increased.

Herpes zoster is caused by the reactivation of the patient's varicella virus. It is transmissible to susceptible individuals as chickenpox but there is no evidence that it can be acquired from another individual with chickenpox. Although more common in the elderly, it can occur in children and is especially common in immunosuppressed individuals of any age. 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 paraesthesia.

Risks to the fetus and neonate from maternal chickenpox are related to the time of infection in the mother. [2,3]

- **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[2]. In this study no cases of congenital varicella syndrome occurred among the 477 pregnancies in which maternal varicella occurred after 20 weeks gestation.

- **In the second and third trimesters of pregnancy.** Herpes zoster in an otherwise healthy infant.

- **A week before, to a week after delivery.** Severe and even fatal disease in the neonate. Before the introduction of Human Varicella-Zoster Immunoglobulin (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 either before or during birth or in the first week of life.

Varicella vaccine

Varicella vaccine is a live attenuated vaccine derived from the Oka strain of varicella zoster virus. It is available from GlaxoSmith Kline (Varilrix™, Oka-RIT) as a lyophilised preparation which on reconstitution is given as a 0.5ml dose. It is stored at +2 to +8ºC and has a shelf life of 24 months. It is not affected by freezing.

Varicella vaccine (VARIVAX®, Oka/Merck) will be available from Aventis Pasteur MSD in spring 2004 as a lyophilised preparation, stored at +2 to +8º C, which on reconstitution is also given as a 0.5ml dose.

The vaccine should be administered by subcutaneous injection.

The vaccination schedule varies with age: For individuals aged 13 and over, two doses 4-8 weeks apart; for children aged 1-12 years, a single dose. Up to 10% of adults and 5% of children develop a vaccine-associated rash, either localised at the injection site or generalised, within 1 month of immunisation.[4] Varicella vaccine rashes may be papular or vesicular. Transmission of vaccine virus from immunocompetent vaccinees to susceptible close contacts has occasionally been documented but the risk is very low. Transmission in the absence of a post-vaccination rash has not been documented.[4]

The two-dose vaccination schedule in adolescents and adults provides about 75% protection and the single dose schedule in children about 90% protection [4]. In both age groups most of the breakthrough infections are modified and vaccinated individuals who contract varicella have fewer lesions and less systemic upset than unvaccinated individuals.

The Oka strain can establish latency in immunocompetent individuals and result in herpes zoster but the risk is lower than with wild varicella infection.

The Oka strain is sensitive to aciclovir.

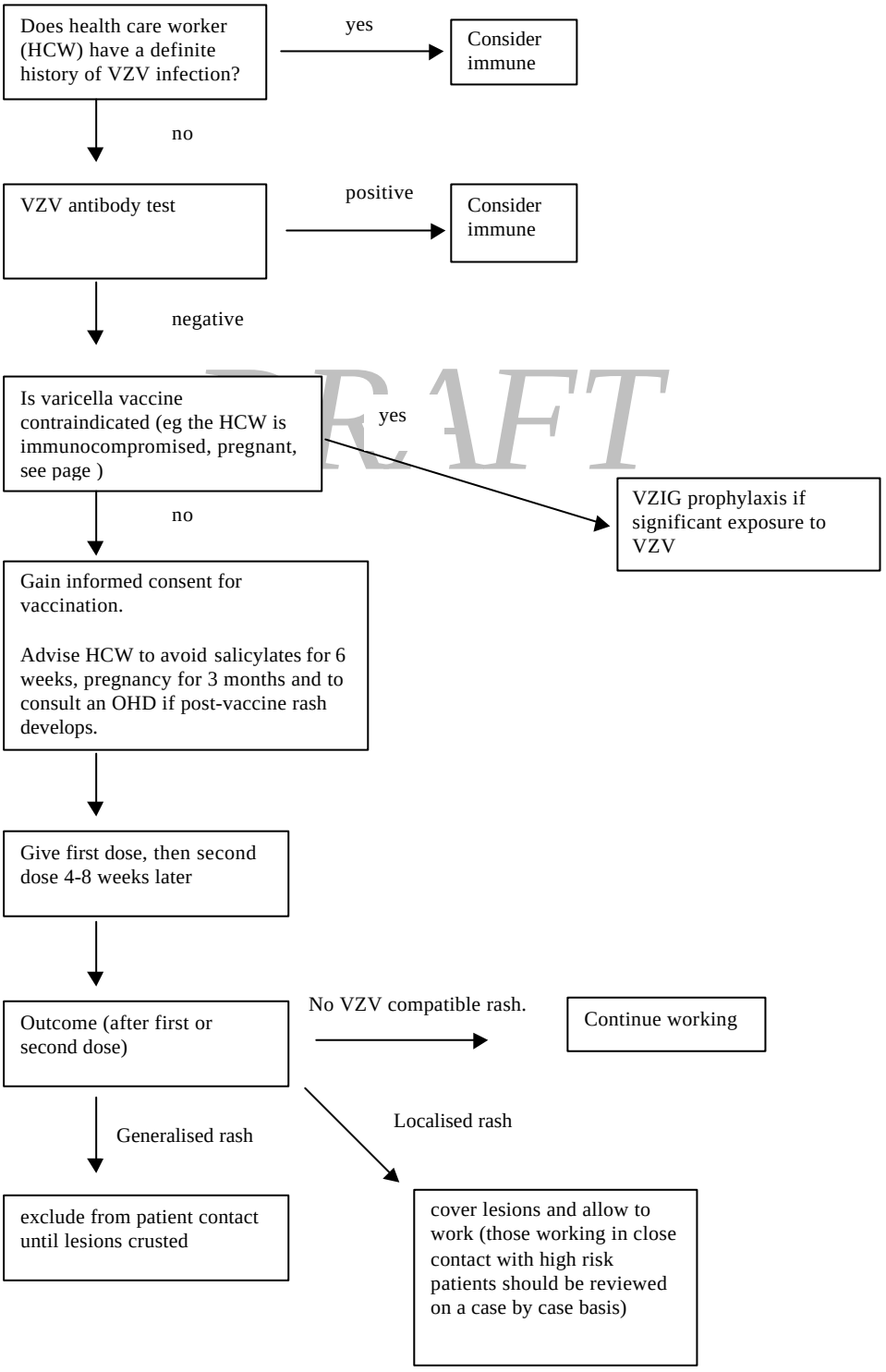
Varicella vaccines are well tolerated. Extensive clinical and post-marketing safety surveillance data from the United States (for the Oka/Merck strain, VARIVAX®) shows the most commonly reported reactions are complaints at the injection site (pain, redness, rash). Generalised symptoms such as fever and rash can also occur but less frequently. Management of these reactions in health care workers (HCWs) is detailed below.

Recommendations for use of varicella vaccine

Health care workers (see figure 34.1)

- Varicella vaccine is recommended for susceptible health care workers (HCWs) who have no contraindication to vaccination (see below). This recommendation is designed both to protect the susceptible HCW and to protect patients from contracting varicella

Figure 34.1 Procedure for vaccinating health care workers



from a HCW. The definition of a HCW includes those working in general practice and hospitals, who have patient contact, e.g. cleaners on wards, catering staff, ambulance staff, receptionists in general practice as well as medical and nursing staff, whether employed directly or through contract.

Those with a definite history of chickenpox or herpes zoster can be considered protected. HCWs with a negative or uncertain history of chickenpox or herpes zoster should be serologically tested and vaccine only offered to those without VZ antibody. A recent survey showed that a history of chickenpox is a less reliable predictor of immunity in individuals born and raised overseas (personal communication, E McMahon).

- Salicylates should be avoided from the first dose until 6 weeks after the second dose. Pregnancy should be avoided for 3 months.

- HCWs should be told at the time of vaccination that they may experience a local rash around the site of injection or a more generalised rash in the month after vaccination. In either case they should report to their occupational health department for assessment before commencing work. If the rash is generalised and consistent with a vaccine-associated rash (papular or vesicular) the HCW should avoid patient contact until all the lesions have crusted. HCWs with localised vaccine rashes that can be covered with a bandage and/or clothing should be allowed to continue working unless in contact with high risk patients. In the latter situation an individual risk assessment should be made.

- Routine post-vaccination serological testing is not advised.

Varicella vaccine is not currently recommended for routine use in children. However, it may be given to healthy susceptible contacts of immunocompromised patients where continuing close contact is unavoidable (e.g. siblings of a leukaemic child). Varicella vaccine can be given at the same time but at a different site from MMR vaccine. If the MMR and varicella vaccines are not given simultaneously they should be separated by at least 30 days.[13]

Contraindications to varicella vaccine

- Varicella vaccine is contraindicated in immunocompromised patients. Clinicians considering vaccinating such patients should seek advice from the manufacturer.
- Pregnancy (see below).
- Hypersensitivity (anaphylactoid) reaction to neomycin or gelatine.
- Hypersensitivity to a previous dose.

Note: Inadvertent vaccination in pregnancy

Surveillance of cases of inadvertent vaccination in pregnancy in the US has not identified any specific risk to the fetus. Follow up to March 2002 of 697 women in the US who have been vaccinated with Oka/Merck strain (VARIVAX®) while pregnant has identified no cases of congenital varicella in any liveborn infant. In addition, the rate of occurrence of congenital anomalies has been similar to that reported in the general population.[11] However, it is nevertheless important to record such cases and to document the outcome of pregnancy. Surveillance of inadvertent vaccination in pregnancy is being established by the Immunisation Division of the Health Protection Agency to whom such cases should be reported (0208 200 6868 ext 4405). Any such cases in Scotland should be reported to the Scottish Centre for Infection and

Environmental Health (SCIEH) by telephoning 0141-300-1191 and in Wales, cases should be reported to the National Public Health Service for Wales (tel. 01352 700227 ext 4055). These will, in turn, contribute to the UK figures via the Immunisation Division of the Health Protection Agency.

Human Varicella-Zoster Immunoglobulin (VZIG)

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 non-UK donors with 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.

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 iì of VZ antibody per ml) with added thiomersal and sodium chloride. On keeping, a slight turbidity or occasional particles may appear.

VZIG should be stored in a refrigerator between +2 to +8°C. Under these conditions it has a nominal shelf life of 3 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.

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

Recommendations for use of VZIG

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

- a clinical condition which increases the risk of severe varicella; this includes immunosuppressed patients, neonates and pregnant women (see below).
- no antibodies to varicella-zoster (VZ) virus (see below).
- significant exposure to chickenpox or herpes zoster (see below).

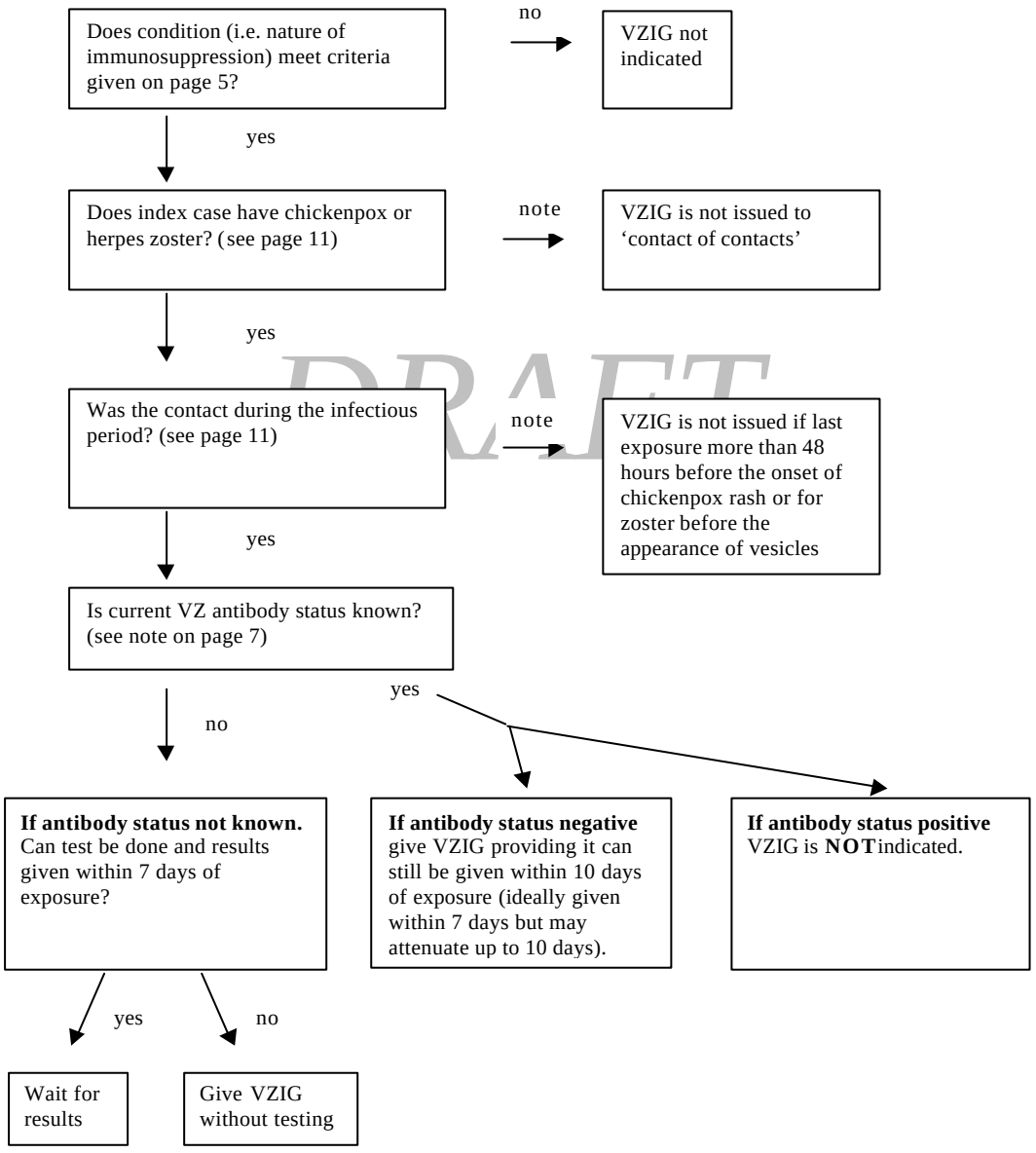
The post-exposure management algorithms for immunocompromised patients, neonates and pregnant women are summarised in figures 34.2, 34.3 and 34.4 respectively.

Immunosuppressed patients

These are defined in Chapter 7 and include the following:

- patients currently being treated with chemotherapy or generalised radiotherapy, or within 6 months of terminating such treatment;
- patients who have received an organ transplant and are currently on immunosuppressive treatment
- patients who have received a bone marrow transplant and who are still considered to be immunosuppressed, including those with graft versus host disease.

- **Figure 34.2 VZIG algorithm for immunocompromised patients**



- children who within the previous 3 months have received **high dose steroids**, orally or rectally, namely a daily dose of prednisolone (or its equivalent) of 2 mg/kg/day for at least 1 week, or 1 mg/kg/day for 1 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 1 week in the previous 3 months.

- patients on lower doses of steroids, given in combination with cytotoxic drugs (including antithymocyte/lymphocyte antibodies or other immunosuppressants).

- patients with evidence of impaired cell mediated immunity, for example severe combined immune deficiency syndromes, Di George syndrome and other combined immunodeficiency syndromes.

- Symptomatic HIV positive patients or asymptomatic patients with low CD4 counts

Note

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

Whenever possible, immunosuppressed contacts should be tested irrespective of their history of chickenpox. However, 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. 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 are likely to be related to defects in cell-mediated immunity.

Effectiveness in immunocompromised patients: About half of susceptible immunosuppressed home contacts will develop clinical chickenpox despite VZIG prophylaxis and a further 15% will be infected subclinically.[5] Severe or fatal varicella can occur despite VZIG prophylaxis. Immunocompromised contacts given VZIG should therefore still be monitored and aciclovir used at the first signs of illness.

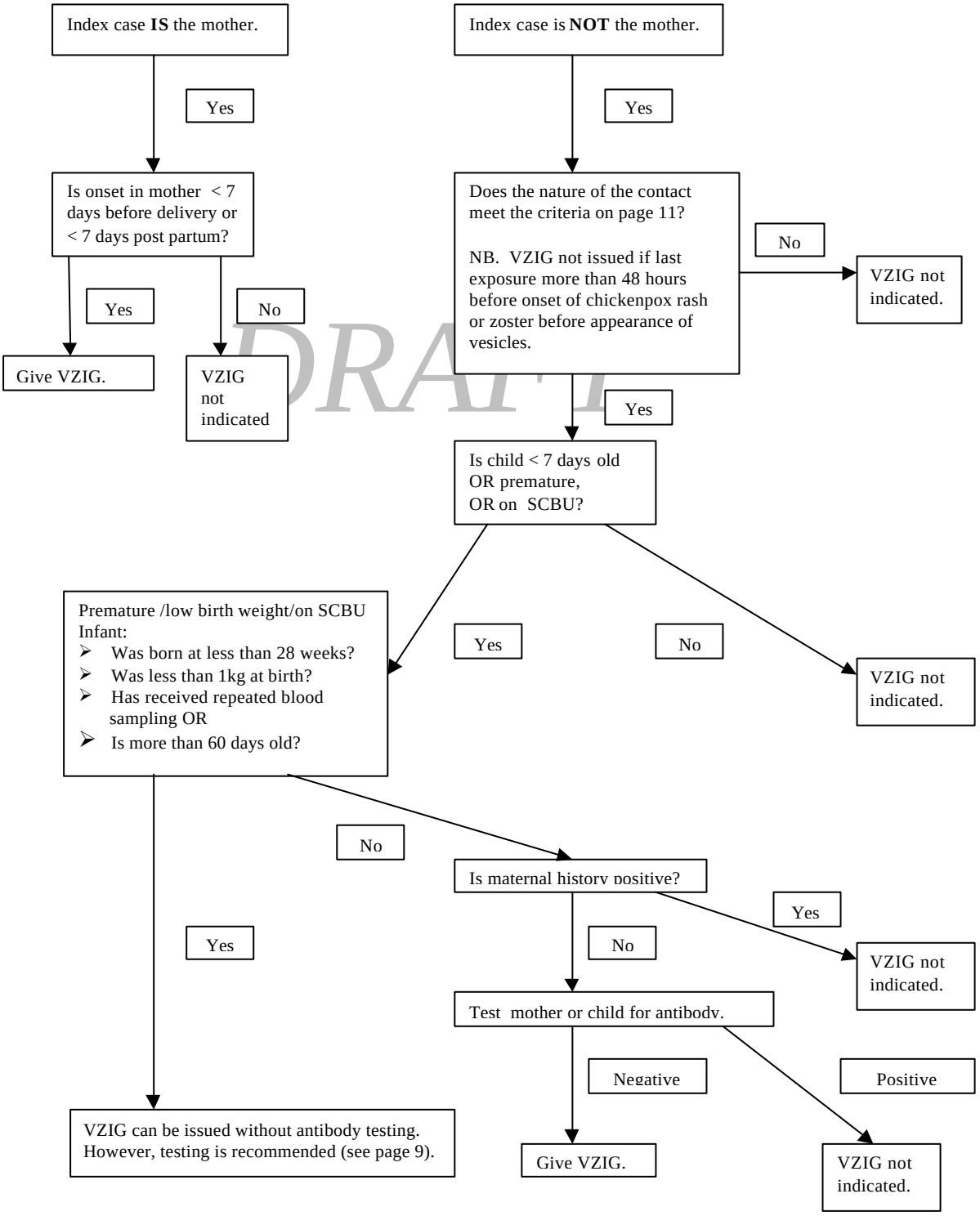
Neonates

VZIG is recommended for the following:

- Infants whose mothers develop chickenpox (but not herpes zoster) in the period 7 days before to 7 days after delivery. VZIG can be given without antibody testing of the infant.

VZIG is not usually required for infants born more than 7 days after the onset of maternal chickenpox or whose mothers develop zoster before or after delivery as these infants will have maternal antibody.

Figure 34.3 VZIG algorithm for neonates



VZIG is also recommended for the following:

- VZ antibody-negative infants exposed to chickenpox or herpes zoster (other than in the mother) in the first 7 days of life.
- VZ antibody-negative infants of any age, exposed to chickenpox or herpes zoster while still requiring intensive or prolonged special care nursing.

For infants in these two exposure groups who are born before 28 weeks gestation, weighed less than 1000g at birth, are more than 60 days old, or have had repeated blood sampling with replacement by packed red cell infusion, maternal antibody may not be present despite a positive maternal history of chickenpox [6,7]. It is therefore recommended that where possible, such infants are tested to determine their VZ antibody status in the event of a contact. Other infants whose mothers have a positive history of chickenpox and/or a positive VZ antibody result will usually have maternal antibody and do not require VZIG.

Effectiveness in neonates: About half of neonates exposed to maternal varicella will become infected despite VZIG prophylaxis.[3] 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 aciclovir is recommended for infants in this exposure category who develop varicella despite VZIG prophylaxis.

Pregnant women

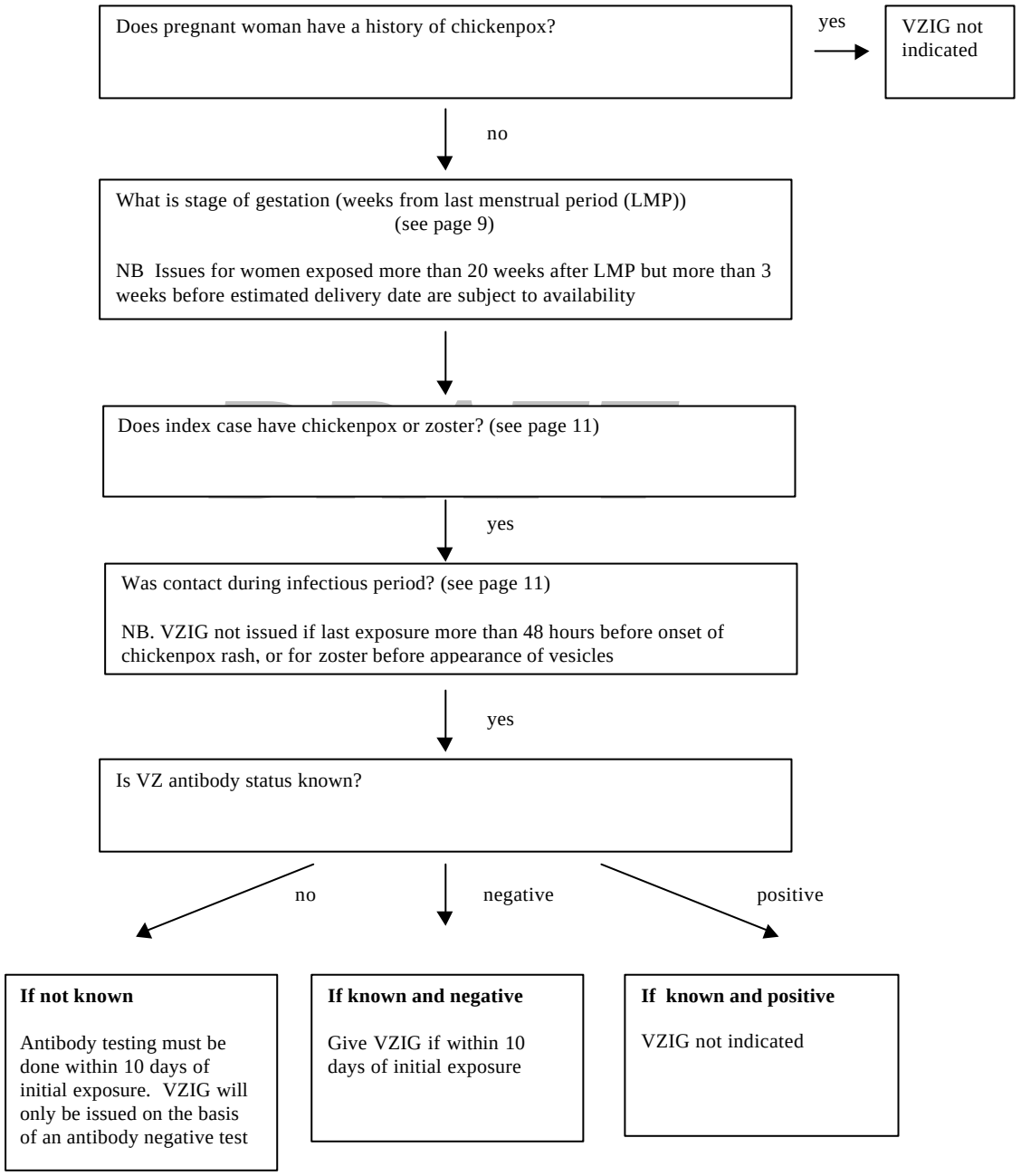
VZIG is recommended for VZ antibody negative pregnant contacts exposed at any stage of pregnancy, providing VZIG can be given within 10 days of contact (for household contacts count from day of onset of rash). However, when supplies of VZIG are short, issues to pregnant women may be restricted. Clinicians are advised to check availability of VZIG (see supplies section below) before offering it to pregnant women.

Pregnant contacts 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 (see below). The outcome in pregnant women is not adversely affected if administration of VZIG is delayed up to 10 days after initial contact.[1,8] There is, therefore, still time to test for VZ antibody even when the woman presents relatively late after contact.

Effectiveness in pregnant women The rationale for the use of VZIG prophylaxis in pregnant women is two fold: reduction in severity of maternal disease and reduction of risk of fetal infection for women contracting varicella in the first 20 weeks of pregnancy. The risk of fatal varicella is estimated to be about five times higher in pregnant than non-pregnant adults with fatal cases concentrated late in the second or early third trimester.[1]

One study showed a significant reduction in the risk of congenital VZV infection in women who developed varicella after VZIG prophylaxis compared with women who developed varicella without VZIG prophylaxis; however, the study was too small to assess whether the risk of congenital varicella syndrome was reduced. [2] A case of congenital varicella syndrome has been reported in the infant of a woman exposed at the eleventh week of gestation and who developed clinical varicella despite post exposure prophylaxis with VZIG. [9]

Figure 34.4 VZIG algorithm for pregnant women



About 50% of susceptible pregnant women given VZIG after a household exposure to chickenpox will develop clinical varicella, although the disease may be attenuated; the clinical attack rates are similar whether VZIG is given within 72 hours or 4-10days after contact,[1,8] A further quarter will be infected subclinically.[8] Severe maternal varicella may still occur despite VZIG prophylaxis. Prompt treatment with aciclovir is indicated in such cases.

Determination of VZ immune status

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.[5] 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. Urgent VZ antibody testing is required; for patients presenting late, VZIG can be ordered (see below) at the same time that the blood is sent for testing and can be returned if the result is positive. VZ antibody testing should be available within 24 to 48 hours, seek advice from the local public health or hospital laboratory.

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.

About 15% of patients given VZIG who remain symptom-free after a home contact will have had a subclinical infection and seroconvert asymptomatically .[5,8] Patients who have received VZIG in the past following a close exposure should, therefore, be re-tested for VZ antibody in the event of another exposure.

Definition of a significant exposure to varicella-zoster virus

Three aspects of the exposure are relevant:

- **Type of varicella-zoster infection in the index case**: The risk of acquiring infection from an immunocompetent 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),

- **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 crusting of lesions, or day of onset of rash until crusting for those exposed to localised zoster.

- **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, e.g. while having a conversation.

- In the case of large open wards, air-borne transmission at a distance has occasionally been reported and 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).

Management of health care workers exposed to VZV infection

Vaccinated HCWs or those with a definite history of chickenpox or zoster and with a significant exposure to VZV (as above and including those dressing localised zoster lesions on non-exposed areas of the body) should be considered protected and allowed to continue working. As there is a remote risk that they may develop chickenpox, they should be advised to report to their occupational health department for assessment before having patient contact if they feel unwell or develop a fever or rash.

Unvaccinated HCWs without a definite history of chickenpox or zoster and with a significant exposure to VZ virus (see above), should either be excluded from contact with high risk patients from 8 to 21 days after exposure or be advised to report to their occupational health department before having patient contact if they feel unwell, or develop a fever or rash. There is some evidence that varicella vaccine administered within 3 days after exposure may be effective in preventing chickenpox[12] (Varivax® is licensed for post-exposure prophylaxis.) In any case, irrespective of the interval since exposure, vaccine should be offered to reduce the risk of the HCW exposing patients to VZV in the future (see above).

Management of a health care worker with zoster

HCWs with localised herpes zoster on a part of the body that can be covered with a bandage and/or clothing should be allowed to continue working unless in contact with high risk patients when an individual risk assessment should be made.

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. It must not be given intravenously.

If a second exposure occurs after 3 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 (i.e. 4 ml/kg for a 5% solution) instead. This will produce serum VZ antibody levels equivalent to those achieved with VZIG.[10]

Treatment

VZIG has no place in the treatment of severe disease.

Supplies

England and Wales: Available from Public Health Laboratories and the Communicable Disease Surveillance Centre (CDSC) (Tel. 0208 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

Aberdeen & North East of Scotland Blood Transfusion Centre
Foresterhill Road
Foresterhill
ABERDEEN
AB9 2ZW
Tel: 01224 685685

North of Scotland Blood Transfusion Centre
Raigmore Hospital
Inverness
IV2 3UJ
Tel: 01463 704212

Dundee & East of Scotland Blood Transfusion Centre
Ninewells Hospital
Dundee
DD1 9SY
Tel: 01382 645166

The West of Scotland Blood Transfusion Centre
Gartnavel General Hospital
25 Shelly Road
GLASGOW
G12 0XB
Tel: 0141 357 7700

Edinburgh & South East of Scotland Blood Transfusion Centre
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh EH16 4SA
Tel: 0131 242 7520 (Irene McKechnie)

VZIG is issued free of charge to patients who meet the criteria given above. Clinicians who wish to issue VZIG for patients not meeting these criteria should approach the manufacturer directly to purchase a dose.

No other licensed VZIG preparations for intramuscular use apart from the BPL and PFC products are available in the UK

Safety of VZIG

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.

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

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

for the all the immunoglobulin preparations manufactured by BPL and PFC is sourced from non-UK donors. All donors are screened for HIV, hepatitis B and C, and all plasma pools are tested for presence of RNA from these viruses. A solvent detergent inactivation step for envelope viruses is included in the production process.

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