– Part 4 –
Passive Immunizing Agents

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, such as tetanus immune globulin. 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 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, as may be the case when an unimmunized patient sustains a wound that may be contaminated with tetanus bacilli. In the latter situation, passive immunization is used in combination with toxoid to ensure both immediate (conferred by passive immunization) and long-term protection. Passive immunization may also have a role in the management of immunosuppressed people unable to respond to a vaccine. The beneficial effects provided by passive immunizing agents are of relatively short duration, and 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, including these blood-derived products, the risks and benefits need to be explained before administration, and the lot number should be recorded.

Immune Globulin (Human)

Immune globulin (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 lgA 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 at 2° C to 8° C. Maximum plasma levels are reached about 2 days after intramuscular injection, and the half-life in the recipient's circulation is 21 to 27 days.

Intravenous immune globulin (IGIV) 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 IGIV is beyond the scope of this document**. Consult appropriate sources and the manufacturer's package instructions.

Recommended Usage

Prophylactic use of IG has been shown to be effective in a limited number of clinical situations. Commonly recommended doses are used for the following conditions (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 of 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 within 4 to 6 days 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 months later, provided the individual is ≥1 year of age and there are no contraindications to the vaccine.

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 (see page 93, Hepatitis A chapter).

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 exposure, since it is of very little value administered more than 2 weeks afterwards.

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.

If used, a dose of 0.55 mL/kg should be given intramuscularly within 48 hours of contact. Serum rubella antibody measurements before and for several months after IG administration can determine whether infection occurred.

4. Hepatitis C

IG is not efficacious in preventing or treating hepatitis C and should not be used.

Safety of Immunoglobulin Preparations

Human IG preparations are among the safest blood-derived products available. Plasma found positive for hepatitis B surface antigen, 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 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

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 or other immune globulins.

Precautions

Currently available preparations, with the exception of IGIV, 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.

IG administration may interfere transiently with the subsequent immune response to measles, mumps and rubella vaccines. See Table 7, page XX, for specific recommendations regarding the interval between the administration of IG and these vaccines.

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

Specific Immune Globulins

Specific immune globulins 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 immune globulin should be used whenever possible. *Before antisera of animal origin is 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 (consult with 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 for repeated exposures to botulism toxin because of particular food habits, the repeated use of prophylactic antitoxin can lead to an increased

incidence of severe reactions. Caution should therefore be exercised in the use of botulism antitoxin in such circumstances, even if preliminary sensitivity tests are negative.

2. Diphtheria antitoxin (equine)

This preparation, which also contains phenol as a preservative, is available on an emergency basis (consult with 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 in 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 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 of the three-dose course of the hepatitis B vaccine. It is important that HBIG be given within the first few 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. See Table 2 and pages 5-6 for further details concerning prevention of hepatitis B.

4. Rabies immune globulin (RIG)

Passive immunization with this product is undertaken as part of post-exposure prophylaxis against rabies (see page 193). Rabies immune globulin (RIG) provides rapid protection that persists for only a short period of time (half-life about 21 days). Vaccine and RIG can be administered concurrently but **under no circumstances should vaccine be administered in the same syringe or at the same site as RIG.** A dose of up to 20 IU/kg of RIG should be administered once, as soon as possible after exposure. If

anatomically feasible, the full dose of RIG should be thoroughly infiltrated into the wound and surrounding area. Any remaining volume should be injected intramuscularly at a site distant from vaccine administration. When more than one wound exists, each should be locally infiltrated with a portion of the RIG. Because of interference with active antibody production, the recommended dose should not be exceeded. Since vaccine-induced antibodies begin to appear within 1 week, if the vaccine has been administered without the administration of RIG, there is no value in giving RIG more than 8 days after the vaccine course was initiated.

5. Respiratory syncytial virus immune globulin intravenous (human) (RSV-IGIV)

RSV-IGIV is an intravenous IG derived from pools of human plasma with high concentrations of protective antibodies that neutralize RSV. RSV-IGIV was approved in August 1997 for prevention of RSV infection among children aged < 2 years old with bronchopulmonary dysplasia (BPD) or a history of premature birth (≤ 35 weeks' gestation). Rates of re-admission for RSV infection among premature infants have ranged from 2% to 22% during the first year of life and require further study. RSV-IGIV in a placebo-controlled trial was shown to decrease the RSV-related hospitalization rate by 41%, the RSV-related length of stay by 53% and the duration of oxygen therapy by 60%.

Adverse events are the same as for all IG products given by intravenous infusion. Fluid overload may be precipitated by infusion of infants with pulmonary disease, especially those with BPD. Appropriate precautions, as outlined in the product monograph, must be taken.

Children with cyanotic congenital heart disease treated with RSV-IGIV were observed to have a greater frequency of severe or life-threatening adverse events than similar children who received no infusions during the study period. Until the relation between the infusions and subsequent adverse events is better understood, it is recommended that children with cyanotic congenital heart disease not be given RSV-IGIV. It is unknown whether RSV-IGIV can prevent significant RSV disease among immunocompromised hosts.

RSV-IGIV has no proven benefit in the treatment of established RSV infection.

It is anticipated that RSV-IGIV prophylaxis may be most beneficial for the following children:

- Infants and children < 2 years of age with BPD who are currently receiving or have received oxygen therapy within 6 months before the onset of the RSV season.
- Infants who were born at 32 weeks of gestation or less, including those without BPD:
  - infants born at 28 weeks of gestation or less may benefit from prophylaxis up to 12 months of age;
  - infants born at 29-32 weeks of gestation may benefit from prophylaxis up to 6 months of age.

The recommended dose is 750 mg/kg given every 4 weeks, starting before and continuing through the local RSV season. In Canada, the annual RSV outbreak usually begins in November or December and extends through April or May. Regional variations occur. It is best to consult local experts to determine the usefulness of RSV-IGIV on an individual patient basis. A more detailed discussion can be found in the statement published by the Canadian Paediatric Society (see Selected References).

Local and practical issues in delivery, the costs involved, and the data showing that prevention is not complete after administration of RSV-IGIV all preclude a universal recommendation being made at this time. Thus each centre has to consider a number of factors before embarking upon an RSV-IGIV prophylaxis program. The use of RSV-IGIV may not prove to be very feasible or practical in many centres when these factors or circumstances are taken into account.

6. Tetanus immune globulin (TIG)

The use of TIG in the management of wounds is discussed in the section on Tetanus Toxoid (see pages 208-213). 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 (VZIG)

VZIG is prepared from pooled plasma of people with high antibody titres to varicella-zoster virus (VZV). VZIG is available through the Canadian Blood Services and HÉMA-QUÉBEC distribution centres.

Passive immunization with VZIG is indicated after exposure to chickenpox or zoster in susceptible individuals whose risk of serious morbidity or mortality from chickenpox is substantially increased. Varicella vaccine may also be considered as an acceptable alternative to VZIG (see pages 223-232)

People with chickenpox are most contagious from 1 to 2 days before and for a few days after onset of the rash. The contagious period may extend to 5 days after onset and in immunocompromised patients until crusting of lesions. Skin lesions of zoster or shingles are infectious only until the eruption has crusted and dried. The following contact situations are considered significant exposures to VZV:

- continuous household contact (living in the same dwelling);
- playing indoors for more than 1 hour with a contagious case;
- sharing the same hospital room with a contagious patient;
- prolonged face-to-face contact of a worker or staff member with an individual with chickenpox.

The determinants of susceptibility to varicella are as follows:

- People with a history of chickenpox are usually considered immune.

- All recipients of heterologous bone marrow transplants should be considered susceptible in the early post-transplantation period regardless of a history of varicella or positive serologic test results.
- People with a negative or uncertain history of chickenpox should be tested serologically to establish susceptibility, since as many as 70% to 95% of such individuals have immunity to varicella. Prospective serologic testing to determine susceptibility may eliminate the need for emergency post-exposure tests. Prospective testing should be considered for health care workers without a history of chickenpox, and for individuals with congenital or acquired immunodeficiency due to disease or therapy, including those undergoing solid-organ heterograft transplantation and those with hematologic or reticuloendothelial malignant disease. VZIG may give detectable levels of antibody causing false-positive tests of varicella immunity for up to 2 months after administration.

VZIG is recommended for the following susceptible people, providing significant exposure has occurred:

Infants and children

1. Immunocompromised patients, such as those with congenital or acquired immunodeficiency due to disease or treatment, including some patients receiving corticosteroid therapy (see pages 20-30). Patients receiving regular monthly infusions of 100 to 400 mg/kg of IGIV and whose most recent dose was within 3 weeks before exposure do not require VZIG.
2. Newborn infants of mothers who develop varicella during the 5 days before or 48 hours after delivery.
3. Hospitalized premature infants exposed during the first weeks of life. Exposed infants of < 28 weeks' gestational age should receive VZIG regardless of maternal immune status. Exposed infants of 29 to 37 weeks' gestational age should receive VZIG if the mother was not immune.

Adults

1. Pregnant women. Because the risk of complications of chickenpox in pregnant women may be greater than in other adults, VZIG should be given to exposed, susceptible pregnant women. There is no evidence that VZIG will prevent or alter disease in the fetus.
2. Immunocompromised adults. See previous section on immunocompromised infants and children and pages 20-30.
3. Healthy adults. The value of VZIG in healthy adults is unclear. Chickenpox can be more severe in healthy adults than children, but the risk of pneumonia is now considered less than was formerly believed. In addition, VZIG may prolong the incubation period to 28 days, which has implications for health care workers. Finally, acyclovir therapy initiated within 24 hours after onset of the rash is

effective in accelerating skin lesion healing and is thus a therapeutic alternative to prophylactic VZIG in this population.

The recommended dose of VZIG is 125 units (1 vial) per 10 kg body weight to a maximum of 625 units, administered intramuscularly. The optimal dose for adults is uncertain.

VZIG is of benefit if administered within 96 hours after the exposure. Protection is believed to last for 3 to 4 weeks. Subsequent exposures more than 3 weeks after a dose of VZIG may require additional doses.

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