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REVIEW

Chickenpox in adults – Clinical management

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Summary Acute varicella zoster virus (VZV) infection, or chickenpox, is still perceived by many as a mild infection of childhood. However, chickenpox is increasingly common in adults and adolescents who together with immunosuppressed individuals are at a higher risk of severe infection. Antiviral therapy is available which both ameliorates symptoms and decreases the severity of chickenpox if administered early in the course of the infection. Passive immunisation with varicella zoster immunoglobulin (VZIG) may prevent or attenuate infection following exposure to varicella of an immunocompromised or pregnant individual or a neonate. Active immunisation is available and is universal in many developed countries.

This review reflects current best practice in management of chickenpox in adults by specialist physicians in the UK. The accompanying flowchart has been formulated to guide emergency physicians and general practitioners through the decision-making process regarding treatment and admission for specialist care.

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Introduction

Chickenpox, or varicella, is a well-recognised systemic infection caused by varicella zoster virus (VZV). In temperate countries chickenpox is usually a mild, self-limiting infection, affecting pre-school children. In the UK 90% of adults over the age of 18 years are seropositive for VZV.¹

However, in many tropical countries the epidemiology is different, with less than 60% of adults being immune.² Factors contributing to this may include population density and climatic effects.³ In temperate climates the incidence of chickenpox in adolescents and adults is increasing,⁴ which may in part be due to increased world travel and economic migration of susceptible individuals. Morbidity and mortality is greater in adults than in children.^{4,5} Specific risk factors include pre-existing lung disease, smoking, and immunocompromise, including immunosuppressive drug therapy, HIV infection and malignancy.⁵ For every 100,000 individuals who develop chickenpox, between four and

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nine will die, of whom 81–85% will be adults.^{6,7} Chickenpox is five times more likely to be fatal in pregnancy than in the non-pregnant adult.⁸

Pathogenesis

During primary infection VZV colonises the upper respiratory tract, followed by seeding of the reticuloendothelial system. Viraemia is followed by spread to the skin and mucosal surfaces, with development of the characteristic vesicles. Infection is controlled by both humoral and cell mediated immune responses. Following primary chickenpox, the virus establishes latency in the dorsal root ganglia. Subsequently a reduction in cell mediated immune function or senescence may allow reactivation of the virus, resulting in the dermatomal vesicular rash of shingles, also known as herpes zoster.

Infectivity

Chickenpox has a high attack rate, affecting 90% of non-immune exposed individuals. The incubation period is 10–21 days.⁹ Infectivity is at its highest from 2 days prior to onset of the rash, with airborne droplet spread playing an important role in transmission. The virus is also directly shed from vesicles, and may be transferred by heavily contaminated clothing or bedding until all the vesicles have crusted over and dried, usually after 5–6 days.

A non-immune individual can develop primary chickenpox after significant exposure to shingles. It is important to reassure contacts that anyone who has had chickenpox or shingles in the past can be considered to be immune.¹⁰ Re-exposure to VZV protects against herpes zoster.¹¹

Clinical chickenpox and its differential diagnosis

The clinical diagnosis is rarely in doubt, although disseminated herpes zoster or herpes simplex in immunocompromised individuals may be difficult to differentiate from primary VZV infection. Fever, malaise and lethargy precede the eruption of the rash by 24 h. The rash starts on the trunk and face, develops in crops, and typically spreads to involve much of the skin surface. It is initially macular, proceeding to papules and vesicles that are fluid filled and become pustular, often turning yellow. The lesions are intensely itchy, with surrounding erythema. Most patients have a moderate rise in temperature. The mucous membranes of the oropharynx and genital tract may become involved. In immunocompetent individuals the rash peaks at 48 h. The vesicles will then begin to crust over before drying up; new lesions may appear for up to 5 days. Scabs usually separate and are shed within 2 weeks of the onset of infection. Full resolution of the skin lesions may take up to a month (Fig. 1).

A typical presentation may occur, particularly in the immunocompromised, e.g. with the development of abdominal pain due to visceral disease prior to onset of the classic skin rash.¹² In bone marrow transplant recipients the syndrome of acute right upper quadrant pain due to hepatic necrosis may be misinterpreted in the early stages as graft versus host disease.¹³

It may be important to differentiate chickenpox from other vesicular rashes. Chickenpox rash is centripetally distributed, particularly involving the face and trunk, with fewer lesions on the limbs. Early in the disease lesions at all stages of development may be seen. Variola (smallpox) lesions classically appeared firstly on the tongue and palate and as small macules on the face before centrifugal spread. The vesicles or nodules were firm, well-circumscribed, deeper in the skin, and all at the same stage of development. Although global eradication of smallpox was announced in 1979 the virus remains of interest because of bioterrorism concerns. Other conditions that may be confused with chickenpox include impetigo (may begin as regional vesicles before crusting develops), drug related eruptions, contact dermatitis, erythema multiforme and Stevens–Johnson syndrome, enteroviral infections (hand, foot and mouth disease; typically a peripheral distribution of whitish-grey tender flat vesicles), disseminated molluscum contagiosum, plus scabies, poison ivy and pityriasis rosea, the latter three being intensely itchy conditions.

Assessment of a patient with chickenpox

Clinical examination may reveal little apart from the rash. The absence of respiratory signs does not preclude the presence of pneumonitis.¹⁴ Chest radiography and pulse oximetry should be performed on all patients who are at particular risk of pneumonitis (see below) or who develop symptoms of cough or breathlessness. Any patient with signs of severe disease (see Table 1) should be assessed by a specialist physician in hospital.

Thrombocytopenia and moderately raised liver transaminases are often seen, but usually resolve with the acute illness.¹⁴

Complications of chickenpox

Pneumonitis may be life-threatening and is a particular risk in pregnant women, the immunocompromised, those with pre-existing lung disease (not including asthma), and smokers. Between 5 and 14% of adults with chickenpox will develop pulmonary involvement.¹⁵ Patients with more than one risk factor are more likely to develop severe varicella pneumonitis requiring respiratory support.¹⁶ Close monitoring of respiratory rate and oxygen saturation is essential as pneumonitis can progress rapidly.

Central nervous system involvement may result in acute cerebellar ataxia which usually occurs during the recovery period and is most likely to be immunologically mediated – it is usually benign and self-limiting in children. More rarely varicella encephalitis occurs which carries a mortality of up to 20%. Significant invasive infection, causing multi-system failure, may occur in immunocompromised patients.¹⁷

Secondary bacterial infection with *Staphylococcus aureus* or Group A Streptococci is a common complication of chickenpox and may result in skin and soft tissue infection, osteomyelitis, septicaemia or toxic shock syndrome. A significant rise in temperature 2 or 3 days into the illness may indicate a secondary bacterial infection and treatment with appropriate antibiotics, such as flucloxacillin, co-amoxiclav or a macrolide should be considered.

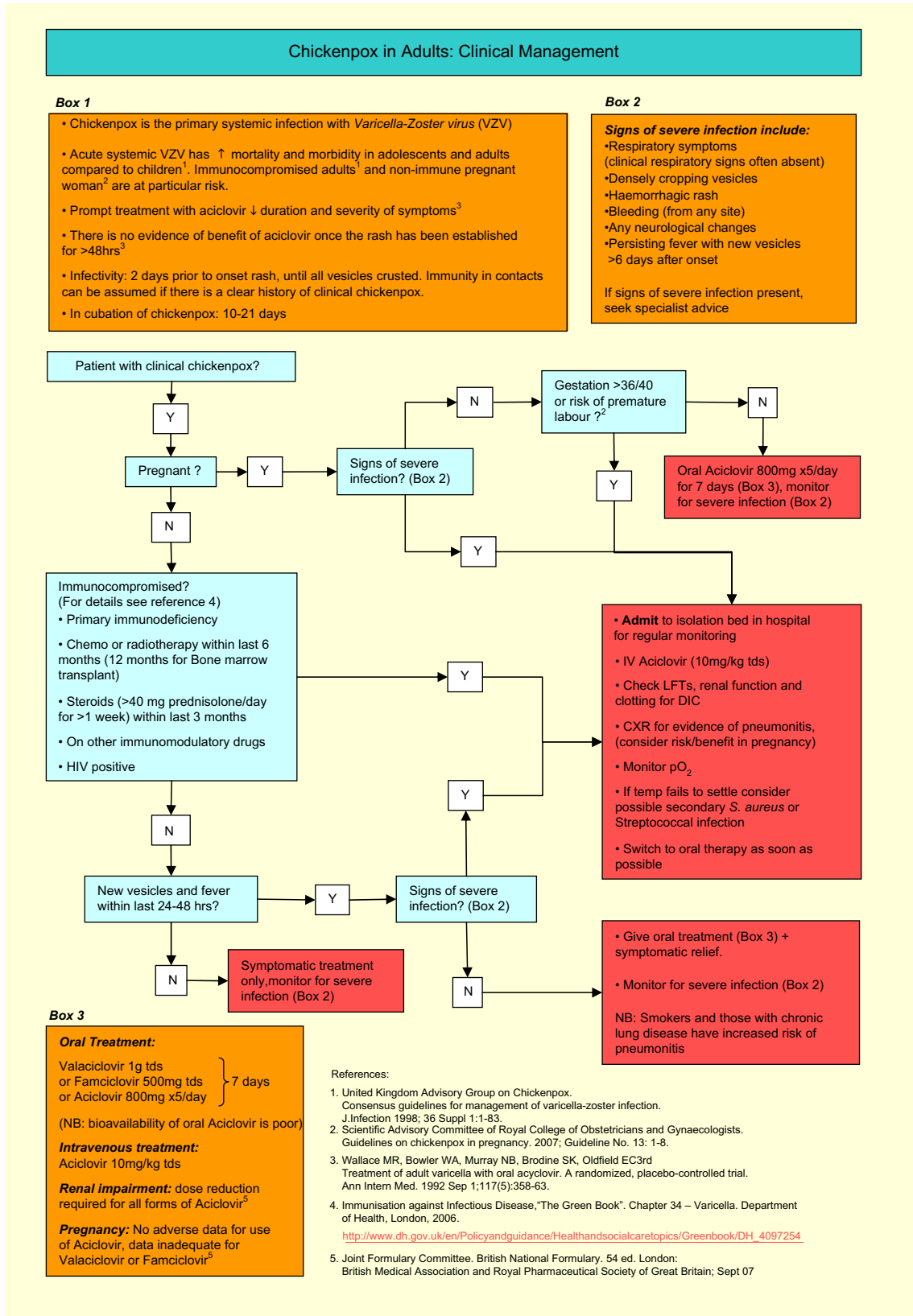


Figure 1 Chickenpox in adults – clinical management.

Table 1 Indicators of severe disease in acute varicella infection¹⁴

- Respiratory symptoms (clinical respiratory signs are often absent).
- Densely cropping vesicles.
- Haemorrhagic rash.
- Bleeding (e.g. from gums, haemoptysis, GI bleeding).
- Any neurological changes (cerebellar signs, encephalopathy).
- Persisting fever with new vesicles >6 days after onset.

Haemorrhagic complications include pulmonary and gastrointestinal bleeding, intra-cerebral haemorrhage and disseminated intravascular coagulation. Evidence of bleeding, e.g. easy bruising, haemorrhagic skin lesions, bleeding gums, or haemoptysis, should be urgently investigated with prompt admission to hospital.

Investigation of chickenpox

Although the majority of diagnoses are made clinically, the virus may be detected by molecular techniques (PCR) or virus isolation from fluid/cells from the base of the vesicular lesion. This may be helpful in the management of the immunocompromised patient, in whom a vesicular rash may have other causes such as disseminated herpes simplex infection or graft versus host disease.

Treatment of chickenpox

Aciclovir inhibits VZV replication, reducing severity and shortening duration of symptoms if given within 24 h of the onset of infection.^{18–21} While it is rare for patients to present within such a short time frame, a pragmatic approach is to consider antiviral agents in patients who present within 24–48 h of new vesicles, implying that the disease is still evolving.²² For immunocompetent individuals presenting more than 48 h after the development of new lesions symptomatic treatment only is advised, but they should be monitored for signs of severe infection (see Table 1).

Aciclovir has a good safety profile and is well-tolerated. However, the bioavailability of oral aciclovir is poor, requiring dosing at 800 mg 5 times daily. In addition the IC₉₀ of VZV for aciclovir and related compounds is higher than for herpes simplex virus and therefore levels may be suboptimal for inhibition of viral replication. The pro-drug valaciclovir, at a dose of 1 g 3 times daily, greatly enhances bioavailability,²³ resulting in 3- to 4-fold higher plasma aciclovir levels that can be achieved with oral aciclovir. Famciclovir, the pro-drug of penciclovir, dosed at 500 mg 3 times daily, also has enhanced bioavailability when compared with aciclovir. These second generation antiviral drugs are recommended first line for the treatment of shingles (herpes zoster), as they accelerate healing, reduce pain and reduce dosing frequency compared to aciclovir.^{24–26} They are becoming the preferred oral formulations for chickenpox in many cases.²⁷

The relatively low frequency of serious complications of VZV infection in adults means that trials of aciclovir treatment have been insufficiently powered to demonstrate a reduction in the complication rate, although a retrospective analysis of 46 reports of 272 patients with varicella pneumonia showed a 3.6-fold higher mortality rate in those who did not receive aciclovir.²⁸ Qualitative cost analysis does however suggest that treatment of all adults and adolescents is worthwhile.^{29,30} A minimum of 1 week of antiviral therapy is recommended. Two weeks therapy may be appropriate in severe disease or in the immunocompromised, for whom intravenous therapy is usually recommended, although with rapid improvement an early switch to oral therapy may be considered. In the UK, the use of aciclovir is not recommended in immunocompetent children under the age of 12,³¹ as the complication rate is low and treatment confers minimal benefit when compared to adolescents and adults.²⁰ Aciclovir should be used in children if they or their sibling contacts have a significant medical condition.³² A placebo-controlled study does recommend aciclovir for adolescents, as they have more severe disease than younger children.²⁰

Aciclovir at a dose of 10 mg/kg intravenously every 8 h should be used for those who have or are at risk of severe disease.³¹ Intensive supportive therapy may be required and antibiotic cover is appropriate if secondary bacterial sepsis is suspected. A small retrospective study of the use of steroids in severe varicella pneumonia showed some benefit,³³ but there is no data from prospective randomised controlled trials and steroids are not currently recommended. There is no evidence that varicella zoster immunoglobulin (VZIG) reduces the severity of infection.

Supportive therapy, such as anti-pruritic drugs can be helpful for all age groups. Mouthwashes and soothing topical lotions, plus anaesthetic gels for the genital area if there is mucosal involvement, are also useful for symptomatic treatment.

Chickenpox in pregnancy

Pregnant women are at significant risk of varicella pneumonia and severe disease. The risk is highest after 20 weeks gestation as T-cell function starts to decline or in those who smoke, have chronic lung disease, are immunosuppressed or have more than 100 skin lesions.^{15,34} The risk of miscarriage and premature labour in later pregnancy is also increased.³⁵ Fetal varicella syndrome is a recognised complication of infection in the first half of pregnancy, affecting approximately 0.4% of infants born to mothers infected up to 12 weeks, and 2% of those infected between 13 and 20 weeks of gestation.^{36–39} There have been rare cases of fetal varicella syndrome reported in infants exposed between 20 and 28 weeks gestation.³⁸ Shingles in the mother does not present a risk to the infant.³⁹

Neonates have a significant risk of severe varicella infection when the onset of maternal infection is within 5 days prior to or 2 days after delivery, due to the lack of transfer of protective maternal antibodies and the relative immaturity of the neonatal immune system. Mortality is thought to be up to 30% without active treatment,⁴⁰ and VZIG is recommended for all infants whose mothers develop chickenpox 7 days before to 7 days after delivery. Intravenous aciclovir should be given to these infants if they

develop chickenpox, whether or not they received VZIG. Shingles in the first two years of life is thought to be a reactivation of chickenpox acquired in utero.³⁹

There are no data to suggest an increased risk of adverse events following aciclovir exposure at any stage in pregnancy.^{31,35} The Royal College of Obstetrics and Gynaecology guidelines state that any pregnant woman at more than 20 weeks gestation should be treated with aciclovir,³⁵ which is likely to be of benefit to the mother with minimal risk to the fetus. However, in each case of chickenpox in early pregnancy (i.e. <20 weeks), the risk–benefit of treatment should be considered by an expert in the management of infections, so that the patient is able to make an informed decision. The International Aciclovir Pregnancy Register reported on 1129 prospectively followed pregnancies of which 712 involved aciclovir exposure in the first trimester with no evidence of adverse outcome. It is usual practice in many parts of the world to treat pregnant women with antiviral therapy in all trimesters.

Limited data on the use of valaciclovir in pregnancy, mainly for conditions other than VZV infection, provide some useful pharmacokinetic data and do not reveal any evidence of toxicity. The Valaciclovir Pregnancy Registry has reported on 56 valaciclovir exposed pregnancies, 14 involving first trimester exposure, with no evidence of an adverse outcome. A prospective double-blind trial of aciclovir versus valaciclovir for herpes simplex infection in the third trimester showed significantly higher peak serum aciclovir concentrations in the valaciclovir group than in the aciclovir group.⁴¹ No laboratory or clinical evidence of toxicity was detected, although patient numbers were small. High dose valaciclovir has also been used in a trial of treatment for symptomatic intrauterine cytomegalovirus infection; therapeutic concentrations of aciclovir were obtained in fetal blood.⁴² There are no data for the use of famciclovir in pregnancy.

VZIG is commonly used in pregnant non-immune chickenpox contacts to prevent or attenuate disease. Studies have not been sufficiently powered to examine the effect of VZIG administration on the incidence of fetal varicella syndrome; a case has been described in the baby of a mother who did receive VZIG.³⁸ If passive immunity is to be offered, it should be given as soon as possible up to 10 days after the exposure. There is also no evidence that aciclovir reduces the incidence of fetal varicella syndrome, again due to a lack of studies with sufficient power to demonstrate a change in what is a rare event. The obstetric team should be informed of the cases of chickenpox in pregnancy to enable monitoring for the syndrome.

For mild disease in pregnancy oral aciclovir is the current recommendation in the UK, administered at a dose of 800 mg 5 times daily for 1 week.³⁰ However, second generation antiviral drugs should be considered on expert advice. If there is any concern about severity of the disease (see Table 1), referral to hospital should be made for consideration of parenteral therapy. Women who are close to term should be admitted to an isolation facility with access to specialist obstetric and paediatric services because of the significant risk of premature labour and of neonatal infection. Intravenous aciclovir should be administered, and if possible, delivery of the infant delayed until at least 5 days after the onset of infection.³⁵

Chickenpox in the immunocompromised

Patients in the categories shown in Table 2 should be considered as being at risk of severe VZV infection,⁴³ and should receive antiviral therapy as soon as possible. Early assessment in hospital is recommended, as parenteral treatment is most appropriate to prevent complications.⁴⁴ New lesions may appear over several days in the immunocompromised, and antiviral treatment should be administered if new lesions or fever have been observed in the previous 24–48 h, regardless of time since onset.

Primary prevention of chickenpox

There are 2 varicella vaccines currently licensed in the UK: Varilrix® (GSK), and Varivax® (SPMSD). Both are live attenuated vaccines and are administered to non-immune adults

Table 2 Immunocompromised patients in whom acute varicella infection is likely to develop into severe disease⁴³

1. Patients with severe primary immunodeficiency such as Severe Combined Immunodeficiency (SCID) or Wiskott–Aldrich syndrome.
2. All patients receiving immunosuppressive chemotherapy or radiotherapy for malignant disease, up to 6 months after completion of treatment.
3. All patients on immunosuppressive therapy following a solid organ transplant.
4. All patients who have undergone bone marrow transplantation, up to 12 months after completing all immunosuppressive therapy, or longer if graft versus host disease has occurred.^a
5. Patients taking high doses of systemic steroids, e.g. in adults 40 mg/day for >1 week; in children 2 mg/kg/day for >1 week or 1 mg/kg for >1 month. Risk is maintained up to 3 months after treatment has stopped.
6. Patients receiving other immunomodulatory drugs such as azathioprine, cyclosporine, methotrexate, cyclophosphamide and the cytokine inhibitors, and/or chronic low dose steroid therapy.
7. Patients with HIV infection, particularly if the CD4 count is less than 200 cells/mm³.^b
8. Neonates, either exposed by maternal infection 7 days before or after birth, or any exposure up to 7 days after birth.
9. Non-immune pregnant women.^c

^a Patients who have undergone bone marrow transplantation should be offered vaccination once all immunosuppressive therapy has been stopped for more than 12 months.

^b Patients with HIV who have not previously had chickenpox, and have a CD4 count greater than 400 cells/mm³ should routinely be offered vaccination; at CD4 counts 200–400 cells/mm³, vaccination should be considered if the patient is stable on anti-retroviral therapy.⁵¹

^c Non-immune pregnant women should be considered for Varicella vaccine as soon as possible after delivery,^{35,47} although it is not licensed for use during breastfeeding.

and children over the age of 12 in a 2 dose schedule. In countries with a universal varicella immunisation programme a marked reduction in the incidence of chickenpox has led to a decline in attributable morbidity and mortality, and to a fall in varicella-related healthcare utilisation and cost of the disease management.⁴⁵ Currently there are no plans to vaccinate children routinely against VZV in the UK⁹ but expert groups are recommending its implementation across Europe.⁴⁶ However, vaccination is advised for seronegative children if a member of their household is at risk of severe disease, e.g. siblings of a child with leukaemia, or children with a parent undergoing chemotherapy, in view of the high attack rate in close contacts.⁴³ It is considered that only a universal immunisation programme would adequately reduce morbidity and mortality in pregnancy.

Varicella vaccination is now recommended in the UK for all non-immune healthcare workers in primary care and hospital settings, as the rate of transmission in the health care setting is high and vulnerable patients may be put at risk.⁹ All healthcare workers should be asked about a history of chickenpox or shingles, and have antibody testing and subsequent vaccination as appropriate. Women are advised not to become pregnant within 1 month of vaccination.⁴⁷ Varicella vaccination is also recommended for non-immune healthy close contacts of immunocompromised patients. A clear history of chickenpox or shingles is considered to be adequate evidence of immunity in those brought up in temperate climates,¹⁰ although it can be less reliable in adults born and raised in areas of low seroprevalence.⁴⁸ Lack of immunity should be confirmed by testing for VZV IgG in serum prior to immunisation as asymptomatic infection is common.

Prevention of chickenpox following exposure

Varicella zoster immunoglobulin (VZIG) reduces the risk of infection following exposure by 40% and can attenuate the severity of disease.⁴⁹ It should be considered for individuals who fulfil all three of the criteria listed in Table 3.⁵⁰

VZIG may be offered up to 10 days after exposure, but is ideally administered within 7 days of contact with an infective case of chickenpox or exposed shingles.⁴³ Further guidance on prophylaxis of at risk individuals, including pregnant women, is available in the Department of Health 'Green Book' available via the internet.⁴³ Patients who have received VZIG should be advised that medical advice should still be sought if chickenpox occurs, as antiviral therapy may be required. In those for whom VZIG is not indicated the use of aciclovir may be considered for use as prophylaxis.⁵⁰

Table 3 Main criteria for patients requiring VZIG

1. Have a clinical condition which puts them at risk of severe varicella infection (see Table 2).
2. Are seronegative for antibodies to VZV.
3. Have a significant^a exposure to chickenpox or shingles.

^a Significant exposure can be defined as contact for more than 15 min in the same room or a 5 min face-to-face conversation with a case of chickenpox from 48 h before the rash until skin lesions are crusted, or contact with disseminated or 'exposed' shingles, i.e. ophthalmic zoster.⁴³

Conclusion

These guidelines reflect current best practice for the management of chickenpox in adults by specialist physicians in the UK. Recommendations include antiviral treatment for adults who present within 24–48 h of rash onset, and treatment of women in early pregnancy. The latter is supported in the most recent version of the guidelines published by the UK Royal College of Obstetricians and Gynaecologists.³⁵ It is unlikely that sufficiently powered treatment studies will be performed to demonstrate a reduction in the complication rate of adult chicken pox, or a reduction in fetal varicella syndrome, but the suggested drug regimens have a good safety record. Furthermore, the demonstrated reduction in the number of days with fever and the number of vesicles has potential economic benefits for the workforce.²⁹

The flowchart on management of chickenpox in the adult has been designed for patients presenting to primary care or an emergency admissions service. Perceptions of chickenpox as a mild disease of childhood lead to an underestimation of its potential to cause severe disease in adolescents and adults. This flowchart will facilitate early initiation of treatment, the evidence for which is presented above. A flowchart for the management of susceptible individuals following exposure to chickenpox is already available in the UK in the Department of Health 'Green Book'⁴³ and from the Health Protection Agency.⁵⁰

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