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Reviewed and approved by specialists at the IWK Health Centre, Halifax NS, and the Janeway Children's Health and Rehabilitation Centre, NL.

Guidelines for Varicella Zoster/Herpes Zoster in Immunocompromised Children

APPHON/ROHPPA supportive care guidelines are developed by Atlantic Provinces health professional specialists using evidence-based or best practice references. Format and content of the guidelines will change as they are reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, any physician or health professional using these guidelines will be responsible for verifying doses and administering medications and care according to their own institutional formularies and policies and acceptable standards of care.

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BACKGROUND

Varicella zoster virus is a highly contagious DNA virus. Prior to the introduction of universal varicella vaccine, it presented as chickenpox (varicella) in young children with generalized itchy, vesicular eruptions/rash and fever. The lesions usually first appear on the back of the head and ears, and then spread to the face, neck, trunk and proximal extremities. The number of lesions may vary from 10 to several hundred. Although the vaccine is very effective (1 dose 85% effective, 2 doses 98% effective), breakthrough chickenpox may occur in vaccinated children with fewer skin lesions and milder illness and can be difficult to diagnose. In persons with compromised immune systems progressive varicella can be a serious illness. It may be associated with viremia, dissemination of the virus to lungs (pneumonia), liver (hepatitis) and brain (CNS complications such as encephalitis, transient ataxia, aseptic meningitis, and transverse myelitis). Thirty percent of children with leukemia who develop varicella will have disseminated disease, and the accompanying mortality rate was 7% before the availability of varicella zoster immunoglobulin (VariZIG) (Feldman). Arthritis, glomerulonephritis, myocarditis, and purpura fulminans are other rare complications associated with varicella.

After primary chickenpox infection, the virus becomes latent in sensory ganglia neurons for life. The virus may reactivate, and causes "shingles", also called Herpes zoster. In the immune compromised host reactivation can sometimes also be a systemic infection, similar to chickenpox.

Varicella zoster virus (VZV) spreads from a person with chickenpox via the airborne route from respiratory secretions and direct contact with fluid from lesions. A person with shingles can spread the virus via direct contact with lesions, or by exposure to airborne infectious material. It is possible, although uncommon, to get chickenpox more than once, especially if the first episode was before two years of age.

RISK

Who is at risk? Children who are at high risk for severe or disseminated chickenpox or shingles are those in any of the following patient groups:

- Receiving chemotherapy or radiotherapy, without a previous history of chickenpox illness, or 2 doses of varicella vaccine.
- Known immunodeficiency, or immunosuppressed state (e.g. post solid organ transplant)
- Receiving high doses systemic corticosteroids (≥2 mg/kg per day of prednisone or equivalent) for at least 14 days or long-term pulse corticosteroids (e.g. acute lymphoblastic leukemia including during maintenance therapy where lymphocyte function may be reduced due to long term corticosteroid use)
- Completed chemotherapy within last six months, without a previous history of chickenpox illness, or 2 doses of varicella vaccine.
- Up to 24 months after Hematopoietic Stem Cell Transplant (HSCT) or longer if still on immunosuppression - HSCT patients should still be considered at risk, even with normal levels of IgG, until one year post transplant and off all immunosuppression (for at least 3 months) with good T cell function.

Who is <u>not</u> at risk? Children who have previously received two doses of the varicella vaccine or had a previous history of chickenpox are at low risk for acquiring chickenpox. If the child has serum antibody to varicella, they are considered immune and the risk of acquiring chicken pox is very low. If the child has received blood product transfusion (including IVIG) within the previous 3 months this may result in a false positive serum antibody result to varicella.

DIAGNOSIS

Clinical picture is usually diagnostic in an unimmunized person.

1) Varicella (VZV)
    - There may be a prodrome of cough, coryza, fever and malaise during which the affected person is contagious; this typically precedes the eruption of the rash by 1-2 days.
    - vesicular rash - vesicles, becoming pustules, becoming scabs often associated with fever and intense pruritus
    - can occur anywhere on the body including in the mouth; scalp is often the first area involved
2) Herpes Zoster (HZ) ("shingles" or "zoster")
    - appears as grouped vesicular lesions in the distribution of 1 to 3 dermatomes, often preceded or accompanied by localized pain or parasthesias

Labs

- Lesions: swab in viral transport media (aggressively swab BASE OF LESION(S))
- CSF: send for PCR – for suspected VZV encephalitis; can distinguish wild type strains from vaccine virus (very sensitive).

TRANSMISSION

Varicella is highly contagious and acquired by airborne transmission or direct contact with lesions. It is infectious for 24-48 hours prior to onset of chickenpox and until the last vesicle is scabbed over. The most contagious phase is during the phase of development of the vesicles.

INCUBATION PERIOD

- Usually 14-16 days up to 10-21 days.
- May be prolonged for as long as 28 days after receipt of Varicella-Zoster Immune Globulin (variZIG) or Immune Globulin (IVIG).
- In addition to routine practices, Airborne/ Contact Precautions are required for patients with varicella until all lesions are dry and crusted. In patients with varicella pneumonia, precautions are prolonged for the duration of illness. For immunized patients with breakthrough varicella with only maculopapular lesions, isolation is recommended until no new lesions appear within a 24-hour period, even if lesions have not resolved completely.
- For exposed patients without evidence of immunity, airborne/ contact precautions are required from days 8 until 21 after onset of the rash in the index patient; these precautions should be maintained until 28 days after exposure for those who received variZIG or IVIG.
- May consult Infection Prevention and Control prior to discontinuing isolation precautions.

PREVENTION

The best way to prevent chickenpox is to provide varicella immunization. Children, adolescents, and adults should receive two doses of varicella vaccine

Avoiding contact:

- Avoid visiting anyone with known chickenpox. Avoid contact with anyone who has had contact with an individual with chickenpox during the isolation period (8-21 days, and 8-28 days for those who received variZIG). Communicability period differs from incubation period in that an individual can be contagious for 2 days prior to the onset of rash.
- Avoid school if an outbreak of chickenpox occurs within the school for 21 days following rash onset in the last identified case.
- Notify school to increase school awareness of chickenpox illness in classmates of the child. Notify caregivers and friends of the risk to these children and the necessity of informing the family and the appropriate health care professional of contacts.
- Siblings' immunity should be documented by history of previous disease or vaccination. If not immune, they should be vaccinated at time of child's diagnosis. If siblings have a significant contact with chickenpox and are not immune, allow them to stay at home, and immunize them within 3 but up to 5 days post exposure if vaccine is not contraindicated.
- Airborne (negative pressure) isolation for all admitted cases.

Zoster immunoglobulin (variZIG) *All new oncology patients will have baseline serological testing for varicella immunity (preferably prior to any blood transfusions).*

Administration time of variZIG: Should be given within 72 hours of contact. Maximum 96 hours. Beyond 96 hours consult Infectious Disease.

VariZIG is recommended for the prevention or reduction in severity of infection following recent exposure to the varicella zoster virus. The decision to administer variZIG should be based on fulfilling **<u>ALL</u> of the following four criteria:**

1. The exposed person is susceptible to varicella (including recipients of HSCT who are considered susceptible).
2. There has been a significant exposure to a person with varicella or herpes zoster. The following situations with unprotected exposures to varicella zoster virus are considered significant:
    - continuous household contact (living in the same dwelling) with a person with chickenpox, either with a rash or during the preceding 48 hours of rash development, or being indoors for more than 1 hour with a case of varicella
    - being in the same room for more than 1 hour, or more than 15 minutes of face-to-face contact with a person with varicella
    - touching the lesions of a person with active varicella
    - close contact with herpes zoster (HZ) includes:
        - touching the rash, exposed lesion or vesicle fluid
        - contact with an individual who has disseminated HZ
        - contact with articles freshly soiled by discharges from vesicles
        - contact with articles freshly soiled by mucous membrane secretions of a person with disseminated HZ e.g. swimming pools or hot tubs.

- exposure to an immunocompromised person with localized HZ anywhere on the body as their viral shedding may be greater.

3. The exposed person is at increased risk of severe varicella including:
    - immunocompromised persons (recipients of HSCT regardless of pre-transplant varicella immune status, history of varicella disease or vaccination, or positive serologic test results)
4. Post-exposure immunization with live varicella vaccine is contraindicated.

Who should be considered for passive immunization with variZIG:

1. All patients at risk who have had a significant shingles or chickenpox contact (as defined above). The turnaround time for varicella serology should be within 3 days. If it is possible to obtain varicella titer prior to 96 hours and patient is immune VariZIG should not be given.

History of chickenpox, shingles, or vaccine administration	Baseline Serology	Action
Negative	Negative	Give variZIG
Positive	Negative	Give variZIG
Negative	Positive	Give variZIG
Positive	Positive	No variZIG*

*In acute lymphoblastic leukemia (ALL), loss of IgG to VZV (Manley 2008, Patel 2014, Bochennek 2014) and systemic VZV infection (i.e. not zoster) in patients who were VZV IgG positive at diagnosis ((Manley 2008) have been documented. This may be due to defects in lymphocyte function due to prolonged exposure to chemotherapy agents such as alkylating agents, purine nucleoside analogs and corticosteroids. Children with ALL and lymphoblastic lymphoma, especially in maintenance phase, with exposure to varicella virus should be considered for variZIG.

2. All HSCT recipients at risk who have had a significant contact, regardless of their immune status at diagnosis and who have not received complete series of varicella vaccine post-transplant.

VariZIG Dosing Guidelines:

Patient Weight	Dose (maximum dose 625 units)	Route
10 kg or less	125 units (1 vial)	Intramuscular (IM)
10.1 – 20 kg	250 units (2 vials)	IM
20.1 – 30 kg	375 units (3 vials)	IM
30.1 – 40 kg	500 units (4 vials)	IM
More than 40 kg	625 units (5 vials)	IM

- Effective for approximately 3 weeks. Repeat dose for further exposure more than 21 days after the last dose, if varicella did not develop.
- In addition to routine practices, Airborne/ Contact Precautions will be implemented when presenting to the health centre, (e.g. in clinic or on the wards), from day 8 to day 28 post last exposure.

- Chickenpox may still occur as an attenuated illness. If this occurs, immediately contact a pediatric hematologist/oncologist. It must be treated with antiviral (e.g. acyclovir, valacyclovir).

- If VariZIG is unavailable, or for patients with a bleeding diathesis, intravenous immune globulin (IVIG) 400 mg/kg over 3-4 hours attains an antibody titre approximately equivalent to variZIG.
- Children who have received IVIG within 3 weeks prior to varicella exposure are considered protected and do not require VariZIG.
- Acyclovir can be given starting 7 days after an exposure if VariZIG not available or not given in consultation with Infectious Disease.
- All children treated for ALL who are exposed within 6 months of the end of anti-cancer therapy should be considered to receive treatment with VariZIG.

TREATMENT OF VARICELLA (CHICKEN POX) AND VARICELLA ZOSTER (SHINGLES)

All immunosuppressed patients should consult their physician **immediately** at first signs of chickenpox and shingles infection. Diagnosis is often clinically obvious but in some cases confirmation by direct viral PCR may be required.

Who requires admission to hospital?
Most immunosuppressed children who develop *chickenpox or shingles* **should be admitted to hospital for observation and complete an intravenous course of acyclovir**. A few low risk patients may be treated on an outpatient basis see criteria below (this must be done in consultation with the pediatric oncologist or pediatric infectious disease specialist).

A) Criteria for admission to hospital of child with chicken pox or shingles include:

1. Disseminated rash with or without fever.
2. Any lesions with signs of secondary bacterial infection.
3. Elevated liver enzymes.
4. Any number of lesions with pulmonary signs and symptoms.
5. Any child who is neutropenic.
6. Any non-neutropenic child who is unwell.
7. Any child under the age of 2 years.

B) Criteria for outpatient management of chickenpox and shingles: (requires consultation with pediatric oncologist or pediatric infectious disease specialist)

1. No criteria specified above that requires admission
2. Localized or non-disseminated disease
3. Strict monitoring and follow-up available
4. Compliance with oral antiviral not an issue
5. Unconfirmed rash likely not chickenpox or shingles in a well non-neutropenic child

MANAGEMENT

1. Implement Airborne/ Contact Precautions for all patients with chickenpox or shingles in more than one dermatome until all lesions are crusted. For immunocompromised patients with shingles in a single dermatome that can be covered, implement Airborne/ Contact precautions until 24 hours after antiviral therapy started; then as for localized zoster in normal host may be switched to contact precautions. May consult Infection Prevention and Control prior to discontinuing isolation precautions.
2. Stop chemotherapy and consult with oncologist concerning any administration.
3. Start acyclovir immediately AND within 24 hours of rash onset (for maximum benefit).
4. Treat for a total of 7-10 days and until no new lesions appear within 48 hours.
5. If child has disseminated disease, or is at risk for disseminated disease, or is neutropenic (ANC < 1 x 10^9/L) complete the full antiviral course with IV acyclovir due to poor oral bioavailability of oral acyclovir. May consider oral valacyclovir in certain patients as below.
6. If child is at low risk for disseminated disease and responds to IV acyclovir within 48 hours of start (i.e. no new lesions) they can be stepped down to valacyclovir* (age > 2 yrs) to complete the 7-10 day antiviral course.
7. If child it at low risk for disseminated disease (e.g. children with leukemia in maintenance or children with localized shingles (1 dermatome, or 2 adjacent dermatomes) may treat with full antiviral course as an outpatient with strict monitoring and follow-up. If rash worsens admit patient to complete course with IV acyclovir.
8. Although VariZIG (or if not available, intravenous immunoglobulin) given shortly after exposure can prevent or modify the course of disease, immunoglobulin preparations are not effective treatment once disease is established.
9. Antiviral therapy:

   Varicella (Chicken pox):
   - Acyclovir 10-15 mg/kg/dose IV q8h for 7-10 days AND continue for greater than or equal to 48 hours after the last new lesions have appeared.
   - If completing a course orally, use acyclovir 20 mg/kg/dose orally 4 times per day doses (maximum 3200 mg/day or 800 mg/dose) OR valacyclovir* 20 mg/kg/dose orally 3 times per day (maximum 3000 mg /day)

   Zoster (Shingles):
   - Acyclovir 10 mg/kg/dose IV q8h for 7-10 days and resolution of rash.
   - For less severe disease in children > 2 years of age; valacyclovir* 20 mg/kg/dose 3 times per day (maximum 3000 mg/ day)

   **Note valacyclovir suspension needs to be compounded by community pharmacies which could result in a delay of therapy*
10. Ensure adequate hydration at a minimum of 1500 mL/m²/day when using IV acyclovir
11. Monitor for systemic involvement - liver function tests, respiratory and neurological status.
12. Monitor renal function.
13. General management:
    - Local control measures: cut finger nails short, keep nails clean, treat secondary infection, Calamine® and/or oral antihistamine for itchiness, cool baths soothe and Aveeno® baths may lessen itchiness.
    - Discourage breakage of blisters.
    - Encourage oral intake with clear fluids.
    - Monitor fever, appetite, fluid intake and appearance of lesions.
    - Notify infection control

14. After discharge, instruct the family to contact the physician to be seen, or return immediately if child develops:
    - secondary fever
    - cough
    - zoster (shingles) dissemination
    - jaundice
    - signs of bleeding into the lesions if the platelets are low (risk of hemorrhagic varicella is low but the child must return if occurs.)
15. For recurrent cases or for high risk patients (e.g. HSCT, severely neutropenic for prolonged periods of time, patients with active disease in their bone marrow) the pediatric hematologist/oncologist in consultation with the pediatric infectious disease specialist may consider varicella zoster prophylaxis. If prophylaxis is considered appropriate dose acyclovir as below:
    - Acyclovir 12.5-25 mg/kg/dose PO divided q6-12h (maximum 800 mg/day) OR for frequent reoccurrences 25 mg/kg/dose PO divided 3 times daily (maximum 2400 mg/day).

VARICELLA VACCINE (VARIVAX® III or VARILRIX® or PRIORIX-TETRA or PROQUAD):

Efficacy of 2 doses of varicella vaccine is approximately 98% in normal hosts.

Who should receive the vaccine?

- All vaccine-eligible household contacts (see contraindications below) without a previous history of varicella disease or vaccination should receive the varicella vaccine at the time of an oncology diagnosis in a child.
- Household contacts who are not immune to chickenpox (no previous disease or vaccination), and experience a chickenpox exposure, should receive the varicella vaccine immediately. Consider post-exposure vaccination of siblings if child with cancer comes in contact with varicella and the sibling was not vaccinated at diagnosis or is not immune already.
- All patients (except HSCT), with a titre that is non-immune at the end of therapy, should receive varicella vaccine series 6 months after completing chemotherapy.
- In consultation with pediatric hematology/oncology and immunology, all HSCT patients should receive the varicella vaccine series 18-24 months after transplant. Consideration should be given to administering this live vaccine based on a risk benefit assessment and level of immune suppression and assessment of immune competence and T cell number and function. Varicella vaccine should not be administered if evidence of GVHD or continued immunosuppression is present and until 3 months after stopping all chronic GVHD therapy, if greater than 18 months post transplant.

Contraindications to Varicella Vaccine:

- Pregnancy
- Age less than one year old
- Receiving chronic systemic steroids (≥2 mg/kg per day of prednisone or its equivalent) or other immunosuppressive therapy for 14 days or more.
- Immunodeficiency state
- Immediate hypersensitivity to vaccine components

Administration of the vaccine:

Please follow APPHON/ROHPPA immunization guidelines for children with cancer and APPHON/ROHPPA Transplantation (Hematopoietic Stem Cell Transplantation (HSCT)) Immunization Recommendations.

Note: A **local** rash at the site (or the portion of the limb) of vaccination is expected in 4% of children and 8% of adults. If this occurs, the site should be kept covered. VariZIG is not indicated if the oncology patient has not been directly exposed to the lesions. A **disseminated** rash (widespread or spread beyond the local area of the injection site) is rare. If this occurs, the oncology patient should receive acyclovir.

CHEMOTHERAPY

The decision to hold chemotherapy during the incubation period is based on the intensity of exposure, the general condition of the patient, and the intensity, phase and type of the chemotherapy. High risk patients may be asked to temporarily hold chemotherapy during the incubation period. **Chemotherapy and other therapy during the incubation period must be discussed with the pediatric hematologist/oncologist.**

GUIDELINE REVIEW

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External Reviewers included a variety of health care professionals from the Atlantic Provinces. All the feedback was collated and put into a spreadsheet and the APPHON guideline committee reviewed the comments and made changes based on consensus within the group.

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