NORMAL IMMUNOGLOBULIN (HUMAN): INDICATIONS AND SAFETY

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Human normal immunoglobulin (NIGH) refers to the antibodies in pooled plasma which, injected, can be used as a form of passive immunisation to boost the immunoglobulin G (IgG) of patients and therefore temporarily increase immunity against common infections. Samples are not tested for the amount or type of IgG present. It is assumed that pooled plasma from blood donors contains high levels of antibodies specific to infections found in that population. If an infection is not common in Australia, the antibody level in pooled plasma is low or negligible, so an injection of NIGH would not prevent or modify the infection. If the infection is common, the antibody level is high. For example, measles and hepatitis A are common diseases, so antibody levels should be high and immunisation will be effective. Typhoid and cholera are uncommon, so the immunoglobulin from the Commonwealth Serum Laboratories Limited (CSL), which is taken from the Australian donor pool, would not be useful in prevention.

Human immunoglobulin does not appear to protect a recipient against hepatitis C. In any case, anti-hepatitis-C-positive blood is excluded from the pool.

Where an infection is common, protection is immediate. For immunisation given intramuscularly at the recommended dosage, antibodies usually remain at protective levels for four to six weeks, and longer for hepatitis A.

Two specific forms of immunoglobulin are prepared – one for intramuscular and the other for intravenous use. The intramuscular form is the more common.

INTRAMUSCULAR IMMUNOGLOBULIN

Intramuscular immunoglobulin may be used as prophylaxis for susceptible contacts if given early in the infection. The optimal timing depends on the disease.

The NSW Health Department recommends intramuscular immunoglobulin for the following non-immune contacts of people with hepatitis A as soon as possible, but within two weeks of exposure:

- household or sexual contacts;
- staff and children in an associated day-care centre; and
- food handlers in an associated catering establishment.

The department recommends intramuscular immunoglobulin for infants (children under one year of age) within six days of first exposure to measles.

Intramuscular immunoglobulin is also useful for:

- travellers to areas endemic for hepatitis A for whom hepatitis A vaccine is not practicable;
- treatment of patients with abnormal antibody production; and
- prophylaxis for certain contacts of cases of poliomyelitis, varicella-zoster etc.

The following specific-use intramuscular immunoglobulins are available: tetanus, zoster, hepatitis B and Rh(D) immunoglobulins.

The intramuscular form must not be given intravenously, as it may cause severe adverse reactions.

Preparation of the intramuscular form

The Commonwealth Serum Laboratories prepare immunoglobulin from blood obtained from volunteer blood donors in Australia. Australian Red Cross blood transfusion services screen the blood for evidence of active infection with hepatitis B virus (HbsAg), hepatitis C virus (anti-HCV), human immunodeficiency virus 1 and 2 (anti-HIV1, anti-HIV2), human T cell lymphotropic virus type 1 (anti-HTLV-1) and syphilis.

The plasma is extracted and treated with the Cohn cold-ethanol fractionation process. Thiomersal is added as an antimicrobial agent.

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin is prepared differently from the intramuscular form. It may be used for:

- treatment of congenital or acquired primary hypogammaglobulinaemia;
- prophylaxis for infection in patients with secondary immunodeficiency; and
- treatment of autoimmune disorders.

Specific intravenous tetanus and cytomegalovirus immunoglobulins are available for use in certain cases.

SAFETY

There are no known reports of transmission of infectious diseases from NIGH manufactured by CSL in Australia.

Blood donors are screened in a process designed to select those who are unlikely to carry infection. First, volunteer donors are considered to offer a lower risk of infection than paid donors or donors from institutions such as prisons. Donors complete and sign a questionnaire about their medical history and health risks. Any donor with declared risk factors or a history of hepatitis or HIV is not accepted. Only blood negative for syphilis, hepatitis B surface antigen, antibody to hepatitis C, antibody to HIV-1, antibody to HIV-2 and antibody to HTLV is used. However, blood taken during the incubation periods of these infections, when the virus is multiplying but the antibodies have not reached detectable levels (window period), would be accepted unwittingly. Transmission of the virus during this stage should be reduced by following the inactivation procedure.

Cohn cold-ethanol fractionation has been shown to inactivate viruses – especially HIV, which is relatively fragile. The addition of thiomersal prevents bacterial contamination after the procedure.

Cohn cold-ethanol fractionation procedure reduces hepatitis B virus and HIV indicators in the final product to negligible levels, but not necessarily for hepatitis C virus. However, the reduction in risk would depend on the viral load in the initial plasma.

Any alteration in the Cohn cold-ethanol procedure could alter its effectiveness. The inactivation of viruses by ethanol is dependent on the concentration of ethanol used and temperature at which the process is carried out.
Since the introduction of routine HBsAg screening of donated blood in the 1970s and anti-HIV screening in the mid-1980s, no cases of hepatitis B or HIV transmitted by immunoglobulin products have been reported in Australia. In the United States and Europe there have been reports of transmission of non-A, non-B hepatitis or hepatitis C—arising from intravenous preparations. In most cases the preparation method deviated from the Cohn cold-ethanol fractionation process—because the product was new to the market or experimental, or the procedure itself had been altered. One product was responsible for 200 cases of hepatitis C, despite screening for hepatitis C with EIA-2, and was withdrawn from the market. No other viruses appear to have been transmitted by immunoglobulins.

In the US the residual risk of developing viral infections from intravenous immunoglobulins has been estimated to be 1 in 420,000 for HIV, 1 in 250,000 for hepatitis B (less than in the general population) and 1 in 100,000 for hepatitis C. In Australia there have been no recorded cases of transmission.

### CONCLUSION

The mortality rate for hepatitis A is 1 in 1,000 for the population in general, and 27 in 1,000 for people over 50 years of age. Measles has a mortality rate of 2-3 per 1,000 and has serious sequelae. The use of NIGH as recommended can prevent the morbidity and mortality of these common infections.

It must be remembered that immunoglobulin is a human product and so the risk of the disease being prevented must be weighed against the risk of intravenous disease.

Health care workers should advise patients that human immunoglobulin is safe, but cannot be guaranteed to be 100 per cent safe. The patient (or the patient’s guardian) should make an informed decision whether to receive this form of treatment.

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