Recommendations for the use of albumin and immunoglobulins

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Albumin

Introduction

Human albumin is a physiological plasma-expander; its limited availability and high cost make it essential to define recommendations for its appropriate use, as an alternative to other therapeutic strategies including solutions of crystalloids and non-protein colloids, and have also stimulated numerous studies, which have sometimes reached contradictory conclusions[1-8].

In 1998 a meta-analysis of 30 randomised trials suggested that the use of albumin was associated with an increased mortality rate among critically ill patients[9,10]. This conclusion, also reached by two subsequent Cochrane reviews[11,12], was not confirmed by a meta-analysis in 2001 or by more recent studies[13-23].

A review in 2006 showed that renal damage can be induced by the use of hydroxyethyl starch and gelatine in sepsis and surgery[24].

The limited power of all these studies could lie in their having combined results from heterogeneous types of patients with different baseline albumin concentrations[25,26].

Notions of physiology

Albumin is the main factor determining the oncotic pressure of blood and, therefore, the regulation of plasma volume and tissue fluid balance; it is also involved in the transport of numerous endogenous substances, such as unconjugated bilirubin and hormones, and exogenous ones, including drugs[27-29].

The body content of albumin is 4-5 g/kg, distributed predominantly in the extracellular space; 30-40% is found in the intravascular compartment (40-50 g/L of plasma) and is responsible for about 80% of the osmotic pressure of the plasma[19].

It has not been clearly determined whether there is a threshold concentration of albumin below which its oncotic function is compromised to a clinically relevant degree; there is, however, a consensus that oncotic activity remains physiologically adequate at values of albumin ≥ 2 g/dL and total proteins $\geq$ 3.5 g/dL.

The infusion of human albumin causes, within a few minutes, the movement of fluids from the interstitial space into the circulation; this passage of fluids is, however, limited or absent in dehydrated patients unless the dehydration is corrected.

The half-life of endogenous albumin is about 3 weeks, while that of blood-derived albumin is only 12-16 hours and is reduced notably in conditions of increased capillary permeability.

Preparations of albumin

Solutions of albumin are prepared from the plasma of healthy donors. The albumin is pasteurised at 60 °C for 10 hours [30]. It can be infused independently of the recipient's blood group.

Preparations of 5%, 20% and 25% have been registered. The solutions of 5% human albumin have an osmotic pressure almost identical to that of normal plasma; the 20% and 25% solutions are hyperosmotic. All the preparations contain 130 - 160 mEq of sodium per litre.

Indications

On the basis of clinical evidence, the use of albumin can be indicated in acute conditions[31], in which it is necessary to expand the volume and maintain the circulation, and in some chronic states of low serum albumin; there are some widely shared

Blood Transfus 2009; 7: 216-34 DOI 10.2450/2009.0094-09

and fully agreed indications for the appropriate use of human albumin and indications that are occasionally appropriate, that is, when other criteria are fulfilled (table I)[32,33]. Albumin is also used in all cases in which there is a contraindication to the use of non-protein colloids.

Acute conditions

Haemorrhagic shock (occasionally appropriate indication)

Albumin is used as a **second choice** *(Grade of recommendation: 1A)*[8-16,18,32-38], when **solutions of crystalloids or non-protein colloids (first choice treatment)** have already been used at maximum doses without having produced a clinically adequate response and in cases in which non-protein colloids are contraindicated.

Crystalloid and colloid solutions must not be considered as blood replacements when oxygen-transporting capacity is reduced. Albumin 5% must be used.

Major surgery (occasionally appropriate indication)

The use of albumin may be indicated in subjects undergoing major surgery (> 40% resection of the liver, extensive intestinal resection) when, after normalisation of circulatory volume, the serum albumin is < 2 g/dL *(Grade of recommendation 2C+)*[14,15,17,18,31-33,39,40].

The use of albumin in the immediate post-operative period is never advised for any other type of operation.

Table I –Indications for the use of albumin

Indication	Notes	GoR
Appropriate indications (for which there is widespread consensus)		
Paracentesis	5 g of albumin/L ascitic fluid removed, after paracentesis of volumes > 5 L.	1C+
Therapeutic plasmapheresis	For exchanges of > 20 mL/kg in one session or > 20 mL/kg/week in more than one session.	2C+
Spontaneous bacterial peritonitis	In association with antibiotics.	1C+
Occasionally appropriate indications (when other criteria are fulfilled)		
Heart surgery	Last-choice treatment after crystalloids and non-protein colloids.	2C+
Major surgery	Albumin should not be used in the immediate post-operative period. Only indication for use: serum albumin < 2 g/dL after normalisation of circulatory volume.	2C+
Cirrhosis of the liver with refractory ascites	Generally ineffective, except in patients with serum albumin < 2 g/dL.	2C
Contraindications to the use of non-protein colloids	- pregnancy and breastfeeding; - perinatal period and early infancy; - acute liver failure; - moderate-severe renal failure (particularly when anuria/oligouria); - dialysis treatment in the presence of severe abnormalities of haemostasis and baseline albumin < 2 –2.5 g/dL; - intracranial haemorrhage; - hypersensitivity.	2C
Haemorrhagic shock	Only in the case of : - lack of response to crystalloids or colloids; - contraindication to the use of non-protein colloids.	1A
Hepatorenal syndrome	In association with vasoconstricting drugs.	2B
Nephrotic syndrome	Only in patients with albumin < 2 g/dL with hypovolaemia and/or pulmonary oedema.	2C
Organ transplantation	In the post-operative period after liver transplantation to control ascites and peripheral oedema, to replace the loss of ascitic fluid from the drainage tubes, if albumin < 2.5 g/dL with a haematocrit > 30%.	1C
Burns	In the case of burns of > 30% body surface area, after the first 24 hours.	2C+

Dose

The dose needed to obtain a serum albumin ≥ 2.5 g/dL is calculated using the following formula:

Dose (g) = [desired albumin concentration (2.5 g/dL) –actual albumin concentration (g/dL)] x plasma volume (0.8 x kg)

GoR: Grade of Recommendation

Burns
(occasionally appropriate indication)

There is no indication to use albumin in the resuscitation phase in the first 24 hours after burn injuries, that is, in the period of increased capillary permeability. Subsequently, albumin 5% is indicated, using different doses according to the amount of body surface area (BSA) involved *(Grade of recommendation: 2C+)*[7,15,18,38,41,42]:

- BSA 30 - 50%: 0.3 mL x kg x % of burnt BSA, in 24 hours;
- BSA 50 - 70%: 0.4 mL x kg x % of burnt BSA, in 24 hours;
- BSA 70 - 100%: 0.5 mL x kg x % of burnt BSA, in 24 hours.

In the post-resuscitation phase, once the problems of circulatory volume caused by the marked capillary permeability have been overcome, albumin 5% or 20% is infused at a dose of 1 - 2 g/kg/die if:

- albumin < 1 g/dL (end-point 2 g/dL);
- albumin 1-2 g/dL and the patient cannot tolerate an enteral diet or has massive tissue oedema or pulmonary dysfunction, which could be aggravated by a low oncotic pressure (end-point 2 g/dL).

Heart surgery
(occasionally appropriate indication)

Albumin can be used as a post-operative volume expander, as a last choice of treatment after crystalloids or non-protein colloids, following heart surgery.

Crystalloids are the first choice for priming the circuitry in the case of extracorporeal circulation[43,44]; the association with non-protein colloids can be preferable to avoid the accumulation of fluid in the pulmonary interstitium *(Grade of recommendation: 2C+)*[14,43-46].

Organ transplantation
(occasionally appropriate indication)

Albumin can be useful in the post-operative period following liver transplantation, in order to control the ascites and peripheral oedema and to replace the loss of ascitic fluid through the drainage tubes; it is administered in the following circumstances: albumin < 2.5 g/dL, pulmonary capillary pressure < 12 mmHg, haematocrit > 30% *(Grade of recommendation: 1C)*[13,32,33,47].

There is not definitive evidence that albumin and/or non-protein colloids are effective during or after kidney transplants[32,33].

Therapeutic plasmapheresis
(appropriate indication)

The use of albumin is appropriate only for the exchange of large volumes of plasma: more than 20 mL/kg in a single session or 20 mL/kg/week in successive sessions. In the case of exchange of small volumes of plasma, it is worth considering, for cost-benefit reasons, crystalloid solutions or the association of albumin/crystalloids *(Grade of recommendation: 2C+)*[32,33,48-50].

Chronic states of low albuminaemia

Liver cirrhosis with refractory ascites

There is a lack of consensus on the use of albumin in advanced liver disease, but there is some evidence to support its use in the following circumstances:

1) ascites not responsive to diuretics;
2) large volume paracentesis;
3) hepatorenal syndrome;
4) spontaneous bacterial peritonitis.

Ascites not responsive to diuretics
(occasionally appropriate indication)

This is the most controversial indication. Albumin is usually ineffective, except in patients with serum albumin < 2 g/dL. Subjects with ascites are at risk of diuretic-induced hyponatraemia and deteriorating renal function (prerenal uraemia); the risk is highest in subjects with hypoalbuminaemia and advanced disease. Albumin can improve the response to diuretics and prevent complications related to the treatment, favouring the passage of fluid from the peritoneal space to the vascular compartment; it can also correct the altered pharmacokinetics of loop diuretics typically seen in patients with cirrhosis. The patients who can gain most benefit from this treatment are those in the most precarious clinical condition, with hypovolaemia and ascites that responds poorly to diuretics: in these cases albumin can be administered even when the concentration of albumin is > 2.5 g/dL *(Grade of recommendation: 2C)*[51-59].

Large volume paracentesis
(appropriate indication)

Total paracentesis is considered the treatment of choice in subjects with refractory or tense ascites. A paracentesis volume > 5L can, in some cases, lead to hypovolaemia and particularly unfavourable haemodynamic changes, with the possible risk of:

- deterioration of renal function;

Blood Transfus 2009; 7: 216-34 DOI 10.2450/2009.0094-09

- dilutional hyponatraemia;
- rapidly recurrent ascites;
- shortened survival.

In order to reduce the risks in such cases, albumin is used at a dose of 5 g/L of fluid removed, in a single administration at the end of the paracentesis. The 20% - 25% preparations are preferable *(Grade of recommendation: 1C+)*[32,33,55,60-64].

Hepatorenal syndrome (HRS)
(occasionally appropriate indication)

HRS consists of a deterioration in renal function, which occurs in 10% of subjects with advanced cirrhosis and ascites[65]. It is considered the extreme outcome of the haemodynamic dysfunction of cirrhosis, associated with impaired cardiac function due to the reduced venous return.

The deterioration in renal function can be rapidly progressive (type 1 HRS) or stable-slowly progressive (type 2 HRS); the mortality rate of patients with type 1 HRS is very high, with a median survival (without therapy) of less than 1 month.

The treatment of choice is liver transplantation. Medical treatment consists of a combination of vascoconstrictors and high doses of albumin *(Grade of recommendation: 2B)*[32,33,65-68].

Spontaneous bacterial peritonitis
(appropriate indication)

Spontaneous bacterial peritonitis is a common and severe complication of ascitic cirrhosis and occurs in about 20 - 30% of patients; it is characterised by spontaneous infection of the ascitic fluid, in the absence of abdominal sources of infection, and can evolve, in about 30% of the cases, into HRS.

Albumin 20% - 25%, in association with antibiotics, can be used in the treatment of spontaneous bacterial peritonitis and reduces the probability of the onset of HRS and mortality *(Grade of recommendation: 1C+)*[69-74].

Nephrotic syndrome
(occasionally appropriate indication)

Short-term infusion of albumin 20% - 25%, in association with diuretics, is appropriate in patients with serum albumin < 2 g/dL, with marked hypovolaemia and/or acute pulmonary oedema and/or acute renal failure *(Grade of recommendation: 2C)*[32,33,75-77].

Malnutrition syndromes
(occasionally appropriate indication)

Albumin must not be used for nutritional purposes; the correct treatment is enteral nutrition, using peptide-based formulas, or total parenteral nutrition.

However, the administration of albumin can be useful in patients with diarrhoea who cannot tolerate enteral nutrition in the following circumstances: volume of diarrhoea > 2 L/die; serum albumin < 2 g/dL; continuing diarrhoea despite the administration of short-chain peptides and mineral formulas; no other cause to explain the diarrhoea *(Grade of recommendation: 2C)*[32,33].

Inappropriate indications

Albumin is not indicated in the following conditions (table II)[32,33]:

- albuminaemia > 2.5 g/dL (with the exception of the particular cases listed above);
- hypoalbuminaemia in the absence of oedema and acute hypotension;
- malnutrition;
- wound healing;
- non-haemorrhagic shock[78,79];
- ascites responsive to diuretics;
- burns in the first 24 hours;
- protein-losing enteropathies and malabsorption;
- acute or chronic pancreatitis;
- haemodialysis[80-83];
- cerebral ischaemia[84];
- acute normovolaemic haemodilution in surgery;
- ovarian hyperstimulation syndrome[85-87].

Calculation of the dose of albumin to administer

Dose (g) = (2.5 g/dL –actual albumin concentration) x (kg x 0.8) (table I).

Legend:

2.5 g/dL: desired concentration of albumin; kg: body weight; 0.8: coefficent to calculate the volume of plasma.

Monitoring indices for clinical auditing

The use of albumin therapy in the following circumstances:

- albuminaemia > 2.5 g/dL;
- malnutrition;
- non-haemorrhagic shock;
- ascites responsive to diuretics;
- acute or chronic pancreatitis;

Side effects and adverse reactions

Albumin is usually well tolerated. However, immediate allergic-type reactions are possible with fever, shivers, nausea, vomiting, urticaria, hypotension, increased salivation, and effects on respiration and heart rate[32,33,88]. Very fast infusions (20 - 50 mL/minute) can cause a brusque fall in systemic blood pressure and, in elderly subjects and those at risk of congestive heart failure, it can induce manifest congestive heart failure, particularly when the more concentrated solutions of albumin are used. Albumin is considered a safe blood derivative from the point of view of transmission of infections, although there are some questions about the potential transmission of prions.

Recommendations

It is recommended that the details of the product infused, including the batch number, are registered in the patient's clinical records.

Table II – Inappropriate indications for the use of albumin.

1)	Albuminaemia > 2.5 g/dL
2)	Chronic hypoalbuminaemia in the absence of oedema and/or acute hypotension
3)	Malnutrition
4)	Wound healing
5)	Non-haemorrhagic shock
6)	Ascites responsive to diuretics
7)	Burns, in the first 24 h
8)	Protein losing enteropathies and malabsorption
9)	Acute or chronic pancreatitis
10)	Haemodialysis
11)	Cerebral ischaemia
12)	Acute normovolaemic haemodilution in surgery
13)	Ovarian hyperstimulation syndrome

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Immunoglobulins

Introduction

Immunoglobulins (IG) are registered for a limited number of indications[1], but are used much more extensively in clinical practice. Many of the uses do not always appear fully justified by the data in the literature.

Intravenous immunoglobulins (IVIG) are used as replacement therapy in immunodeficiency states and in the treatment of autoimmune diseases and systemic inflammatory disorders.

In Italy preparations of soluble IG have been available for subcutaneous infusion since 2007.

Notions of pharmacokinetics

Following intravenous administration, normal human IG are immediately and completely bioavailable: the peak serum level is dose-related. The IG distribute relatively quickly between the plasma and extravascular fluids; the equilibrium between the intravascular and extravascular compartments is reached after approximately 3-5 days[2,3]. The initial decrease in serum levels is the result not only of the extravascular redistribution, but also of other factors, including metabolism of denatured molecules and clearance of immune complexes that may have formed after an interaction with an antigen. The half-life of IG is estimated to be about 18-32 days, which is similar to that of endogenous IgG. There is, however, a considerable individual variability that reflects various factors, including the level of IG before the infusion, the peak level after the infusion and the presence of infections or burns.

Preparations of immunoglobulins

IVIG, like all other plasma derivatives, are prepared using pools of human plasma; this leads to significant idiotypic diversity, which guarantees the recipient a greater antibody cover. The preparations of IVIG contain structurally and functionally intact immunoglobulins, with a normal half-life and proportion of the subclasses: 95% of monomeric IgG, small quantities of dimers, variable quantities of IgA and IgM[2,4-10]. They do not contain high molecular weight immune complexes or contaminants such as vasomotor peptides and endotoxins.

They are prepared from plasma from healthy donors and, furthermore, undergo industrial processing[4,5,10], chemical and physical removal and inactivation of bacteria and viruses.

Mechanism of action

In humoural immunodeficiencies, the IG are administered intravenously to replace those that are lacking because of a deficiency in their production.

Numerous studies have shown that IVIG also have powerful immunomodulatory and anti-inflammatory effects, although the *in vivo* mechanisms of these effects are partly unknown. Various mechanisms have been proposed over time to explain the effects of IVIG in disorders of immune system regulation[2,7,11-25]:

- interaction of the Fc fragment with specific receptors (FcγR)[2,7,17,19,25];
- control of the complement pathway and activation of mechanisms inducing solubilisation of circulating immune complexes[2,7,15,18,25];
- interaction with the idiotype anti-idiotype network[2,7,17,18,23,25];
- modulation of the production of some cytokines and their antagonists[2,7,13,17,18,25];
- increased catabolism of IgG[2,7,17];
- apoptosis of B and T cells through activation of the Fas receptor (apoptosis stimulating fragment - CD95)[7,14,25];
- blockage of the binding between T cells and superantigens[2,7,11,25];
- control of autoreactivity and induction of tolerance to self[2,7,18,25];
- inhibition of the differentiation and maturation of dendritic cells[2,24,25].

Indications

Table I, drawn from the *Gazzetta Ufficiale* N. 260 of 6/11/2002[1], provides a summary of the indications and doses recommended for the diseases that are listed[1,2,7,18,23,25-69]. Table II, on the other hand, presents the clinical conditions for which the routine use of IVIG is not recommended, despite their being reports of the use of this product; the low levels of evidence are due to the lack of studies in sufficiently large series of patients, in turn a consequence of the rarity of the diseases[2,7,18,25,35,36,44,45,51-58,64,70-96].

Finally, table III lists the inappropriate indications[2,7,22,26,36,40,44,45,51,52,54,56,64,71,97-106].

Replacement therapy

The use of IVIG for the treatment of patients with

Table I – Recognised indications for IVIG (Gazzetta Ufficiale of 06/11/2002, N. 260)[1]

Indication	Dose	Frequency of administration
Immunodeficiencies		
Primary immunodeficiency[7,18,26-36,46,47]	initial dose: 0.4-0.8 g/kg maintenance: 0.2-0.8 g/kg	every 2-4 weeks to obtain an IgG level of at least 4-6 g/L
Secondary immunodeficiency[7,18,26,29,31-45]	0.2-0.4 g/kg	every 3-4 weeks to obtain an IgG level of at least 4-6 g/L
Children with AIDS[7,18,33-36,39]	0.2-0.4 g/kg	every 3-4 weeks
Immunomodulation		
ITP or Werlhof's syndrome[7,18,25,35,36,44,45,48-50]	0.8-1.0 g/kg	on day 1, possibly repeated a single time within 3 days
	or 0.4 g/kg/die	for 2-5 days
Guillain-Barré syndrome[2,7,18,23,25,35,42-44,46,47,51-64]	0.4 g/kg/die	for 3-7 days
Kawasaki's disease[7,18,25,26,35,36,65-69]	1.6-2 g/kg	in several doses over 2-5 days in association with ASA
	or 2 g/kg	in a single dose in association with ASA
Allogeneic bone marrow transplantation		
Treatment and prophylaxis of infections and GvHD[7,18,25,35,36,44,45]	0.5 g/kg	every week from day -7 until 3 months after the transplant
Persistent deficit of the production of antibodies[7,35,36,44,45]	0.5 g/kg	every month until normalisation of the levels of antibodies

Table II - Clinical conditions for which the routine use of IVIG is not recommended, although their use has been reported

Clinical conditions	Indications and dose	GoR
Haematology		
Alloimmune neonatal thrombocytopenia [7,35,36,44,45,71,73,75]	IVIG are recommended in symptomatic neonates, at high risk of intracranial bleeding, if other strategies have been unsuccessful, not tolerated or contraindicated. IVIG can be used prior to delivery in high-risk mothers, with a history of alloimmune neonatal thrombocytopenia and foetal or neonatal thrombocytopenia. 1g/kg per week (to the mother).	2C
Autoimmune haemolytic anaemia (AEA)[7,25,35,36,44,45,70]	IVIG can play a role in patients with AEA due to warm antibodies (Ab) not responsive to cortico-steroids or splenectomy, or in those in whom the abovementioned treatments are contraindicated. 0.4 g/kg/die for 5 days.	2C
Haemolytic disease of the newborn (HDN)[7,36,44,45,71,72]	IVIG are recommended in neonates with severe HDN (0.5-1g/kg/die for three doses), if other therapeutic strategies are not feasible. The IVIG may be given to the mother before delivery if other strategies have been unsuccessful, not tolerated or contraindicated.	2C
Immune-mediated neutropenia[7,44,45]	IVIG may have a role in patients in whom other strategies have been unsuccessful, not tolerated or contraindicated.	2C
Post-transfusion purpura[7,36,44,45,73,74]	IVIG may be considered in severely affected patients.	2C

follows

Clinical conditions	Indications and dose	GoR
Pure red cell aplasia[44,45,96]	IVIG can be used in patients with documented Parvovirus B19 infection and severe anaemia. 0.4 g/kg every 28 days.	2C
Refractoriness to platelet transfusion[7,73]	IVIG may have a role in patients in whom other strategies have been unsuccessful, not tolerated or contraindicated.	2C
Infectious diseases		
CMV prophylaxis in solid organ transplants[7,18]	IVIG can be used in CMV-negative recipients of CMV-positive organs. 0.4 g/kg every 28 days.	2C+
Neurology		
Acute disseminated encephalomyelitis[44,64]	IVIG can be considered if first-line therapy (high-dose steroids) is ineffective or contraindicated. 2g/kg in 2 days for children or in 2-5 days for adults.	2B
Chronic inflammatory demyelinating polyneuropathy[2,7,18,25,35,36,44,51-58,64,79-84]	IVIG are recommended as an equivalent choice to therapeutic plasmapheresis in the acute phase in children and adults. Their use in chronic treatment is currently suggested only from observational studies. 0.4 g/kg/die for 5 days	1A 2C
Intractable childhood epilepsy[44,51,64]	IVIG can play a role in some syndromes (e.g. West,Lennox-Gastaut) as a last strategy, particularly in patients who could be candidates for surgical resection.	2C
Lambert-Eaton syndrome[2,36,44,51,52,55,56,64,86]	IVIG can be considered in patients with a severe syndrome, if other strategies have been unsuccessful, not tolerated or contraindicated. 0.4 g/kg/die for 5 days.	2C+
Multifocal motor neuropathy[2,7,18,25,36,44,51-58,64,77,78]	IVIG can be considered in patients who have a progressive and symptomatic multifocal neuropathy, diagnosed on the basis of electrophysiological findings that exclude other possible conditions that do not respond to this treatment. 0.4 g/kg/die for 5 days.	2C+
Multiple sclerosis[2,7,18,25,35,44,51-53,55,64,85]	IVIG can be considered in patients with moderate or severe manifestations of multiple sclerosis in recurrence-remission, in whom other strategies have been unsuccessful, not tolerated or contraindicated.	2C
Myasthenia gravis[2,7,35,44,51-53,55,56,64,76]	IVIG can be considered in patients with myasthenic crises (0.4 g/kg/die for 5 days or 2g/kg for 2 days). Maintenance treatment is still experimental.	2C+
Stiff-person syndrome[2,7,18,25,36,44,52,55,56,64,87,88]	IVIG were found to be effective in one randomised clinical study (14 patients); they may have a role if GABA-ergic drugs have been ineffective or contra-indicated. 2 g/kg/month.	2B
Rheumatology		
Dermatomyosites, Polymyosites[2,7,18,25,36,44,51-53,55,56,64,89]	IVIG can be used in patients with active, severe disease in whom other strategies have been unsuccessful, not tolerated or contraindicated. 0.4 g/kg/die for 5 days.	2C+
Systemic lupus erythematosus (SLE)[7,25,53]	IVIG can be used in patients with active, severe SLE in whom other strategies have been unsuccessful, not tolerated or contraindicated.	2C+
Systemic vasculitides[7,36]	IVIG can be used in patients with active, severe disease, particularly in those with ANCA-positive vasculitis or other systemic vasculitis, in whom other strategies have been unsuccessful, not tolerated or contraindicated.	2C+
Renal transplantation		
Pre-transplant desensitisation[7,35,90-95]	IVIG can be used (also together with plasmapheresis) in patients with high pre-transplant levels of anti-HLA Ab as a desensitising strategy.	2B

GoR: Grade of Recommendation

Table III –Inappropriate indications for the use of IVIG

Clinical conditions	GoR
Haematology	
Acquired inhibitors of FVIII[44,45]	2C
Acquired von Willebrand's disease[44,45]	2C
Aplastic anaemia[44,45]	2C
Diamond-Blackfan anaemia[22,26]	2C
TTP and uraemic-haemolytic syndrome[44,45]	2C
Infectious diseases	
Burns (prophylaxis from infections)[22,26]	2C
HIV infection (adult)[22,26]	2C
Surgery and/or trauma (prophylaxis)[7]	1A
Rheumatology	
Inclusion body myositis[2,22,26]	1A
Rheumatoid arthritis (juvenile and adult)[7,105]	1A
Miscellaneous	
Acute cardiomyopathy[22,26,99]	2C
Acute idiopathic dysautonomia[22,26]	2C
Acute lymphoblastic leukaemia[22,26]	1A
Acute renal failure[22,26]	1A
Adrenoleucodystrophy[44,64]	2C
Amyotrophic lateral sclerosis[44,51,64]	2C
Autism[7,44,64]	2C
Autoimmune bullous dermatoses[22,26,36]	2C
Autoimmune childhood neuropsychiatric disorders associated with streptococcal infections[44,64]	2C
Behçet's disease[22,26]	2C
Bronchial asthma[7,98]	1A
Chronic fatigue syndrome[22,26]	2C
Congenital cardiac arrest[22,26]	1A
Cystic fibrosis[22,26]	1A
Diabetes mellitus[7]	2C
Diabetic neuropathy[44,64]	2C
Endotoxaemia[22,26]	2C
Euthyroid ophthalmopathy[22,26]	2C
Haemolytic transfusion reaction[44,45]	2C
Haemophagocytic syndrome[22,26]	2C
HTLV-1-associated myelopathy[22,26]	2C
Inclusion body myositis[44,56,64]	2C
Inflammatory bowel diseases (Crohn's disease, ulcerative colitis)[7]	2C
Lower motor neurone syndrome[22,26]	2C
Lyell's syndrome[7,102]	2C
Lyme radiculoneuritis[22,26]	2C
Nephritic syndrome[22,26]	2C
Nephrotic syndrome[22,26]	1A
Non-immunological thrombocytopenia[22,26,44,45]	2C
Opsoclonus-myoclonus[44,64]	2C
Paraneoplastic cerebellar degeneration[22,26,51]	2C
Paraproteinaemic neuropathy[44,51,52,56,64,101]	2C
Parvovirus infection (in general)[22,26]	2C
POEMS syndrome (polyneuropathy, organomegaly endocrinopathy, protein M, skin alterations)[22,26,44,51,64]	2C
Polyneuropathy in the critically ill patient[44,64]	2C
Progressive lumbo-sacral plexopathy[22,26]	2C
Rasmussen's syndrome[22,26,44,51]	2C
Recurrent abortions[7,71,97]	1A
Recurrent otitis media[22,26]	2C
Reiter's syndrome[22,26]	2C
Streptococcal septic shock[22,26,40]	2C
Uveitis[22,26]	2C
Viral myocarditis (presumed)[100]	2C+
Vogt-Koyanagi-Harada syndrome[22,26]	2C

GoR: Grade of Recommendation

primary or secondary antibody deficiencies was authorised in the USA in 1981, since when it has been possible to exploit this product, by then purified of the high molecular weight aggregates responsible for severe reactions, using the Cohn-Oncley separation technique[4].

Compared to the previous treatment based on intramuscular IG, the use of IVIG enabled higher doses of IG to be administered, thus permitting normalisation of blood levels. The aim of treatment is to maintain serum levels (before the next infusion) of IgG > 5 g/dL; the clinical condition of the patient must, of course, always be evaluated[33].

Reaching these levels leads to the patient having fewer febrile episodes and, in general, reductions in the number of recurrent infections, days spent in hospital and time on antibiotic treatment, an improvement in indices of respiratory function and, in paediatric patients, an increase in body weight, which is an indicator of an improved quality of life.

Primary deficiencies

- Humoural immunodeficiencies[22,26]:
  a) X-linked agammaglobulinaemia;
  b) common variable immunodeficiency;
  c) immunodeficiency with hyper-IgM;
  d) transient childhood hypogammaglobulinaemia (sometimes);
  e) deficiencies of IgG subclasses (sometimes with or without IgA deficiencies).
- Combined immunodeficiencies[22,26]:
  a) all types of severe combined immunodeficiencies;
  b) Wiskott-Aldrich syndrome;
  c) ataxia-telangiectasia;
  d) short-limbed dwarfism;
  e) X-linked lymphoproliferative disease.

Treatment with IVIG is indicated if the level of IgG is below 5 g/L. It takes 3 to 6 months after the start of treatment for a balance to be reached. The recommended starting dose is 0.4-0.8 g/kg of body weight; this should be followed by 0.2-0.8 g/kg every 2-4 weeks, in order to achieve minimum IgG levels > 5 g/dL *(Grade of recommendation: 1A)*[1,7,18,26-36].

Secondary deficiencies

a) In lymphoproliferative diseases with antibody deficits (multiple myeloma, chronic lymphocytic

leukaemia, non-Hodgkin's lymphoma) the use of IVIG, to maintain plasma IG levels > 4-6 g/L, is indicated for patients with a documented deficiency in antibodies and recurrent infections; the dose is 0.2-0.4 g/kg every 4 weeks *(Grade of recommendation: 1A)*[1,7,18,26,29,31-45].

b) Acquired immunodeficiency syndrome in childhood: IVIG can be used in HIV-positive children with hypogammaglobulinaemia to prevent opportunistic infections, in cases of recurrent bacterial infections and/or ineffective antibiotic and antiretroviral therapy; the dose is 0.2-0.4 g/kg every 4 weeks *(Grade of recommendation: 2C+)*[7,18,33-36,39,46,47].

c) Allogeneic bone marrow transplantation: IVIG can be used in the treatment of infections and the prophylaxis of GvHD, at the dose of 0.5 g/kg every week from 7 days before the transplant until 3 months after it. In the case of a persistent deficit in antibody production, the dose is 0.5 g/kg every 4 weeks until the levels of IgG normalise *(Grade of recommendation: 2C)*[1,7,18,25,35,36,44,45].

d) Prematurity: prophylaxis with IVIG may play a role in the management of low birth weight neonates (< 1,500 g) or in those with severe infections; the dose is 0.4-0.7 g/kg in 1-7 administrations[22,26].

Immunomodulation

For some years IVIG have also been used in immunomodulatin therapy. High doses of IVIG have immunosuppressive and anti-inflammatory effects and have, therefore, been used in the treatment of autoimmune and/or inflammatory diseases, as well as in haematological, rheumatological and neurological conditions.

The only indications for which there is recognised to be high levels of evidence are: ITP, Kawasaki's disease and Guillan-Barré syndrome.

e) In ITP, IVIG are, in any case, used after other pharmacological treatments have failed; the exceptions to this are acute episodes associated with bleeding or cases in which surgery is considered necessary; in these situations the recommended dose is 0.8-1 g/kg on the first day, which can be repeated within 3 days, or 0.4 g/kg/die for 2-5 days *(Grade of recommendation: 1A)*[7,18,25,35,36,44,45,48-50].

f) The recommended dose in Kawasaki's disease is 1.6-2 g/kg, in divided administrations over 2-5 days or 2 g/kg in a single administration; this latter method of administration has been shown to be more effective in preventing aneurysmal complications of the coronary arteries. Concomitant treatment with acetylsalicylic acid (ASA) is recommended *(Grade of recommendation: 1A)*[7,18,25,26,35,36,65-69].

g) The dose in Guillain-Barré syndrome is 0.4 g/kg/die for 3-7 days *(Grade of recommendation: 1A)*[2,7,18,23,25,35,42-44,51-64].

IVIG are used in numerous other conditions; nevertheless, their routine use is not recommended and they should be employed only in particular situations or as an alternative to other therapeutic measures. Table II lists the diseases for which the use of IVIG has been suggested based on their mechanism of action, results of uncontrolled, single clinical trials or authoritative opinion drawn from clinical experience, descriptive studies or single case reports.

Monitoring indices for clinical auditing

Administration of IVIG treatment in the following conditions:

- replacement therapy when IG > 6 g/L;
- immunomodulation in diseases for which there are not recognised indications.

Side effects and adverse reactions

Side effects of variable severity occur in 1-15% of treated patients, but are usually of limited clinical importance. They include headache, shivers, hyperthermia, fever, allergic reactions, nausea, vomiting, joint pains, and hypotension to the point of anaphylactic shock, even in patients who have not shown signs of hypersensitivity to previous administrations[2,5,7,107]. Although the aetiology remains uncertain, it seems that aggregates of IgG, IgG-dimers and activation of the complement pathway may be involved. The aggregates are able to activate complement even in the absence of the antigen[7].

Patients with an antibody deficiency more frequently have reactions, including anaphylactic ones; slow infusion seems to lower the risks. Most of these reactions resolve with temporary interruption of the infusion or a slowing of its rate of administration, or can be prevented by giving ASA, paracetamol or anti-histamines before the treatment and/or hydrocortisone during it[107]. Severe anaphylactic

reactions have occurred in patients with IgA deficiency. Although the content of IgA in IVIG preparations is modest and, in any case, varies between products, small amounts can cause fatal reactions, especially in patients with anti-IgA immunoglobulin E[2,7].

Thromboembolic events have been reported, particularly in elderly patients, in patients with previous cerebral or cardiac ischaemia, in overweight patients, those who are markedly hypovolaemic and in immobilised subjects[108-110].

Rare cases of reversible aseptic meningitis have also been observed in patients with neurological and neuromuscular diseases treated with high doses of IVIG[111]. The symptoms appear within 6-24 hours of the end of the infusion and disappear without sequelae in 3-5 days.

Increases in creatinine and/or renal failure, particularly acute, have been observed rarely in elderly, diabetic, poorly hydrated patients, with pre-existing renal disease or who are taking nephrotoxic drugs. These problems are probably related to damage caused to the renal tubules by the saccharose included in various preparations as a stabiliser[112,113].

As far as concerns the possibility of transmitting infectious agents with these plasma-derivatives, there is a potential risk of transmission of spongiform encephalopathies (Creutzfeld-Jacob disease, Gerstmann Straussler-Scheinker disease and fatal familial insomnia), since the prions responsible for these diseases are resistant to standard methods of inactivation. Furthermore, solvent/detergent inactivation is ineffective against viruses that do not have a lipid envelope, such as HAV and parvovirus B19[114].

Precautions and recommendations

It is recommended that the details of the product infused, including the batch number, are recorded in the clinical records.

Side effects can be partly prevented by injecting the product slowly at the beginning and monitoring the patient for the appearance of any symptoms. Monitoring should be particularly careful for patients who have never received IVIG, those being given a different preparation from a previous one and when a long period has passed between one infusion and another; in such cases the patients should monitored during the infusion and for the first hour after its completion. All other patients should be observed for at least 20 minutes after the product has been administered.

All patients must be well hydrated prior to the infusion and production of urine and levels of serum creatinine should be monitored. Furthermore, it should be ascertained whether the patient has diabetes or pre-existing renal failure, is taking loop diuretics or nephrotoxic drugs; in these patients preparations containing saccharose, used as a stabiliser, should be avoided.

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Appendix A

Working methods of the study group and grades of recommendation

The process of developing these Recommendations, in compliance with the indications contained in the methodological manual of National Programme for Guidelines[1], was based on a systematic review of the literature and updating of existing recommendations on the subject: the recommendations will be discussed in a multidisciplinary context in a subsequent stage and in the relevant institutions. Furthermore, an explicit evaluation of the quality of the proof and the strength with which the single recommendations are adopted and implemented is provided[1].

The methodology used to prepare the grades of recommendations was drawn from that used by the Consensus Conference of the American College of Chest Physicians in 2004[2].

The recommendations are classified by **grade**, expressed in Arabic numbers (1,2), according to their strength, and in **letters** (A, B, C), according to the evidence and type of study.

In detail (Table I):

- **Grade 1:** the authors are certain that the benefits are greater (or less) than the costs in terms of risk and financial expenditure. This is, therefore, a strong **recommendation.**
- **Grade 2:** the authors are less certain concerning the above points and, therefore, make a weaker recommendation.

As far as regards the classification by letters:

- **Grade A:** a recommendation derived from the evidence of numerous, consistent randomised studies.
- **Grade C+:** a recommendation derived from the analysis of observational clinical studies, but with very consistent results, or from results unequivocally extrapolated from randomised studies.
- **Grade B:** the clinical studies providing the evidence were randomised, but had important limitations (discordant results, methodological flaws).

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- **Grade C:** the recommendation derives from an analysis of observational studies, with less consistent results, or from results extrapolated with a lower degree of certainty from randomised studies; recommendations based on the clinical experience/opinion of experts are also classified as grade C.

The verb "*recommend*" is used for the higher grades (1A, 1C+, 1B, 1C), while the verb "*suggest*" is used for the lower grades (2A, 2C+, 2B and 2C).

In general, any recommendation other than Grade 1A implies that the authors recognise that there are alternative interpretations of the available evidence and that there are other clinical policies that can reasonably be considered appropriate. Furthermore, even the Grade 1A recommendations cannot be applied indiscriminately in every circumstance and in every patient.

The conventional classification of evidence is based on mathematical and statistical criteria, assigning the "strength" of evidence, in order, to: meta-analysis, randomised, controlled, experimental studies, retrospective analyses, prospective follow-ups, transverse population studies, reviews, anecdotal evidence. This is correct as far as concerns the purely clinical studies, particularly therapeutic studies focused on objective outcome evaluations.

In some fields the recommendations remain weak; in others, however, data from clinical studies that have been carried out with methodological rigour in a sufficiently large population have enabled the formulation of specific and more certain recommendations.

Furthermore, it is not always possible to use the aggregated data from meta-analyses: these variables increase the margins of individual decision for each doctor and for each patient**.**

The recommendations are accompanied by indicators intended to enable clinical auditing[1].

The present document will be revised annually, to include new information that has become available in the meantime.

Each member making up the study group has signed a statement declaring a lack of conflict of interests, conforming with that adopted by the National Programmed for Guidelines[1].

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Table I - Grades of Recommendations

Grade of Recommendation	Clarity of Risk /Benefit	Methodological strength of supporting evidence	Implications
1A	Clear	Randomised controlled trials without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1C+	Clear	No randomised controlled trials but strong results from randomised controlled trials can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	Randomised controlled trials with important limitations (inconsistent results, methodological flaws)	Strong recommendations; likely to apply to most patients
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	Randomised controlled trials without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2C+	Unclear	No randomised controlled trials but strong results from randomised controlled trials can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	Randomised controlled trials with important limitations (inconsistent results, methodological flaws)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Evidence obtained from respected authorities or from expert committee reports or opinion of the group of experts responsible for these recommendations	Very weak recommendations; other alternatives may be equally reasonable

Blood Transfus 2009; 7: 216-36 DOI 10.2450/2009.0094-09