SOUTHAMPTON Children's Hospital

Wessex Paediatric Oncology Guidelines: Management of viral infections, viral prophylaxis and vaccination guidance

Scope
This guideline applies to all Paediatric Oncology patients in the region. It does not apply to neonates on neonatal units.

Purpose
Children receiving treatment at the Southampton Paediatric Oncology Principal Treatment Centre (PTC) have open access to the designated Paediatric Oncology Ward at either the PTC or their Paediatric Oncology Shared Care Unit (POSCU) Hospital. Their parents/carers will be in possession of contact details for these wards and have been instructed to contact them for any medical problems that arise while they are receiving treatment. These Guidelines are intended for the use of the medical teams at the PTC or POSCU. If one of the Paediatric Oncology patients presents to a medical service outside of the PTC or POSCU, please contact the medical teams at the PTC or POSCU for advice.

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***Updated version 1.2 with vaccination flow-charts separated out please destroy previous versions. ***

5. Viral Infections - post-exposure prophylaxis and anti-viral treatment

All children with a new diagnosis of malignant disease must have their immune status with regard to viral infections determined from a history and serology (Varicella, Measles, CMV, EBV and Toxoplasma). The results of these should be completed on the oncology "patient information sheet" in the front of the notes. This blood test must have been done before any blood transfusions to reliably confirm immunity.

Most viral infections, including measles and varicella-zoster, are primarily controlled by T-cell mediated immunity. This means that individuals affected by T-cell immune deficiencies are at highest risk of developing severe disease; on the contrary, agammaglobulinemic patients resolve these infections similarly to persons who are immunocompetent. Despite being inefficient in controlling viral infections, antibodies play a major role in preventing them (mainly by binding to viral antigens, thus blocking cellular entry of viruses) and consequently are used for post-exposure prophylaxis. However, if breakthrough infection occurs, individuals with severe defects of cell-mediated immunity may develop severe disease despite post-exposure prophylaxis with immunoglobulins.

For all dosing regimens for anti-viral medications please consult drug dosing table in Appendix X chapter on febrile neutropenia.

5.1. Chickenpox

Chicken Pox is highly infectious and is transmitted directly by personal contact or droplet spread or indirectly via fomites. Vesicles appear on the face & scalp, spreading to trunk and abdomen, and eventually to the limbs. Healthy children are contagious from 2 days prior to the onset of the rash until spots are dry, although this may be prolonged in immunosuppressed children. Incubation period is 11-20 days (or up to 28 days if the patient has received VZIG). In the home the secondary infection rate from a case of chicken pox can be as high as 90%. Occasionally susceptible individuals may develop chickenpox after contact with shingles: either if exposed to ophthalmic shingles, or if in contact with an immunosuppressed person with shingles in whom viral shedding can be greater. Infection from contact with an immunocompetent person with non-exposed shingles is unlikely.

Chickenpox in children with cancer can be life threatening, and the infection is associated with a significant number of hospital admissions and treatment delays. It is therefore essential to identify susceptible patients and also non-immune household members:

- At diagnosis it should be recorded in the notes whether the patient (and any siblings) have a definite clinical history of Chicken Pox
- Pre-transfusion VZV IgG status should be checked for all patients at diagnosis

Susceptible individuals:

- All patients who are seronegative at diagnosis – during and for 6 months after any chemotherapy

- All patients who are unlikely to maintain adequate antibody levels from past exposure or vaccination:
    - *patients who have undergone autologous HSCT within last 12 months (regardless of VZV IgG status)*
    - *patients who have undergone allogeneic HSCT within last 18 months, and for at least 12 months after all immunosuppression (regardless of VZV IgG status)*

- Patients who are VZV IgG positive at diagnosis can be assumed to be immune unless less they undergo HSCT, and repeat VZV IgG testing of (e.g. at exposure) is **not** routinely recommended.

Significant exposure

The risk of acquiring infection from an immunocompetent individual with non-exposed shingles is remote. Contacts with Chicken Pox, exposed shingles or non-exposed shingles in an immuncompromised individual are considered significant if:

- *Chicken Pox;* within 48 hrs before onset of rash until no new lesions cropping / crusting of lesions
- *Shingles:* from day of onset until crusting of lesions.

and

- in the same room (or hospital bay/classroom) as infected individual for 15 minutes or more, or if any direct face-to face contact.

Prevention of Chicken Pox:

- The family should be encouraged to immunise household contacts over 1 year of age that have not had Chicken Pox, ideally organised via the family GP if possible. There is a small risk of vaccine-related Varicella; if this does occur the immunocompromised patient should be given prophylactic VZIG (see below).

- *Post-exposure prophylaxis* is recommended for **susceptible** children who have had a **significant exposure** to chickenpox. VZIG, aciclovir and intravenous normal Immunoglobulin and aciclovir can call be used as post-exposure prophylaxis. In Southampton, VZIG is generally used as currently insufficient evidence to guide whether VZIG or aciclovir is superior as first line post-exposure prophylaxis, with additional. In Southampton, VZIG has historically been used as post-exposure prophylaxis, but many UK oncology centres recommend oral aciclovir occasionally added in very high risk patients (post-allogeneic HSCT), but there is national variation in practice. Either is therefore acceptable and a local choice can be made depending on parental preference, anticipated compliance with oral medication etc. See flow chart below, as well as *Appendix A, "VZIG risk assessment and prescription form",* available as individual document on UHS Staff Net). VZIG can be given at the POSCU or PTC.

    - For non-HSCT patients re-check VZV IgG at time of exposure to confirm still negative, and give VZIG within 7 days (ideally within 4 days) of exposure. (ideally with 96 hours). If patient is now VZV IgG positive then observe and do not give VZIG or aciclovir.

    - If post-HSCT (as defined above) VZV IgG re-testing is not needed. If VZIG is chosen as prophylaxis this should be administered as soon as possible after contact and should not be delayed past seven days after initial contact. If oral aciclovir is to be given then this should be administered from 7-21 following the contact.

    - In severely immunocompromised (e.g patients post-allogeneic HSCT still receiving immunosuppresion), aciclovir should be discussed with virologist, and may on

occasion be considered for aciclovir in addition to VZIG (VZIG as soon as possible after exposure and aciclovir for 2 weeks starting from day 7 post-exposure), after discussion with PCT and / or virology consultant.)

About half of susceptible immunosuppressed home contacts will develop clinical chicken pox despite VZIG prophylaxis and a further 15% will be infected sub-clinically (and therefore will seroconvert).

Importantly, patients without history of chickenpox or VZV immunisation who are VZV IgG positive from a recent blood transfusion or immunoglobulin infusion do not require VZIG for that contact with chicken pox. However, this may only provide temporary immunity and re-testing of serology on each exposure is therefore recommended (in contrast to patients who are VZG IgG positive at diagnosis where immunity can be assumed to be maintained)

See flow chart after exposure to Varicella

VZIG is given by intramuscular injection or by deep subcutaneous injection in case of bleeding disorders**,** and provides protection for 3-4 weeks.

If for any reason, you cannot get antibody status confirmed within the time period to give VZIG, then at least take sample for future reference, but do not delay administration of VZIG.

VZIG is now prepared from plasma sourced from outside UK. In Southampton it is kept in pharmacy. VZIG can be prescribed by filling the VZIG risk assessment and prescription forms available on the UHS staff net (see appendix A of this document). Both risk assessment and prescription forms should be handed to UHS Pharmacy and the on call pharmacist will supply VZIG where necessary (leave till next working day, unless over a long weekend this leads to an unnecessary delay). POSCU's will have local policy for acquiring VZIG.

Information to give to parents after VZIG:

- Child can still develop Chicken Pox despite having had VZIG
- After VZIG, the incubation period is prolonged, up to 28 days.
- If the child develops Chicken Pox will need admission for IV aciclovir
- Protection will last for 3-4 weeks, re-exposure after that point will require re-testing of immunity and further dose of VZIG if VZV IgG negative.

Alternatives to VZIG:

Many UK paediatric oncology centres use oral aciclovir as first line post-exposure prophylaxis and there is currently no evidence to guide whether this of VZIG offers better protection. **Oral aciclovir** is cheaper than VZIG and avoids the need for IM injections or blood products. It is therefore an acceptable alternative to VZIG. Oral aciclovir should be given from 7 – 21 days following initial contact.

Treatment of Chicken Pox

If an immunosuppressed child develops what appears to be chicken pox, but there is doubt, the diagnosis may be confirmed by swabbing the skin lesions (swab must be sent in viral transport medium) and by sending the sample to virology for VZV PCR. Blood (EDTA) for VZV PCR is an alternative if no vesicular fluid. If in doubt, it is safest to admit the child, and treat as if chickenpox. The course of aciclovir may be terminated early if chicken pox subsequently seems unlikely. If it is clearly chicken pox it is not necessary to collect vesicle fluid.

If patient develops chickenpox, admit, start **iv aciclovir** and stop all cytotoxic drugs, including steroids.

Valaciclovir has a better bioavailability than oral aciclovir and may be considered as an alternative treatment to IV or oral aciclovir, once the lesions are improving:

5.2. Shingles

Herpes zoster is caused by reactivation from latency of the patient's Varicella-zoster virus. The risk of acquiring infection from an immunocompetent individual with non-exposed zoster lesion is remote. In an immunosuppressed patient the viral shedding may be greater even from covered areas. Exposed lesions e.g. ophthalmic zoster also represent a risk and seronegative patients in contact should be given VZIG.

Immunocompromised patients who develop shingles are at less risk from this than chicken pox, and can usually be treated on an out-patient basis with oral aciclovir. Consider discontinuing chemotherapy. If lesions not healing or progressing stop chemotherapy (if haven't already done so) and give IV high dose aciclovir (as for Chicken Pox).

Valaciclovir has a better bioavailability than oral aciclovir and should be considered.

5.3. Measles

Measles is highly infectious and can be a fatal disease, particularly in the immunocompromised.

Prodromal period consisting of fever, malaise, cough, coryza, and conjunctivitis is followed by erythematous, macular rash, starting at head and spreading to trunk and limbs over 3-4 days. Koplik spots may appear in mouth 1-2 days before rash. Rash is frequently absent in immunocompromised patients.

Incubation period is usually 10 days (range 7-18) with a further 2-4 days before rash appears. Children are contagious from the onset of prodromal symptoms until 4 days after the onset of the rash. Diagnosis may be confirmed on IgM from blood or saliva or by PCR (throat swab, NPA): see Appendix B.

Prevention of measles (please see Appendix B, also available on the UHS staff net):

- Measles immunisation is contraindicated in immunosuppressed patients, and should not be given until at least 6 months after completion of chemotherapy (longer for HSCT).

- Siblings / household contacts who have not been immunised should receive MMR vaccination – *vaccine-acquired infection can not be transmitted*.

- Post-exposure prophylaxis: should be considered if **significant contact** in **susceptible** individual:

Significant contact with measles:

- play or direct contact for more than 15 minutes with an individual with virologically confirmed or clinically diagnosed measles (every attempt should be made to confirm the diagnosis) **during the infectious period** (from up to 4 days prior to, to 4 days after, the onset of the rash)

Susceptible individuals:

- **All children** who are measles **IgG negative at diagnosis** should be assumed to be **susceptible**. Please note that infants, particularly if younger than 6 months, may be measles IgG positive due to the presence of passively acquired maternal antibodies. Test measles IgG at exposure and give Human Normal Immunoglobulin (HNIG) if negative.

- **All children with ALL** (during and for 6 months after treatment) and all patients **post-HSCT** (12 months post-autograft, at least 12 months after all immunosuppresion for allogeneic HSCT) **should be assumed to have lost any pre-existing immunity and be susceptible**. Test measles IgG at exposure and give Human Normal Immunogloubulin (HNIG) if negative.

- Other children receiving standard chemotherapy or radiotherapy are likely to have maintained adequate levels of immunity if IgG positive at diagnosis. Test measles IgG at exposure and only give Human Normal Immunogloubulin (HNIG) if negative.

Administration of **Human Normal Immunoglobulin (0.15 g/kg by intravenous infusion)** should not be delayed beyond 3 days of exposure. However, for this group, IV HNIG may still be considered beyond six days after exposure.

- Protective effects of HNIG last approximately 3 weeks, consider further doses of NHIG if re-exposure to measles after this period.

- Non-immune healthy family members exposed to measles may be given a dose of MMR within 3 days of contact. Those receiving MMR after an exposure may develop a rash because of either true measles (infectious) or because of a vaccine-associated measles (non-infectious). Any rash, which develops in the 18 days after exposure should be assumed to be caused by wild type measles virus infection and appropriate measures taken. See appendix B for details about measles testing (IgM, IgG and PCR).

5.4. Immunisations for oncology patients: ***Based on CCLG guidelines published Dec 2014 incorporating changes from updated version December 2016.***

5.4.1 Standard chemotherapy for leukaemia & solid tumours

General principles:

- Avoid all live vaccines in patients receiving chemotherapy and for 6 months afterwards.
- Avoid administration of live vaccines to siblings, **except** MMR, Varicella, live attenuated Influenza and Rotavirus (during chemotherapy and for 6 months afterwards).
- Inactivated influenza vaccine should be offered to all patients. This should be given as soon as available in the autumn (during treatment and for 6 months after). Household contacts should be offered vaccination, and may receive live attenuated influenza vaccine if appropriate for their age.
- Consider administration of non-live vaccines according to the childhood immunisation schedule, providing the child's general condition is stable (ie free from infection & major organ toxicity) and is expected to stay so for 3 weeks after immunisation. Although it is likely that responses will be suboptimal, some patients may achieve protective antibody levels. Avoid during periods of steroid administration. Realistically most patients on short term chemotherapy will therefore have their immunisations delayed until after completing chemotherapy, but in patients on ALL treatment there may be a window of opportunity to immunise whilst on maintenance chemotherapy – discuss with consultant first if considering immunisation at this stage.

Please see separate flow-charts for printable re-vaccination schedules for patients after chemotherapy and after HSCT.

5.4.2. Intensive chemotherapy & haemopoetic stem cell transplantation (HSCT)

Re-immunisation should be considered from 12 months after HSCT, provided there is no evidence of GvHD, the patient is off all immunosuppressive treatment for at least 6 months and has not received any IVIG for at least 3 months. The BMT unit responsible for the patient may give individual recommendations as to when they are happy for immunisation to commence. To see our recommendations please see separate flow-chart.

5.5 Other immunisations:

5.5.1 Varicella vaccine

Live attenuated Varicella vaccine of immuncompromised individuals is not routine recommended in the UK, and is associated with a risk of vaccine-related Varicella. In the US varicella vaccination is recommended to all children with ALL in maintenance, 12 months after documented remission (using 2 doses, checking several months later that seroconversion has taken place. They recommend interrupting chemotherapy for 1 week before & after the first dose (but not the second), timing the immunisation such that it is not within a week of the steroid pulse, with a lymphocyte count as above.

Its use may therefore occasionally be considered in certain individuals, provided lymphocyte count is $> 0.7 \times 10^9$/l and immunosuppressive therapy is withheld for 1 week prior to and 1 week after the first dose and no steroids are given for the following 2 weeks. The oncology or haematology consultant must prescribe this if it is to be given.

5.5.2 Influenza vaccine

Influenza vaccine is recommended in the autumn for all patients receiving chemotherapy and in first 6 months after completing treatment. Patients who have received allogeneic HSCT should continue to receive annual immunisation indefinitely.

Immunocompromised patients should receive the inactivated vaccine, administered as an IM injection. The intranasal preparation is a live attenuated vaccine, and should not be administered to immunocompromised patients, but can be administered safely to siblings over 2 years of age. There have been no reported incidences of transmission of flu from those given the intranasal vaccine.

Ideally immunisation should be performed when the child is not neutropenic and not in the 48-hours before intravenous chemotherapy or while the child is taking a course of steroids.

Immunocompromised children age 6 months – 9 years who have not received Influenza immunisation previously should receive 2 doses (at 4 week interval) in first year.

Family members should also be the immunised, especially those of high risk patients such as those undergoing HSCT.

Appendix A

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Varicella zoster Immunoglobulin for post-exposure prophylaxis (PEP)

Please note that UHS Pharmacy will issue VZIG only when both
RISK ASSESSMENT and PRESCRIPTION FORM are completed and handed in

RISK ASSESSMENT FORM: PAGE 1, 2 AND 3 PRECRITPION FORM: PAGE 4 INFORMATION LEAFLET FOR PREGNANT LADIES:

EXPOSURE TO VZV: Risk assessment form to establish if the patient needs PEP with VZIG

VZIG should be prescribed and administered **only** to individuals who satisfy all of the following 3 criteria:

1. Are **at risk of developing severe varicella-zoster virus (VZV) infection** (see table 1 for part 1 of risk assessment)
2. Are **varicella-zoster IgG seronegative** (see table 2 for part 2 of risk assessment)
3. Have had **a significant exposure to VZV** (see table 3 for part 3 of risk assessment)

FALSIFYING THIS RISK ASSESSMENT MAY RESULT IN A PATIENT RECEIVING VZIG INAPPROPRIATELY, PUTTING THEM AT UNNECESSARY RISK OF ANAPHYLAXIS. RISK ASSESSMENTS ARE RETROSPECTIVELY REVIEWED.

Table 1. *Does this patient fall into the categories of individuals at risk of developing severe VZV infection?*

Categories of individuals at risk of severe VZV infection (please tick)		YES	NO
A) Pregnant women *VZIG prevents disease when given within 10 days of 1st exposure*	**? Pregnant women** within 10 days of exposure to chickenpox or shingles *Report date of first contact (mandatory) ___/___/_____*	[]	[]
B) Neonates and Infants *VZIG should be administered as soon as possible after contact and should not be delayed past seven days after initial contact.*	**? Neonate** of mother developing chickenpox (but not shingles) in the period between 7 days before and 7 days after delivery. *Report date of onset of chickenpox in the mother (mandatory) ___/___/_____*	[]	[]
	? Neonate of seronegative mothers exposed to chickenpox or shingles during the first 7 days of life. *Report date of first contact (mandatory) ___/___/_____*	[]	[]
	? Premature (< 28/40) and/or very low birth weight (< 1 Kg) infant irrespective of maternal VZV IgG status ***OR*** **Infant of any age** exposed to chickenpox or shingles while still requiring intensive or special care, irrespective of maternal VZV IgG status. *Report date of 1st contact (mandatory) ___/___/_____*	[]	[]
C) Immune-Compromised Patients *VZIG should be administered as soon as possible after contact and should not be delayed past seven days after initial contact.*	**? Immunocompromised patient** exposed to chickenpox or shingles *Report date of first contact (mandatory) _____/_____/_____*	[]	[]
	IMMUNOCOMPROMISED PATIENTS INCLUDE	PLEASE TICK	
	Individuals with **severe primary immunodeficiency** (e.g. severe combined immunodeficiency –SCID-, Wiskott-Aldrich syndrome and other combined immunodeficiency syndromes);	[]	
	Patients with **malignancies on immunosuppressive chemotherapy or radiotherapy**, and for at least six months after terminating such treatment;	[]	
	Solid organ transplant recipients on immunosuppressive treatment;	[]	
	Bone marrow transplant recipients until at least 12 months after finishing all immunosuppressive drugs;	[]	
	Patients on **systemic high-dose steroids** until at least three months after treatment has stopped. This includes CHILDREN on (oral or rectal) prednisolone (or its equivalent) 2mg/kg/day for at least one week, or 1mg/kg/day for one month and ADULTS on 40mg/day of prednisolone for more than one week. Occasionally, individuals on lower doses of steroids may be at increased risk of infections	[]	
	Patients on **other types of immunosuppressive drugs** (e.g. azathioprine, ciclosporin, methotrexate, cyclophosphamide, leflunomide and the newer cytokine inhibitors) alone or in combination with lower doses of steroids, for at least six months after treatment	[]	
	Patients with immunosuppression due to **HIV infection:** CD4 count < 500 in children less than 5 years of age and CD4 count < 200 in individuals older than 5 years. Please note that CD4 count may not be an accurate representation of the level of immunosuppression. If in doubt contact Virology / Immunology / Genitourinary Medicine / Paediatrician specialist in HIV.	[]	

Risk assessment: requires the "YES" answer in box A or B or C

Table 2. ***VZV IgG status: Is this patient VZV IgG seronegative?*** **Please tick as appropriate**

Please note that: → The immune status of immunocompetent **pregnant women,** without a past history of chickenpox, can be determined by testing the remaining of the samples used for the antenatal screening for infection (stored for the duration of the pregnancy), if there is enough left. **Pregnant contacts with a positive history of chickenpox do not require VZIG** → **Immunosuppressed contacts** should be always tested, irrespective of their history of chickenpox. → The determination of the serostatus to VZV is performed in the Serology Laboratory (Mondays to Fridays from 9am to 5pm and Saturday mornings from 9am to 11 am). → Clotted blood or EDTA blood samples are suitable for antibody test. → Please communicate to the **Serology Laboratory (tel. No 023 8120 6342)** that a sample for urgent testing has been collected. → It can be requested as urgent test (**result available within 1 hour of sample receipt**)	**Sero-Negative** (Eligible for VZIG) []	**Sero-Positive** (NOT eligible for VZIG) []

The VZV IgG statues for some individuals exposed to VZV can be assumed from the patients' history without performing VZV IgG antibody testing (tick below as appropriate)	
The exposed individual is the **Neonate of mother who has developed chickenpox in the period 7 days prior to 7 days post delivery** PLEASE NOTE THAT NEONATES, WHOSE MOTHER DEVELOPS VARICELLA BEWTEEN 4 DAYS PRIOR DELIVER TO TWO DAYS POST DELIVERY, NEED **ACICLOVIR PROPHYLAXIS IN ADDITION TO VZIG**. ACICLOVIR SHOULD BE ADMINISTERD INTRAVENOULSY FOR 7 DAYS AT A DOSE OF 10MG/KG THREE TIMES/DAY.	**These babies are VZV IgG negative and need VZIG** []
The exposed individual is a **Neonate who has been in contact with chickenpox or shingles during the first 7 days of life and whose mothers are seronegative**.	**These babies are VZV IgG negative and are eligible for VZIG** []
Individuals who are unlikely to have developed or to maintain adequate antibody levels from past exposure or vaccination. They include: • Stem cell transplant recipients until 12 months after discontinuation of all immunosuppressive treatment, or longer, in case of graft-versus-host disease, • ALL patients on chemotherapy and until at least six months after its completion	**These patients are regarded as VZIG negative (unless already on replacement immunoglobulin therapy)** []
The exposed individual is an **immunocompetent pregnant woman with history of chickenpox**.	These patients are VZV IgG positive and do not need VZIG []
The exposed individual is an **immunocompromised patient regularly on replacement immunoglobulin therapy**	These patients are VZV IgG positive and do not need VZIG []
If VZV IgG result cannot be obtained → Within seven days of exposure in immunocompromised patients and infants ***OR*** → Within 10 days of exposure in pregnant women (This happens when patients report to the clinicians the exposure to VZV near the end of the window period for administering VZIG post exposure prophylaxis and the testing laboratory is closed – i.e. Saturday afternoons, Sundays and Bank holidays), UHS Pharmacy will issue VZIG even if the VZV serostatus has not been determined (unknown VZV IgG status).	**VZV IgG testing cannot be performed early enough to inform management** []
Risk assessment: requires seronegative status or unknown (yellow boxes)	

Table 3. *Has this patient had a significant contact with VZV?*

Assessment of significant exposure to VZV (please tick):		**YES**	NO
A) Type of VZV infection in the index case *(Indicative of extent of viral shedding and risk of exposure)*	**? Index case has chickenpox** or **disseminated zoster**	[]	[]
	? Index case is an immunocompetent individual with exposed zoster lesions (e.g. ophthalmic zoster) **with or without continuous home contact with the patient at risk**	[]	[]
	? Index case is an immunocompetent individual with lesions at any part of the body and with continuous home contact with the patient at risk (In these cases a significant contact may derive from non-exposed zoster lesions)	[]	[]
	? Index case is an immunosuppressed patient, with zoster lesions on any part of the body (in whom viral shedding may be greater)	[]	[]
B) Timing of exposure in relation to onset of rash in index case	**? Exposure to chickenpox or disseminated zoster in the period between 48 hours before onset of rash until cropping has ceased and all lesions are crusted.** (Please note: the index case is infectious between 48 hours before onset of rash until cropping has ceased and all lesions are crusted).	[]	[]
	? Exposure to localised zoster from the day of onset of rash until crusting. (Please note that the index case is infectious from the day of onset of rash until crusting).	[]	[]
C) Closeness and duration of contact	**? Maternal/neonatal** (always significant exposure)	[]	[]
	? Continuous home contact (always significant exposure)	[]	[]
	? Contact in the same room (house or classroom or a 2-4 bed hospital bay for at least 15 minutes)	[]	[]
	? Face-to-face contact (for example while having a conversation)	[]	[]
	? Large open wards: please note that air-borne transmission at a distance has occasionally been reported in large open wards. In this case administration of VZIG to all susceptible high-risk contacts should be considered.	[]	[]
Risk assessment: requires ≥ one "YES" answer in all 3 boxes (A, B and C).			

Risk assessment for administering VZIG			***Date***
Performed by (block letters)	***Doctor's signature***	***Designation***	***Department/Surgery***
Patient's name	***Patient's date of birth***	***Patient's address / Ward***	
	Hospital number		

All of the following are required:	*Please tick below as appropriate:*	
Table 1: "Yes answer" to one of the 3 boxes ("box A" or "box B" or "box C")	**YES**	NO
Table 2: "VZV IgG Seronegative status" (or "Not determined")	**YES**	NO
Table 3: ≥ one "Yes" answer in all 3 boxes ("box A" and "box B" and "box C")	**YES**	NO

If ALL THREE answers above are "Yes", the Patient REQUIRES VZIG.
Go to page 4 of this document to prescribe VZIG

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Please note: VZIG is issued only when the UHS Pharmacy receives VZIG PRESCRIPTION & the RISK ASSESSEMENT FORMS (required for VZIG returns to the Department of Health
Deliver or Fax (023 8120 6792) prescription and risk assessment forms to main dispensary Southampton General Hospital. If faxed, the original prescription will need to be received by pharmacy within 72 hours.
Out of hours contact the Pharmacist on call through UHS switchboard (Tel 023 80 777 222)

Prescription for Supply of Varicella-Zoster Immunoglobulin (VZIG) for Post-Exposure Prophylaxis

Patient Details

Patient Forename	*Patient Surname*	*Date of Birth*	*NHS or Hospital number*
Patient's Address			

Product Details

Product (including form and strength where necessary)	*Quantity (see table below)*
Varicella zoster Immunoglobulin	

Directions		
	Deep intramuscular injection []	**Deep subcutaneous injection in patients with bleeding disorder []** **Please state kind of bleeding disorder**

Authorising details This section must be completed by the doctor who performed the risk assessment

Name (in block letters)	*Designation*	*Contact number*
Signature	*Ward/Surgery*	*Date*

Collection/Delivery Method: *Please check that arrangements are in place to have the injection(s) administered.* **Please specify**

Patient or Representative collecting []	Taxi or Courier arranged by GP Surgery or Other Hospital []	UHS Pharmacy can send the product to UHS A&E by prior arrangement (A&E phone No available through UHS switchboard). Please state name and contact details of A&E Nurse or Consultant with whom VZIG treatment administration has been agreed.

Pharmacy Use Only **Make sure that VZIG vials are stored within are the cold chain until use**

Screened by	Dispensed by:	Checked by:	Product details:	**Batch No**	**Date:**
			VZIG		**Essential record keeping** **Log details of this supply in the immunoglobulin register. Ensure one copy is made (for the patient/healthcare professional) The original prescription and risk assessment form needs to be filed in the IM immunoglobulin folder. Please file appropriately immediately after checking**

Cost code Inpatients: Ward Outpatients: Pathology SGH	**Stock location** **Fridge, SGH main dispensary**	**Expiry date**	**No of vials**

VZIG treatment details

Dosage		***Timing***
0 – 5 Years	***250mg (1 vial)***	***Pregnant women: within 10 days of contacts.***
6 – 10 Years	***500mg (2 vials)***	***All other vulnerable individuals: as soon as possible after exposure.***
11 – 14 Years	***750mg (3 vials)***	***Give second dose if further exposure occurs and three weeks have lapsed since first dose.***
15 years and older	***1000mg (4 vials)***	

Please note:

Incubation period can be prolonged up to 28 days in exposed individuals treated with VZIG. This should be considered for infection prevention purposes, in case of future hospital appointments.

Severe or fatal varicella can still occur despite VZIG prophylaxis.

Patients developing chickenpox despite VZIG post-exposure prophylaxis should be promptly assessed and acyclovir treatment should be considered. Treatment and route of administration (oral or IV) should be decided according to the patient's immune status and to the severity of the disease.

In some circumstances acyclovir post exposure prophylaxis (PEP) is recommended in addition to VZIG PEP. These cases include:
1) Neonates whose mother has developed chickenpox between 4 days prior to two days post delivery: intravenous acyclovir, 10mg/kg three times/day for 7 days.
2) Severely immunocompromised patients: oral (if drug absorption is not compromised) acyclovir, 800mg 5 times/day for 14 days, or valacyclovir 1 g 3 time/day (valacyclovir is a pro-drug of acyclovir and has a better oral bioavailability) starting 5-7 days after contact. Duration of acyclovir/valacyclovir PEP: 10 days

Dr Emanuela Pelosi, Consultant Virologist, Department of Infection, University Hospital Southampton NHS Foundation Trust: "VZIG, Risk assessment and Prescription forms", updated 11th May 2015

Appendix B

University Hospital Southampton NHS
NHS Foundation Trust

Measles testing and measles post-exposure prophylaxis at University Hospitals Southampton NHS Foundation Trust (UHSFT)

Measles

- The **incubation period** is about 10 days (ranging between 7 and 18 days).
- The **prodromal stage** lasts for 2 to 4 days before the onset of rash and is characterised by the onset of fever, malaise, coryza, conjunctivitis and cough.
- The **rash** is erythematous and maculopapular, starting at the head and spreading to the trunk and limbs over three to four days. Koplik spots (small red spots with bluish-white centres) may appear on the mucous membranes of the mouth one to two days before the rash appears and may be seen for a further one to two days afterwards. Koplik spots are pathognomonic of measles.

  Rash may be absent in immune compromised patients who may present with unexplained pneumonia or encephalitis.
- The following combination of features is strongly suggestive of measles:
  - Rash for at least three days
  - Fever for at least one day, and
  - At least one of the following: cough, coryza or conjunctivitis.
- Measles is spread by **airborne or droplet transmission**.
- **Period of infectiousness**: from the beginning of the prodromal period (when the first symptoms appear) to four days after the appearance of the rash. It is one of the most highly communicable infectious diseases.

A. Measles testing at UHSFT:

Please report patient's clinical details on the request form, including date of onset of rash. Please note that rash may be absent in immune compromised patients			
Test available on Equest Virology	**Measles IgG*** (performed at UHS)	**Measles PCR** (performed at UHS)	**Measles IgM** (performed in Colindale**)
Indications for requesting the test	To check for evidence of protection* to measles virus (past infection or vaccination) in asymptomatic individuals	To check for presence of measles RNA in symptomatic individuals. Detectable from symptoms onset (prodromal period) and first 5 days after onset of rash	To check for early antibody response in symptomatic individuals. Normally detectable from day 3 after rash onset
Type of sample	Clotted blood	Throat swab transport medium (VTM), Nasopharyngeal aspirate and Urine (the latter is less reliable)	Clotted blood
Turnaround time	3 hours from sample receipt during working hours, Mondays to Saturday morning. For same day results send samples not later than 3:30 pm. Please phone Serology on ext. 6342 to discuss urgent testing	24 hours from sample receipt, Mondays to Fridays. For same day results please phone the laboratory on ext. 6408 to discuss	24-48 hours from sample receipt in reference laboratory during working hours.

* Measles IgG Elisa: the cut off value for the assay is equivalent to 175 mIU/ml (well above the protective measles IgG level is > 120 mIU/ml). **Satisfactory evidence of protection in immunocompetent individuals** would include documentation of having received two doses of MMR, or positive antibody tests for measles IgG.

**The Immunisation & Diagnostic Unit at Colindale, Public Health England (telephone number 0208327 6253).

B. Post exposure prophylaxis

- **Human Normal Immunoglobulin (HNIG)** indicated to prevent or attenuate an attack in
  - Immune compromised contacts
  - Pregnant women
  - Infants under the age of 6 months
- **MMR vaccine** indicated to prevent an attack in immune competent individuals (children over the age of 6 months and adult; there is no upper age limit)

<table>
<tr><td colspan="4">Measles post exposure prophylaxis</td></tr>
<tr><td colspan="4">Incubation period for onset of prodromal symptoms: 7-18 days (average: 10-12 days)
Period of infectiousness of measles: from 4 days prior to 4 days post onset of rash</td></tr>
<tr><td colspan="4">HNIG (available from UHSFT Pharmacy)</td></tr>
<tr><td colspan="4">Where a second exposure occurs more than three weeks after a first dose of HNIG, a further dose should be given</td></tr>
<tr><td>Immunocompromised patients (any age) not on IV HNIG replacement treatment.
See also Appendix</td><td>Direct exposure for a very short time (minutes) OR not direct exposure such as entering a room within a short period after a measles case has left</td><td>Administration should not be delayed beyond 3 days of exposure. However, for this group, IV HNIG may still be considered beyond six days.</td><td>0.15 g/kg of intravenous HNIG (Flebogamma) **
OR
0.6 ml/kg of HNIG by subcutaneous infusion or intra-muscular injection (Subgam) **</td></tr>
<tr><td>IgG negative infants below the age of 6 months</td><td rowspan="2">Face-to-face contact (irrespective of the time of exposure)
OR
Exposure for 15 minutes or longer in the same room</td><td rowspan="2">Most effective if given within 72 hours of exposure, but may still be effective if given within 6 days</td><td>Infants: 0.6 ml/kg of HNIG up to maximum of 1 vial, by subcutaneous infusion or intra-muscular injection (Subgam) **</td></tr>
<tr><td>IgG negative pregnant women who do not have history of vaccination@ &</td><td>Pregnant women: 2,250 mg of HNIG (3 vials), by subcutaneous infusion or intra-muscular injection (Subgam)**</td></tr>
<tr><td colspan="4">MMR vaccine ***</td></tr>
<tr><td colspan="4">Within 3 days of contact (MMR can be given during incubation of measles and in individuals already immune)</td></tr>
<tr><td>Unvaccinated healthy children over 6 months of age and adults&

Including HCWs and family contacts</td><td>Face-to-face contact (irrespective of the time of exposer)
OR
Exposure for 15 minutes or longer in the same room</td><td colspan="2">Where exposure is ongoing (for example following a single case in a nursery or during a community outbreak), MMR offered beyond three days may provide protection from subsequent exposures.

Individuals who have received only one previous dose of MMR may be given a second dose provided there is an interval of at least one month from the first dose.

Children under 12 months of age should also receive 2 MMR vaccines above a year of age as per the normal schedule of childhood vaccinations.</td></tr>
</table>

@ HNIG may attenuate the infection in the mother and (although no direct evidence) an attenuated maternal infection is likely to have a reduced risk of fetal loss.

** To be administered by subcutaneous infusion or intra-muscular injection: **Subgam (BPL)**, ideally in divided doses at different sites; by intravenous infusion: **Flebogamma DIF** (Grifols).

*** MMR vaccine should not be administered to individuals who had anaphylactic reactions to previous doses of measles, rubella or mumps containing vaccines, who are allergic to neomycin and gelatine and to pregnant women.

& **For healthy individuals, satisfactory evidence of protection** includes:
documentation of having received **two or more doses of measles containing vaccine** and/or **positive measles antibody test, past history of measles.** Over 90% of UK adults are measles IgG positive (99% of healthy individuals born before 1970 are measles IgG positive following natural infection while about 90% of those born between 1970 and 1989 are measles IgG positive following natural infection or vaccination).

Infection control considerations

Please note that appropriate infection control procedures should be followed in health care settings, considering that neither immunoglobulin nor single dose measles vaccine are 100% effective in preventing measles. Therefore, exposed patients in hospital should be isolated from 6 days following exposure until 19 days post exposure, despite post-exposure prophylaxis.

Healthcare workers: protection of healthcare workers from measles is important both for their own benefit and also for the benefit of their patients (i.e. prevention of transmission of measles infection to vulnerable patients). See on page 2, bottom: "satisfactory evidence of protection".

Appendix

Classification of immune suppressed individuals

Group A	Group B
Individuals able to develop and maintain adequate antibody level from any prior successful vaccination or infection. Can therefore be managed on the basis of reliable history or previous measles IgG test results. For those with unknown status at the time of exposure, management on the basis of history and rapid antibody testing is recommended	Individuals who are unlikely to have developed or to maintain adequate antibody levels from past exposure or vaccination. Unless already on replacement immunoglobulin therapy, these patients would require urgent testing within three days of exposure, regardless of a past history or a previous positive measles antibody result.
• Patients with **malignant disease, other than those in group B**, for six months after completion of immune suppressive chemotherapy or radiotherapy • Solid organ transplant recipients on immune suppressive treatment • Patients on **systemic high-dose steroids**, until three months after discontinuation of treatment. This includes: **CHILDREN**: oral or rectal prednisolone, at a daily dose (or its equivalent) of 2mg/kg/day for at least one week, or 1mg/kg/day for one month. **ADULTS:** at least 40mg of prednisolone per day for more than one week • HIV positive patients who do **not have AIDS** • Patients on other types of immunosuppressive drugs (e.g. azathioprine, cyclosporin, methotrexate, cyclophosphamide, leflunomide, anti-TNF alpha and the newer cytokine inhibitors) alone or in combination with steroids, for six months after their discontinuation.	• Acute Lymphoblastic Leukaemia (ALL) patients on chemotherapy and until at least six months after its completion • Bone marrow transplant recipients until 12 months after discontinuation of all immunosuppressive treatment, or longer, in case of graft-versus-host disease (GvHD). • Patients with severe primary immunodeficiency (who would not be expected to have made a good initial response to vaccine or disease in childhood) • HIV positive patients **with AIDS**

Notes

- All immune suppressed patients, not on IVIG replacement therapy, should be assessed at the time of exposure.
- Persons on IV immunoglobulin replacement therapy: IV IG replacement dose, received in the 3 weeks preceding measles exposure, are normally sufficient to prevent infection.
- For people with severe defects of cell mediated immunity, however, passive immunoglobulin may be indicated even in the presence of measurable antibody
- Measles immune status of family contacts of immune compromised patients should be considered: see "satisfactory evidence of protection", page 2, bottom note.

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"Measles testing and post-exposure prophylaxis", Southampton University Hospitals NHS Foundation Trust, October 2013,Updated 11.05.2015