Memoranda
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Memoranda are statements concerning the conclusions or recommendations of certain WHO scientific meetings ; they are signed by the participants in the meeting.

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Appropriate uses of human immunoglobulin in clinical practice: Memorandum from an IUIS/WHO meeting*

There is a consensus among clinical immunologists that an effort should be made to define the criteria and indications for the administration of immunoglobulin to patients. This Memorandum sets out current recommendations for the use and dosage of immunoglobulin in the prophylaxis of viral and bacterial infections, and in replacement of antibodies in immunodeficient patients. It also points out clearly the situations where immunoglobulin is not useful or is contraindicated. The report also summarizes the current knowledge on adverse reactions to immunoglobulin injection, and outlines the qualities required for safe and useful immunoglobulin preparations.

There is a consensus among clinical immunologists that an effort should be made to define for non-specialists the criteria and indications for the administration of immunoglobulin (gammaglobulin, immune serum globulin) to patients. In addition to the well established preparations for intramuscular injection, immunoglobulin suitable for intravenous administration has recently become available, opening new prospects for use of this material.

This Memorandum sets out current recommendations for the use and dosage of immunoglobulin in the prophylaxis of viral and bacterial infections and in replacement of antibodies in immunodeficient patients. It also points out clearly the situations where immunoglobulin is not useful or is contraindicated. Inappropriate use of this valuable material results in excessive and unnecessary costs for health services, is wasteful, and carries some risk to the patient.

This report also summarizes the current knowledge on adverse reactions to immunoglobulin injection and outlines the qualities that are most desirable for safe and useful immunoglobulin preparations.

INDICATIONS AND DOSAGE

Prophylaxis and treatment

Prophylaxis by passive immunization with immunoglobulin from a pool of normal human donors, or with special hyperimmune globulin from selected donors, has been of demonstrated efficacy in several diseases, if given before contact or early in the incubation period. Where feasible, active immunization is always preferable to passive prophylaxis, which protects for only a short time. Certain diseases, e.g., tetanus, should be treated with hyperimmune globulin. The uses of immunoglobulin are listed in Table 1. Use is recommended only where the efficacy has been proved; where efficacy has not been established conclusively, use is listed as optional. The target populations listed in the table have been well defined in controlled studies, and use should be limited to these individuals. However, there may occasionally be indications for the administration of these agents to non-immune persons who cannot be satisfactorily protected by other means.

When hepatitis B vaccines become available, it is likely that they will be administered together with hepatitis B immune globulin (HBIG) in order to achieve longer lasting and possibly improved protection, as is now done with tetanus immunization.

Immunoglobulin has been used together with other treatment for overwhelming sepsis in otherwise normal persons and for cases of neonatal sepsis or meningitis. It has also recently been reported that immunoglobulin may be of use in patients with idiopathic thrombocytopenic purpura, but, at present, data on which to base definite recommendations are not available.

Table 1. Appropriate uses for human immunoglobulin in the prevention and treatment of disease

Agent/ Condition	Target population	Preparation[a,b]	Dose[c]	Status
Hepatitis A	Family contacts Institutional outbreaks	IG	0.02 ml/kg of body weight (3.2 mg/kg of body weight)	Recommended for prevention
	Travellers exposed to unhygienic conditions in tropical or developing countries	IG	0.02 – 0 05 ml/kg of body weight (3 2 – 8.0 mg/kg of body weight) every 4 months	Recommended for prevention
Hepatitis, non-A, non-B	Percutaneous or mucosal exposure	IG	0.05 ml/kg of body weight (8 mg/kg of body weight)	Optional for prevention
Hepatitis B	Percutaneous or mucosal exposure	HBIG	0.05 – 0.07 ml/kg of body weight (8 – 11 mg/kg of body weight) Repeat in one month	Recommended for prevention
	Newborns of mothers with HBsAg	HBIG	0 05 ml (8 mg) at birth, 3, and 6 months	Recommended for prevention
	Sexual contacts of acute hepatitis B patients	HBIG	0.05 ml/kg of body weight (8 mg/kg of body weight) Repeat after one month	Optional for prevention
Rubella	Women exposed during early pregnancy	IG	20 ml	Optional for prevention
Varicella-zoster	Immunosuppressed contacts of acute cases, or newborn contacts	VZIG[d]	15 – 25 units/kg of body weight; minimum 125 units	Recommended for prevention
Measles (rubeola)	Infants less than 1 year old or immunosuppressed contacts of acute cases exposed less than 6 days previously	IG	0 25 ml/kg of body weight or 0.5 ml/kg of body weight if immunosuppressed	Recommended for prevention
Rabies	Subjects exposed to rabid animals	RIG	20 IU/kg of body weight	Recommended for prevention
Tetanus	Following significant exposure of unimmunized or incompletely immunized person or immediately on diagnosis of disease	TIG	250 units for prophylaxis 3000 – 6000 units for therapy	Recommended for prevention or treatment
Rh isoimmunization	Rh(D)-negative mother on delivery of Rh-positive infant, or after uncompleted pregnancy with Rh-positive father, or after transfusion of Rh-positive blood to Rh-negative mother	RhIG	1 vial (200 – 300 μg) per 15 ml of Rh(+) blood exposure	Recommended for prevention

[a] IG = immune globulin (human); HBIG = hepatitis B immune globulin; VZIG = varicella-zoster immune globulin, RIG = rabies immune globulin; TIG = tetanus immune globulin, RhIG = rhesus factor immune globulin

[b] Hyperimmune immunoglobulins have also been used in prophylaxis of mumps and prophylaxis and treatment of pertussis and diphtheria; there are no conclusive data available, and no recommendations can be given.

[c] Dose based on intramuscular administration of 16.5% solution

[d] Of limited availability at the present time.

Replacement therapy

Immunoglobulin replacement therapy helps patients with antibody deficiency syndromes resulting from defective antibody synthesis, whether primary or secondary. A low immunoglobulin level *per se* is not a sufficient criterion for treatment; a precise diagnosis should be established wherever possible and defects in humoral immunity demonstrated.

Immunoglobulin replacement therapy is definitely indicated in diseases with gross defects in production of all immunoglobulins, such as X-linked agammaglobulinaemia, varied immunodeficiency (common), Ig deficiencies with increased IgM, immunodeficiency with thymoma, and severe combined immunodeficiency. Any patient lacking IgM needs replacement therapy, regardless of any concomitant primary immunodeficiency.

Replacement therapy may be indicated in selective deficiency of one or more classes or subclasses of immunoglobulin, antibody deficiency with normo- or hypergammaglobulinaemia, and repeated or severe infection in infancy associated with immunoglobulin deficiency, which may be transient. Asymptomatic immunoglobulin deficiency found in some infants with transient hypogammaglobulinaemia or mild forms of varied immunodeficiency (common) are not a definite indication for immunoglobulin treatment, but such patients should be followed carefully. Certain patients with symptomatic antibody deficiency due to chronic lymphatic leukaemia or multiple myeloma may benefit from immunoglobulin replacement, but this has not been clearly established.

Patients with severe primary and secondary T-cell deficiencies (e.g., ataxia telangiectasia, Wiskott-Aldrich syndrome, thymic hypoplasia, severe combined immunodeficiency, and drug-induced T-cell defects) benefit from immunoglobulin replacement as adjunctive treatment, but other measures are needed to correct the defects.

In all these circumstances it has been established that the minimum effective maintenance dose of immunoglobulin is 25 mg/kg of body weight per week, regardless of the route of administration. Patients require an initial loading dose of 200–500 mg/kg of body weight, to raise the serum IgG level to at least 2 g/litre, followed by regular doses every one, two, or three weeks, sufficient to maintain the increment achieved by the loading dose. The interval between doses may be altered according to circumstances, but should never be longer than one month. It must be emphasized that these are recommendations for *minimum* effective therapy; the optimum dose has not yet been established and may vary from patient to patient. If symptoms are not controlled, larger doses may be required but it is rarely necessary to exceed a serum level of 10 g/litre.

Immunoglobulin should be used only according to the indications given above. Unfortunately, misuse of immunoglobulin preparations is common.

Contraindications

Treatment of selective IgA deficiency with immunoglobulin is contraindicated since it may induce antibodies against IgA and thus cause an adverse reaction. However, in combined IgA-IgG$_2$ deficiency, where immunoglobulin may be desirable, only preparations that are very low in IgA may be given, under medical supervision.

Generally, immunoglobulins should not be given shortly before or after active immunization to avoid inhibiting the immune response; tetanus and hepatitis B immunization are exceptions to this rule.

Rh prophylaxis should not be given to Rh(D)-positive or Rh(D^u)-positive women.

Inappropriate use

With the exception of the specific indications already mentioned, there is no evidence that standard immunoglobulin is of any prophylactic use in individuals without immunodeficiency. It is useless for the prevention of upper respiratory infections in such subjects.

It is inappropriate to use standard immunoglobulin for the prevention of infection in premature infants or during physiological hypogammaglobulinaemia or for the treatment of malnutrition. The use of immunoglobulin in states of immunoglobulin loss, such as protein-losing enteropathy or proteinuria, is generally ineffective.

ADVERSE REACTIONS
TO IMMUNOGLOBULIN THERAPY

Adverse reactions to immunoglobulin can be local or systemic. When used in prophylactic doses in healthy individuals, adverse reactions are extremely rare.

Systemic reactions can be rapid or late. Rapid reactions occur during or within minutes of receiving therapy, and are anaphylactic in type (flushing, flank pain, rigor, dyspnoea, and signs of shock). Late reactions may occur within hours or days, are usually less severe, and may include urticaria, arthralgia, pyrexia, or diarrhoea. Such reactions are not uncommon when replacement therapy is given to immunodeficient patients, and depend on the route of administration,

the nature of the preparation, and the patient himself.

With intramuscular injections local reactions are relatively common, especially when large volumes are given. Severe systemic reactions are less frequent, occurring once in every 500 – 1000 injections in some series. Systemic reactions are more common with intravenous administration, but depend, to some extent, on the nature of the preparation and the rapidity of infusion. Reactions may occur at any time during the therapy, from the first injection onwards. Individual patient variation is an important factor; patients with X-linked agammaglobulinaemia may tolerate intramuscular preparations better than patients with common varied immunodeficiency.

The causes of adverse reactions are not fully understood. Possible mechanisms include the biological effect of IgG aggregates and sensitization to components such as IgA. Other impurities such as activated enzymes (plasmin, kallikrein, prekallikrein activator, etc.) that cause the release of inflammatory mediators, e.g., prostaglandins, may also be involved. Some adverse reactions may be caused by antibodies in the preparation reacting with antigens in the patient's circulation. Adverse reactions in patients receiving long-term therapy may result from the accumulation of potentially toxic preservatives, present in the immunoglobulin preparation.

Local pain can be prevented by giving smaller volumes more frequently or by giving the injection in association with a local anaesthetic or a systemic analgesic. Severe systemic reactions can be prevented by giving hydrocortisone before the injection; prior administration of antihistamines or aspirin may also be useful.

Patients with recurrent severe reactions who cannot tolerate purified immunoglobulin in any form should be treated with plasma. Where IgA antibodies are present, IgA-deficient plasma or other IgA-depleted preparations should be used.

Treatment of a severe reaction is identical to the treatment of anaphylaxis, and includes subcutaneous epinephrine, intravenous hydrocortisone, and, if necessary, plasma volume expanders.

REQUIREMENTS FOR IMMUNOGLOBULIN PREPARATIONS FOR PARENTERAL USE

Source of material

Parenteral immunoglobulin should be obtained from a pool of at least 1000 donors. Plasma obtained from selected immunized or convalescent donors through plasmaphaeresis may be advisable for certain hyperimmune immunoglobulin preparations.

Safety of the preparations

Immunoglobulins should be prepared according to World Health Organization standards and should be free from prekallikrein activator, kinins, plasmin, and accumulative preservatives or other potentially harmful contaminants. They should have a very low IgA concentration and be as free as possible from IgG aggregates.

Quality control

The preparations should contain at least 90% intact IgG without immunoglobulin fragments; the IgG should be as unmodified as possible and should maintain opsonic, complement-binding, and other biological activities. All IgG subclasses should be present, in proportions as similar as possible to those found in normal pooled plasma. The level of antibody against at least two bacterial species (or toxins) and two viruses should be ascertained, by neutralization in the case of the viruses. In addition, these materials should contain at least 0.1 I.U. of antibody to hepatitis B per ml and a radioimmunoassay antibody titre of at least 1:1000 to hepatitis A/ml.

The manufacturers should provide information on all these points, describe any chemical modification of the immunoglobulin carried out by them, and declare the nature of the diluents used and of any other materials present in the final product.

Hyperimmune immunoglobulin may be designated as such if it contains at least five times the antibody potential of the standard preparation per unit volume.

FUTURE TRENDS

The expanding use and improved safety of intravenous immunoglobulin preparations will probably provide an alternative to the intramuscular injection of immunoglobulin as replacement therapy in immunodeficient patients. It will then be possible to administer larger doses of immunoglobulin comfortably and easily, possibly using subcutaneous infusion pumps. There is an urgent need to establish the optimum dose of immunoglobulin in replacement therapy because, at present, only the minimum effective dose is known. There is also a pressing need for preparations of hyperimmune immunoglobulin for the prophylaxis of pyogenic infections in immunosuppressed patients and splenectomized subjects, and for other viral and bacterial infections (such as cytomegalovirus and herpes simplex). The prospect of treating Gram-negative sepsis and other infections with intravenous preparations of immunoglobulin, especially hyperimmune preparations, remains to be

investigated, particularly for disseminated viral infections in immunodeficient patients.

More work is needed to determine the role of immunoglobulin therapy in preventing neonatal sepsis, especially from group B streptococci, in infants at high risk. In view of the increasing incidence of drug-resistant *Plasmodium falciparum* infection, it may be useful to develop hyperimmune immunoglobulins against this parasite. In view of the high incidence of *Pseudomonas* sepsis in patients with severe burns, controlled studies with hyperimmune or normal immunoglobulin are warranted in this area.

The administration of monoclonal antibodies from murine hybridomas appears to be of limited value at present, since the species of origin of the monoclonal antibodies severely restricts their biological usefulness *in vivo*. Nonetheless, the prospect of obtaining human hybridoma antibodies will expand the potential clinical application of these reagents, not only for treating infections but also for the possible modulation of human immune responses. It may also be feasible to link monoclonal antibodies with chemotherapeutic agents for the treatment of cancer. However, the many unresolved biological issues and potential risks involved in the use of products derived from malignant cells may mean that their use will have to be reserved for the most dire cases.

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