Part 5

Passive Immunization

Passive Immunizing Agents

Three significant changes have been made related to passive immunizing agents since the publication of the 2002 *Canadian Immunization Guide*. Recommendations for the use of palivizumab have replaced those made for respiratory syncytial virus (RSV) immune globulin, which is no longer available in Canada. Recommendations for the interval of time that should elapse from the use of immune globulin preparations and measles vaccine have been generalized to include ALL live viral vaccines with the exception of yellow fever vaccine. Finally, recommendations have been made for the varicella-zoster immune globulin preparation VariZIG™, which has replaced the previously available varicella-zoster immune globulin product.

Protection against certain infections or a reduction in the severity of the illness they cause can be achieved by administration of preformed antibodies derived from humans or animals. The preparations available are of two types: standard immune globulin (Ig) of human origin, sometimes referred to as "immune serum globulin" or "gamma globulin", and special preparations of either human or animal sera containing high titres of specific antibodies to a particular microorganism or its toxin. Products of human origin are preferred over those of animal origin because of the high incidence of adverse reactions to animal sera and the longer lasting protection conferred by human immune globulins.

Passive immunization should be considered when vaccines for active immunization are not available or are contraindicated, or in certain instances when vaccines have not been used before exposure to the infective agent. Passive immunization may also have a role in the management of immunosuppressed people unable to respond to a vaccine. The duration of the beneficial effects provided by passive immunizing agents is relatively short. Protection may be incomplete.

In these guidelines, emphasis is on the prophylactic use of immune sera, and only brief reference is made to their use as therapeutic agents in established infections.

As with all immunizing agents, the risks and benefits of passive immunizing agents need to be explained before administration. The lot number of the product should be recorded in the patient's medical record.

Immune globulin (human)

Ig is a sterile, concentrated solution containing between 100 g/L and 180 g/L (10% to 18%) of protein and the preservative thimerosal. It is obtained from pooled human plasma and contains mainly IgG with small amounts of IgA and IgM. The potency of each lot of final product of immune globulin is tested against international standards or reference preparations for at least two different antibodies, one viral and one bacterial. Ig is stable for prolonged periods when stored between +2° and +8° C . Maximum plasma levels are reached approximately 2 days after intramuscular injection, and the half-life in the recipient's circulation ranges from 21 to 27 days.

Intravenous immune globulin (IVIg) is a preparation that contains 50 g/L (5%) of protein with maltose, sucrose or glycine as a stabilizing agent. It is used for continuous passive immunization for patients with selected congenital or acquired immunoglobulin deficiency states and certain diseases. Detailed discussion of IVIg is beyond the scope of this document. Consult appropriate sources and the manufacturer's package insert instructions.

Recommended usage

Prophylactic use of Ig has been shown to be effective in a limited number of clinical situations, which include exposure to measles, hepatitis A and rubella. The commonly recommended doses are given as follows. The dose may vary by manufacturer, and recommendations in the package inserts should be followed.

1. Measles

Ig can be given to prevent or modify measles in susceptible people within 6 days after exposure. To prevent disease, it should be given as soon as possible after exposure, preferably within 3 days. The recommended dose is 0.25 mL/kg body weight with a maximum dose of 15 mL. The dose of Ig for exposed individuals who have underlying malignant disease or who are otherwise immunologically deficient is 0.5 mL/kg or 15 mL maximum.

Ig should be considered for susceptible contacts of measles, particularly all children < 1 year of age and immunologically compromised individuals for whom measles vaccine is contraindicated. Susceptible immunocompetent people who present more than 72 hours but less than 1 week after exposure, i.e., too late for vaccine, can also be considered for Ig. When clinical measles does not develop in a person given Ig, measles vaccine should be given 5 or 6 months later, depending on the Ig dose used, provided the individual is ≥ 1 year of age and there are no contraindications to the vaccine (see Table 4 in *Recent Administration of Human Immune Globulin Products* chapter, page 54 and the *Measles Vaccine* chapter, page 228).

Ig should not be used in an attempt to control measles outbreaks.

2. Hepatitis A

Hepatitis A vaccine is the preferred agent for pre-exposure prophylaxis against hepatitis A. Ig will provide protection against hepatitis A when administered intramuscularly before exposure or during the incubation period. Its relative effectiveness depends upon both the timing of administration and the dose given. Ig may be indicated if the vaccine is unavailable or unaffordable, as well as for infants < 1 year of age, immunocompromised people who may not respond to the vaccine and people for whom the vaccine is contraindicated (please refer to the *Hepatitis A Vaccine* chapter, page 179, for more information).

The recommended dose of Ig varies according to the duration of required protection. It also varies with the manufacturer, so the package insert should be consulted prior to administration. In general, for protection lasting < 3 months the dose is 0.02 mL/kg; for ≥ 3 months, 0.06 mL/kg should be administered; for > 5 months, 0.06 mL/kg should be repeated every 5 months. For post-exposure prophylaxis, the dose of Ig is usually 0.02 mL/kg. Ig prophylaxis should be given as soon as possible after an exposure.

3. Rubella

Ig given soon after exposure to rubella may modify or suppress symptoms but is not certain to prevent infection, including congenital infection. Therefore, the routine use of Ig in susceptible women exposed to rubella early in pregnancy is not recommended.

4. Hepatitis C

Ig is not efficacious in preventing or treating hepatitis C and should not be used for this indication.

Safety of immunoglobulin preparations

Human Ig preparations are among the safest blood-derived products available. Plasma found to be positive for hepatitis B surface antigen, human immunodeficiency virus (HIV) antibody or hepatitis C is excluded from donor pools. As is the case for other blood or organ donations, individuals with known risks for other blood-borne pathogens are excluded from donating plasma for Ig preparation. The method of preparation includes one or more steps that exclude or inactivate hepatitis B and C viruses, and HIV. There are no known reports of transmission of hepatitis B, hepatitis C, HIV, West Nile virus, new variant Creutzfeld-Jakob disease or other infectious agents after the intramuscular injection of Ig. There have been rare reports of transmission of hepatitis B or hepatitis C following the use of certain intravenous Ig preparations that did not undergo the currently required inactivation steps during the manufacturing process.

Adverse reactions

Reactions at the site of injection include tenderness, erythema and stiffness of local muscles, which may persist for several hours. Mild fever or malaise may occasionally occur. Less common side effects include flushing, headache, chills and nausea. Anaphylactic reactions may occur rarely with repeat administration.

Contraindications and precautions

Ig should not be given to people with known isolated IgA deficiency or with a known allergy to the preservative thimerosal, a mercury derivative. Pregnancy is not a contraindication to the use of Ig.

Currently available preparations, with the exception of IVIg, must not be given intravenously because of the risk of rare anaphylactic reactions.

Large volumes for intramuscular injection should be divided and injected at two or more sites.

People with severe thrombocytopenia or coagulation disorders that contraindicate intramuscular injections should not be given intramuscular Ig unless the expected benefits outweigh the risks (please refer to *Immunization of Persons with Bleeding Disorders* chapter, page 134).

Ig administration may interfere transiently with the subsequent immune response to measles, mumps, rubella (MMR) and varicella vaccines. Please refer to Table 4, page 54, in the *Recent Administration of Human Immune Globulin Products* chapter for specific recommendations regarding the interval between the administration of Ig and these vaccines.

There are no data to indicate that Ig administration interferes with the response to inactivated vaccines, toxoids or the following live vaccines: yellow fever or the oral preparations of typhoid or cholera.

Specific immune globulins

Specific immune globulins (Ig) are derived from the pooled sera of people with antibody to the specific infectious agents. Antisera from animals, usually horses that are hyperimmunized against a specific organism, are used when human products are not available. Because of the relatively high risk of serum sickness following the use of animal products, human Ig should be used whenever possible. *Before antisera of animal origin are injected, testing for hypersensitivity to the preparation should be carried out in accordance with the manufacturer's recommendation.*

Many of the following products are not readily available and, in some instances, their use may require special access applications. In those situations, local and provincial public health departments should be contacted to facilitate their acquisition.

1. Botulism antitoxin (equine)

Trivalent (type A, B and E) and monovalent (type E) antitoxin preparations, both containing phenol as a preservative, are available on an emergency basis with the assistance of local public health authorities. These products are used therapeutically in people with established or suspected botulism as well as prophylactically in asymptomatic people strongly suspected of having eaten food contaminated with botulism toxin. Type E botulism is most likely to be associated with the consumption of uncooked fish or fish products, or the flesh of marine mammals, including whales and seals. The monovalent type E antitoxin should be used only if such foodstuffs are considered the most likely vehicle of disease or if laboratory tests have established that the toxin involved is type E.

In populations at risk of repeated exposures to botulism toxin because of particular food habits, the repeated use of prophylactic antitoxin can lead to an increased risk of adverse reactions.

2. Diphtheria antitoxin (equine)

This preparation, which also contains phenol as a preservative, is available on an emergency basis with the assistance of local public health authorities for treatment of the disease. Antitoxin should be administered before bacteriologic confirmation when there is clinical suspicion of diphtheria. The method of testing for sensitivity to equine serum, as well as the dose and route of administration, are indicated in the manufacturer's package insert. Intramuscular administration usually suffices, but intravenous administration may be necessary in some cases. If sensitivity tests are positive, desensitization must be undertaken according to the manufacturer's recommendations.

Diphtheria antitoxin is not recommended for prophylaxis of close, unimmunized contacts of diphtheria cases, given the substantial risk of allergic reaction to horse serum and no evidence of additional benefit of antitoxin for contacts who have received antimicrobial prophylaxis.

3. Hepatitis B immune globulin (HBIg)

HBIg is prepared from pooled human plasma from selected donors with a high level of antibody to hepatitis B surface antigen. HBIg provides immediate and effective short-term passive immunity. HBIg administered concurrently with vaccine, but at a different site, does not interfere with the antibody response to the vaccine. The indications for use in susceptible individuals are percutaneous or mucosal exposure to blood containing hepatitis B virus, sexual contact with an acute case of hepatitis B, and

birth of an infant to a mother with acute or chronic hepatitis B infection. All infants born to infected mothers should be given an intramuscular dose of 0.5 mL HBIg immediately after birth in addition to the first dose of the three-dose course of hepatitis B vaccine. It is important that HBIg be given within the first 12 hours of birth, since its efficacy decreases sharply after 48 hours. The dose of HBIg for older children and adults is 0.06 mL/kg given intramuscularly. In general, it should be administered to susceptible individuals within 48 hours of exposure. The exception to this is prophylaxis of sexual contacts of an infected individual, when HBIg may be given up to 2 weeks after the last known contact. Please refer to the *Hepatitis B Vaccine* chapter, page 189, for further details concerning prevention of hepatitis B.

4. Rabies immune globulin (RabIg)

Passive immunization with this product is undertaken as part of post-exposure prophylaxis against rabies in unimmunized individuals. Rabies immune globulin (RabIg) provides rapid protection that persists for only a short period of time (half-life about 21 days). Vaccine and RabIg can be administered concurrently **but under no circumstances should the vaccine be administered in the same syringe or at the same site as RabIg**. Please refer to the *Rabies Vaccine* chapter, page 285, for more information on the use of RabIg for post-exposure prophylaxis in unimmunized individuals.

5. Palivizumab (RSVAb)

Respiratory syncytial virus immune globulin (RSVIg) is an intravenous Ig derived from pools of human plasma with high concentrations of protective antibodies that neutralize RSV. RSVIg was approved in August 1997 for prevention of RSV infection in children aged < 2 years old with bronchopulmonary dysplasia (BPD) or a history of premature birth (< 35 weeks' gestation). It is no longer available in Canada.

Palivizumab is a humanized, mouse monoclonal antibody directed against the F protein of RSV. It is effective against both types of RSV. It is 50 to 100 times more potent than RSVIg. Palivizumab is given monthly at a dose of 15 mg/kg of body weight during the period in which the patient is expected to be at high risk of exposure to RSV. Palivizumab is given by the intramuscular route only. Because it is given predominantly to infants, the preferred site of injection is the anterolateral thigh. If the injection volume is over 1 mL, it should be given as a divided dose. Monthly intramuscular doses of 15 mg/kg in children maintain mean trough serum concentrations above 40 mg/mL. In a major clinical trial, children who received palivizumab had a 55% reduction in RSV hospitalization, 42% reduction in the duration of hospital stay, 40% reduction in the length of time they received oxygen and 57% reduction in admissions to the intensive care unit compared with the control group. There may be erythema and pain at the injection site. Fever may occur in 1% to 3%.

Palivizumab prophylaxis is reserved for children who are at highest risk of severe RSV infection, including children 24 months of age or younger with BPD who required oxygen and/or medical therapy for that illness within the 6 months preceding the RSV season, and infants born at 32 weeks and 0 days' gestation or earlier who are 6 months of age or younger (with or without BPD) at the start of the RSV season. Palivizumab does not affect responses to measles, mumps or rubella vaccines. Infants born between 32 and 35 weeks' gestation in isolated communities where hospital care is not readily accessible may be given special consideration for RSV prophylaxis. The appearance of RSV each year varies across Canada, and clinicians should check with local infectious disease specialists or microbiologists to determine when the RSV season begins in their communities. RSV prophylaxis with palivizumab, if undertaken, should be initiated at the start of the RSV season and continued monthly until the end of the season.

Palivizumab is not indicated for the inpatient *treatment* of established RSV infection.

Children less than 2 years of age with hemodynamically significant cyanotic or acyanotic congenital heart disease (who require corrective surgery or are receiving cardiac medication for hemodynamic considerations) should be considered for monthly palivizumab prophylaxis during the winter season. The decision to provide prophylaxis with palivizumab in this population should be made according to the degree of physiological cardiovascular compromise. Infants greater than 32 weeks' gestation with uncomplicated small atrial or ventricular septal defects, patent ductus arteriosus, mild coarctation of the aorta, pulmonic stenosis, uncomplicated aortic stenosis or mild cardiomyopathy, or infants with lesions adequately corrected by surgery and not needing medications for congestive heart failure, without other risk factors, would not be at increased risk of severe RSV, and therefore palivizumab prophylaxis is not recommended for infants with these conditions. Children who have cardiac bypass during surgery should be given repeat doses of palivizumab in the early post-operative period if they remain at risk of RSV infection.

Palivizumab is expensive and so to minimize product wastage, when an entire vial is not required for a patient, residual product may be used for a second patient if administered within the 6-hour expiry time.

6. Tetanus immune globulin (TIg)

Please refer to the *Tetanus Toxoid* chapter, page 309, for more information on the use of TIg in the management of wounds. When used in the treatment of tetanus, TIg should be administered intramuscularly in an effort to neutralize tetanus toxin in body fluids. It has no effect on toxin already fixed to nerve tissue. The optimal therapeutic dose has not been established.

7. Varicella-zoster immune globulin (VarIg)

The VarIg preparation available in Canada is VariZIG™ (Cangene Corporation, Winnipeg, MB). VariZIG™ is a sterile, freeze-dried gamma globulin preparation containing high titres of antibodies to varicella-zoster virus (anti-VZV). VariZIG™ is available through the Canadian Blood Services and Hema-Quebec distribution centres.

The decision to administer VarIg should be based on all four of the following considerations:

- the exposed person is susceptible to varicella (non-immune);
- there has been significant exposure to VZV;
- the person is at increased risk of severe varicella; and
- post-exposure immunization with varicella vaccine is contraindicated.

Persons who are considered immune (non-susceptible) to varicella include those with

- a previous history of varicella illness, from a child's parent or from an adolescent or adult;
- physician-diagnosed varicella;
- laboratory-confirmed varicella (by culture, polymerase chain reaction or antibody seroconversion);
- laboratory evidence of immunity;
- documented immunization with age-appropriate doses of varicella vaccine.

An exception to this is recipients of allogeneic stem cell transplants who should be considered susceptible in the post-transplantation period regardless of a history of varicella or positive serologic test results. These persons should be offered VarIg after known exposure to varicella.

Persons with varicella (chickenpox) are most contagious from 1 to 2 days before and up to 5 days after onset of the rash. Immunocompromised patients may be infectious until the crusting of all lesions. The skin lesions of zoster (shingles) are considered infectious from the onset of lesions until they have crusted and dried. The following situations are considered significant exposures to varicella zoster virus:

- continuous household contact (living in the same dwelling) with a person with varicella;
- being indoors for more than 1 hour with a case of varicella;

- being in the same hospital room for more than 1 hour or having more than 15 minutes of face-to-face contact with a patient with varicella;
- touching the lesions of a person with active varicella or zoster (shingles).

VarIg is recommended for the following susceptible people, provided that significant exposure has occurred.

- Pregnant women.
- Immunocompromised patients, such as those with congenital or acquired immunodeficiency due to disease or those receiving immunosuppressive treatment, including patients receiving high-dose systemic corticosteroid therapy (e.g., a dose of ≥ 2 mg/kg per day of prednisone or equivalent or ≥ 20 mg per day, particularly when given for more than 2 weeks). However, patients receiving regular monthly infusions of ≥ 400 mg/kg of IVIg and whose most recent dose was within 3 weeks before exposure do not require VariZIG™. This monthly infusion of IVIG can maintain sufficient protective serum levels of varicella antibody comparable to that achieved with VarIg.
- Newborn infants of mothers who develop varicella during the 5 days before to 48 hours after delivery.
- For the management of significant varicella exposure in a neonatal or pediatric intensive care setting, consultation with the infectious diseases/infection control specialist regarding the potential use of VariZIG™ is advised.

VariZIG™ is not indicated in healthy adults. Varicella can be more severe in healthy adults than children, but the risk of varicella pneumonia appears to be lower than was formerly believed. Varicella vaccine within 3-5 days after exposure is the post-exposure management of choice for healthy adults. Acyclovir therapy initiated within 24 hours after onset of the rash is effective in accelerating skin lesion healing and can be used for this population as soon as possible after rash onset.

Dosing of VariZIG™ is based on body weight. The recommended dose is 125 IU for each 10 kg of body weight up to a maximum of 625 IU. The minimum dose is 125 IU. VariZIG™ should be given by the intramuscular route. It is of maximal benefit if administered within 96 hours after first exposure. However, since the exact timing of transmission is unknown it can be used within 96 hours of the most recent exposure. Protection is believed to last for approximately 3 weeks. Subsequent exposures more than 3 weeks after a dose of VariZIG™ would require additional doses if the criteria for VarIg, as specified above, still exist.

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