Superior Health Council

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Recommended indications for administering immunoglobulins

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1. INTRODUCTION AND ISSUE

On 31 October 2007, the SHC received a request for advice from the Chief Executive Officer of the Federal Agency for Medicines and Health Products[1] concerning the indications for the use of immunoglobulins as opposed to potential alternatives.

Intravenous immunoglobulin (IVIG)[2] is a therapeutic preparation of polyclonal human immunoglobulins obtained from the pooled plasma of healthy donors. It was initially only used to replace immunoglobulins in the case of primary or secondary immunodeficiencies. It was administered to treat primary immunodeficiencies (prevention and treatment of infections), as well as immune thrombocytopenic purpura (recovery after thrombocytopenia). The latter is a condition with a low platelet count which, in most cases, is related to anti-platelet antibodies. Very low platelet counts can result in an abnormal propensity for bleeding as well as bleeding into the skin.

Since then, improved knowledge on the working mechanisms of IVIG has resulted in its use being extended to a considerable number of other pathologies, including autoimmune or inflammatory disorders. The aim is to modulate autoimmunity and alloreactivity and to enhance anti-infective immunity when providing medical treatment for infections (Kazatchkine & Kaveri, 2001). The immunomodulatory effects of IVIG are said to be linked to the presence of natural antibodies that either interact with the idiotypes of the autoantibodies that they neutralise, or with microbial epitopes that are similar or identical to self antigens. Different phenomena play a role in the working mechanism of IVIG: the modulation of the expression and the function of the Fc-receptors on phagocytes, the inhibition of complement-dependent cytolysis, the modulation of cytokine production and lymphocyte proliferation, the neutralisation of circulating antibodies through interaction with the variable regions of the IVIG, the modulation of dendritic cell maturation and function (Galeotti et al., 2009).

At present, immunoglobulins are not only being used for the key indications, but are also chosen to treat numerous other disorders, many of which are suspected to have an autoimmune or infectious cause, sometimes because there is no other convincing explanation.

[1] Letter from Mr. X. De Cuyper, Chief Executive Officer of the Federal Agency for Medicines and Health Products (reference: XD/TR/WB/07079/12145) of 16/10/07, addressed to Mr. G. De Backer, SHC Chairman.

[2] In this advisory report, we will use the common abbreviation IVIG. It goes without saying that the route of administration does not determine the indication. As regards primary and secondary immunodeficiencies, the subcutaneous route is a therapeutic alternative.

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This increase in demand as well as high production costs and variable supply levels mean that there is a limited availability, even chronic shortage of IVIG. In the hospitals that have set up a committee that monitors its use, a small number of indications (e.g. chronic neuropathies) account for the high annual consumption of IVIG (Darabi et al., 2006). Whenever the availability of these products is very limited, this annual consumption remains stable, in spite of the fact that fewer patients are being treated (Pendergast et al., 2006). Indeed, this concerns exceptional applications under empirical circumstances. This limited availability means that it is crucial to obtain better evidence in support of their clinical effectiveness in treating the disorders for which they are most used. Several countries are implementing recommendations to limit their use (Boulis et al., 2001; AFSSAPS, 2008; EMA, 2008; Provan et al., 2008; AIIEG, 2009; KCE, 2009; ORBCON, 2009). After all, the optimal use of immunoglobulins remains a key step towards making this treatment available to those who need it. Even though strict rules are being set up for their use, a particular effort must continuously be made as regards the standardising and rationalising of the clinical indications, especially in light of the progress made with alternative treatments (Kumar et al., 2006; Orange et al., 2006; Robinson et al., 2007; Lin et al., 2007; Mouthon & Guilpain, 2007; NBA, 2007; Negi et al., 2007; Provan et al., 2008; Raanani et al., 2008; Enk et al., 2009; Donofrio et al., 2009; Shebata et al., 2010, 2010b). With there being many disorders concerned and the level of evidence remaining insufficient, it is inevitable that there should be some differences between the recommended indications.

In order to provide an answer to the question, an expert meeting was organised on 9 May 2008. It was designed to take stock of the knowledge on administering immunoglobulins as opposed to potential alternative treatments.

This advisory report aims at determining whether there is a rational way in which the indications for immunoglobulin treatment can be classified by order of priority, the objective being to allow for wise choices to be made in times of chronic shortage.

2. RECOMMENDATIONS

The SHC takes the view that it is of crucial importance to provide opportunities to discuss the “orphan indications” with clinical experts if there are not enough randomised controlled trials available.

The SHC underlines the fact that alternative treatments must always be considered when deciding whether or not to use immunoglobulins.

Even though immunoglobulins can be looked upon as safe products with moderate side effects, the expertise and experience of a specialist are required to guarantee that they are being used in a safe and optimal manner.

The SHC takes the view that, as regards the selected indications, subcutaneous immunoglobulin can be an alternative to intravenous immunoglobulin.

The SHC recommends that the indications for the use of immunoglobulins should be reviewed at least once every five years. This will allow for these products to be put to the best possible use, in keeping with the latest developments in science and clinical medicine.

The therapeutic role of immunoglobulins in primary immunodeficiencies, post-transfusion purpura and Kawasaki disease has been confirmed.

Treatment with polyvalent immunoglobulins is also recommended in certain presentations of the disorders below:

Immune deficiency caused by a malignant blood disorder, chronic lymphocytic leukaemia or multiple myeloma;
Low levels of IgG in the serum following a haematopoietic stem cell transplantation;
Immune thrombocytopenia – adults and children;
Foetal/neonatal alloimmune thrombocytopenia;
Alloimmune thrombocytopenia – treatment for newborns;
Acquired von Willebrand disease;
Erythroblastopenia caused by a B19 parvovirus infection;
Dermatomyositis resistant to corticosteroids;
Juvenile dermatomyositis resistant to corticosteroids;
Multifocal motor neuropathy;
Chronic inflammatory demyelinating polyneuropathy;
Guillain-Barré syndrome;
Myasthenia gravis;
Haemolytic disease of the newborn (isoimmune haemolytic jaundice);
Multiple sclerosis.

3. ELABORATION AND ARGUMENTATION

List of abbreviations:

aVWD = acquired von Willebrand disease; CIDP = chronic inflammatory demyelinating polyneuropathy; CLL = chronic lymphocytic leukaemia; CMV = cytomegalovirus; CVID = common variable immunodeficiency; DM = dermatomyositis; Fc = crystallisable fragment of an immunoglobulin molecule; GBS = Guillain-Barré syndrome; GvHD = graft versus host disease; HAART = highly active antiretroviral therapy; HDN = haemolytic disease of the newborn; HIV = human immunodeficiency virus; Ig = immunoglobulin; ITP = immune thrombocytopenia; IVIG = intravenous immunoglobulin; MG = myasthenia gravis; MM = multiple myeloma; MMN = multifocal motor neuropathy; MS = multiple sclerosis; NAIT = foetal/neonatal alloimmune thrombocytopenia; PCR = polymerase chain reaction; PTP = post-transfusion purpura; SCIG = subcutaneous immunoglobulin; XLA = X-linked agammaglobulinaemia.

3.1. Methodology

In order to reach its objective, the SHC organised an expert meeting entitled "*Guidelines for the use of immunoglobulins"*, which was held in Brussels on May 9th, 2008. The organising committee therefore gleaned the most relevant contributions from the literature and asked that, in preparing their papers, four speakers pay particular attention to the available meta-analyses and the results obtained from the evidence based medicine approach. Moreover, the speakers were asked to clearly identify any opinion of their own. A printed version of the papers was given to the chairpersons (C.-M. Farber, Brussels and F. Haerynck, Ghent) and the rapporteurs (C.-M. Farber, Brussels, and M. Delforge, Leuven) in order to enable them to prepare the discussions, for which a large amount of time had been programmed.

There were four papers, each on a highly specialised subject:

1. *"Preparation & Mechanism of action of immunoglobulins"* (P. Späth, Bern);
2. *"Rationale for using immunoglobulins"* (S. Kaveri, Paris);
3. *"Clinical indications for the use of immunoglobulins"* (T. Witte, Hannover);
4. *"Side effects of immunoglobulins"* (S. Misbah, Oxford).

Assessing the most recent knowledge on the use of immunoglobulins was performed in several steps. On the one hand, there were papers and subsequent discussions, followed by the final discussion of the meeting, on the other, there were (a) the preparation of the guidelines by the rapporteurs and (b) the endorsing of the recommendations suggested by the members of the SHC working group “Blood and blood products”.

The recommendations that were drawn up by all these experts were endorsed by the working group with the aim of standardising practices with respect to the use of immunoglobulins in Belgian hospitals.

It follows that they are the result of a systematic review of the guidelines, which are themselves based on the best evidence available (*evidence-based guidelines*), and were subsequently complemented with the opinion of the experts.

3.2. Elaboration

3.2.1. Product description

Large-scale fractionation of plasma proteins began in 1943, when the need for albumin was on the increase as a result of World War II. The Cohn-Oncley method of cold ethanol plasma protein fractionation was devised in 1946 (Cohn et al., 1946). In 1952, after the war, the product of protein fractionation was first used to treat immunodeficiencies (Bruton, 1952). However, the productivity of this technique turned out to be less than ideal and several variants were developed. They include the Kistler/Nitschmann (1962) technique, which is widely applied. It aims at increasing the albumin and immunoglobulin yield, whilst reducing the costs. The first stage in most current immunoglobulin production processes is cryoprecipitation (thawing at a controlled temperature of 2 – 3°C). The remaining cryosupernatant then undergoes cold ethanol fractionation. Fewer cold ethanol precipitations are currently being carried out, with ion-exchange chromatography being favoured instead. This enhances purity as well as the recovery of plasma fractions. But the immunoglobulin yield obtained from this precious plasma remains < 50 % (Waller, 2006; Radosevich & Burnouf, 2010). The differences between recovered and source plasma are outlined in Table 1.

Table 1. Characteristics of recovered and source plasma.

	Recovered plasma	Source plasma
Collection method	Whole blood donations; nothing is returned to the donor's circulation	Plasmapheresis; the cellular components are returned to the donor by continuous mechanical separation of the blood
Payment	Usually none (especially in the European Union)	Usually (especially in the United States)
Extent to which worldwide plasma requirements are met	25 – 30 %	70 – 75 %

Pathogen contamination risk

Using plasma products inevitably entails a risk of contamination by pathogens (see Table 2).

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Table 2. Human pathogens for which there is a theoretical or confirmed risk of transmission through blood components or plasma derivatives (GAO, 1998; Müller-Breitkreutz, 2000).

Confirmed route with clinical sequelae **Transfusions[a] have been shown to be a route of transmission with potential clinical consequences**	**Confirmed route without clinical sequelae** **Transfusions[a] have been shown to be a route of transmission with no known clinical consequences**	**No confirmed cases of transfusion-borne transmission**	**Cases of transfusion-borne transmission have been reported [h] but not yet confirmed**
Hepatitis B virus	Hepatitis D virus	TSE agent of classical/sporadic CJD[f] (sCJD)	TSE agent of the variant form of CJD (vCJD)
Hepatitis C virus	Hepatitis F virus	SARS virus[g] (coronavirus)	
HIV 1/2[b]	Hepatitis G virus (GBV-C)		
HTLV I/II[c]	SEN virus[d]		
West-Nile virus	TT virus[e]		
Hepatitis A virus			
Parvovirus B19			
Hepatitis E virus			

a) The term "transfusion" includes the medical use of labile as well as stable blood products.
b) HIV = human immunodeficiency virus
c) HTLV = human T-cell leukaemia virus
d) SEN = anellovirus linked to transfusions and hepatitis
e) TT = transfusion transmitted virus
f) CJD = Creutzfeldt-Jakob disease. Aberrantly folded prion proteins are considered to be the infectious agent of transmissible spongiform encephalopathies (TSEs) (Llewelyn et al., 2004; Peden et al., 2004; Wroe et al., 2006)
g) SARS = severe acute respiratory syndrome
h) In April 2007, four possible cases of transmission through non-leukocyte depleted red cell concentrates were reported (Zou et al., 2008). In 2010, there was a suspected case of transmission through a plasma derivative (Peden et al., 2010)

Although several viruses such as HIV, hepatitis B and hepatitis C can potentially be transmitted through IVIG, hepatitis C is the only virus that has caused epidemics. In the 1970s, before the virus was identified, there were cases in which the hepatitis C virus was transmitted via particular batches of anti-D immunoglobulin (Lawlor et al., 1999). Further outbreaks occurred after the virus had been identified in the late 1980s. In 1993-1994, HCV epidemics caused by the administration of IVIG were reported in several countries, including the United States, France and Ireland. These cases emerged after the introduction of 2nd generation anti-HCV tests. They are most likely to be due to the neutralising anti-HCV antibodies being removed from the plasma that is used to prepare the immunoglobulins (Yap, 1996). After these outbreaks in 1993, additional viral inactivation steps were introduced into the manufacturing processes of IVIG. In addition, nucleic acid testing for hepatitis C has been mandatory for plasma pools that are intended for the preparation of blood products since July 1999 (Lever et al., 1984; Bresee et al., 1996; Healey et al., 1996; Ravzi et al., 2001). Since then, there has not been a single case of transmission reported.

Parvovirus B19, a non-lipid enveloped virus, is extremely resistant to most inactivation/ elimination processes that are used to produce blood products. Nanofiltration is said to be an effective means to eliminate this virus. With this virus showing a high prevalence among the general population, most fractionation pools as well as end products are contaminated, often with high viral loads (up to 10^{13} geq/mL in the plasma pools). In spite of the high prevalence of this virus in blood and blood products, clinical cases are rarely observed. Still, there have been two possible cases of parvovirus B19 transmission reported that were caused by the administration of IVIG (Erdman et al., 1998; Hayakawa et al., 2002). As a precaution, PCR-tests have been mandatory for all plasma pools that are intended for the production of anti-D immunoglobulins since January 2004. The aim is to ensure that the parvovirus B19 DNA-levels do not exceed 10,000 IU/mL (EDQM, 2008).

Finally, serological tests carried out on IVIG recipients can yield false positive results, thus providing false evidence for e.g. hepatitis A, CMV and hepatitis B seroconversion (Strobel & Schöniger, 2006). This is due to the passive transfer of immunoglobulins.

Since it has been shown that the agent of the new variant Creutzfeld-Jakob disease (vCJD) can be transmitted through blood (Zou et al., 2008), there has been a theoretical concern about the potential transmission of these prions through IVIG. A whole series of precautionary measures have been taken to minimise these risks (SHC, 2005). The UK Blood transfusion service in particular has prohibited British plasma from being used to manufacture blood products. It has also introduced the leukodepletion of red cells and has instituted a follow-up of all blood product recipients, including IVIG prepared with the plasma of donors who subsequently developed vCJD (Zou et al., 2008).

Ensuring the highest level of safety against pathogens begins with the collection of plasma and the selection of donors. Other safety measures include repeated testing for different pathogens by means of sensitive techniques such as serological methods and genome amplification tests (NAT). Moreover, the ability to eliminate and/or inactivate pathogens during the production process should be fully optimised. In order to reduce the risk of pathogen transmission to a minimum, these processes need to include at least one, preferably two effective virus reduction measures. The latter can be subdivided into two categories on the basis of their mechanism of action. Inactivation steps result in the destruction of the viral particles and include, on the one hand, thermal methods such as the heating of aqueous solutions (pasteurisation) and lyophilised products, and, on the other, chemical methods such as solvent/detergent treatment, octanoic acid treatment and incubation at low pH (approximately 4). Virus elimination steps cause the pathogens and the targeted proteins to end up in different fractions. The most important method for virus elimination is filtration (nanofiltration). Fractionation processes such as cryoprecipitation, cold ethanol fractionation, depth filtration, octanoic acid precipitation and chromatography can also contribute towards eliminating pathogens, but are not usually considered to be effective. Most pathogen reduction measures are incorporated into the protein fractionation process, though some methods that are based on heat-inactivation are applied to products in their final primary containers. The pathogen reduction methods that are applied during the production process must be validated strictly in accordance with Good Manufacturing Practice (Burnouf 2007).

Ideally, the “full package” for a state-of-the art Ig preparation should contain:

1. Plasma collection and testing;
2. Plasma pooling and production pool testing;
3. Fractionation;
4. Clinical safety and efficacy;
5. Pathogen safety (validated methods);
6. Batch testing and release;
7. Cleaning and traceability (look-back);

8. Pharmacovigilance, post-marketing studies and surveillance programmes;
9. The activities mentioned above have to be performed in strict adherence to Good Laboratory Practice and current Good Manufacturing Practice.

However, immunoglobulins can now be said to be safer than ever before.

Subcutaneous immunoglobulin (SCIG)

The first immunoglobulin treatment was actually administered subcutaneously (Bruton, 1952), but this practice was abandoned in Europe because of the length of time needed for treatment and the appearance of sterile abscesses at the site of injection (Berger et al., 1980; Stiehm et al., 1998). This treatment was soon re-introduced in Sweden and in the UK, where a multicentric study (Chapel et al., 2000) compared subcutaneous and intravenous immunoglobulin treatments in primary immunodeficiencies. This was a multicentric (3 centres), 2-year cross-over study that was conducted in Sweden and the UK. Treatment modalities differed slightly in both countries, with higher doses given in Sweden. Thirty-two patients were admitted, most of whom had common variable immunodeficiency (CVID). There was no significant difference in the number of infections between the 2 groups. The rate of systemic adverse reactions was comparable in both groups: 5 % for IVIG, 3 % for SCIG. Sixteen patients chose for IVIG, 10 for SCIG. Four patients had no preference, and 2 did not receive IVIG (the preparation was not available in the UK; in Sweden this was a choice).

Another study was performed in the United States (Ochs et al., 2006). It involved 65 patients who were initially on IVIG, with a three month wash in/wash out phase to stabilise their IgG levels by means of SCIG. Mild local reactions at the infusion site occurred in 91 % of the cases.

Another American study (Nicolay et al., 2006) compared the quality of life of primary immunodeficiency patients. It compared 2 groups of patients: the first involved 28 patients who were administered IVIG in the hospital/the doctor's practice, whilst the other consisted of 16 patients who received IVIG at home. It showed that patients preferred home treatment. Then subcutaneous treatment was introduced, and it was preferred over intravenous treatment because it had less impact on daily life. The patients who had been receiving IVIG at home did not perceive SCIG as a further improvement. It is interesting to note that SCIG was only recently introduced in the USA, and that, even then, SCIG is usually administered by a nurse, not by the patients themselves or a member of their family. This is valuable information for us here in Belgium, where SCIG has been available since 2005.

The unpublished observations of Dr. Helen Chapel (Clinical Immunology, John Radcliffe Hospital, Oxford School of Medicine, Oxford, UK) teach us that

- the levels of circulating IgG are more stable in patients on SCIG substitution therapy;
- the levels of IgG obtained are identical with both treatment modalities;
- the extent to which serious pulmonary infections are reduced is the same for SC and IV immunoglobulin.

In addition, SCIG induces minor local reactions, but generalised reactions are extremely rare. The preparation is awkward to prescribe: 1.6 g per single prescription (a patient weighing 70 kg will need at least 30 g per month; 7.5 g per week whilst using 2 pumps!).

It is important that these patients may choose between IV and SC preparations at different times of their lives (e.g. SCIG might be the best option until the age 3 or 4, then IVIG might be the best choice; older patients might prefer IVIG because their skin may be too brittle to bear SCIG treatments. Some may not have a partner who can help them if necessary; the patients must receive training as well as their partners, so that the latter can help if necessary (Gardulf et al., 1993).

In Belgium, IVIG will probably become available for home administration in the future. Increasing patient autonomy whenever possible significantly improves their quality of life and, in many cases, their compliance with a treatment that often lasts a life-time.

However, candidates for home treatment should be chosen carefully; they must not be forced into accepting an option they feel uncomfortable with.

3.2.2. POTENTIAL SIDE EFFECTS OF INTRAVENOUS IMMUNOGLOBULIN

The polyclonal immunoglobulin (IVIG) that is currently being manufactured are safe products, and severe side effects are very rare.

These potential side effects can be subdivided into 3 categories:

- adverse effects that occur immediately during or after the infusion (with IVIG administered at either a low or a high dose);
- complications related to the infusion of high doses of IVIG;
- the transmission of infectious agents (see section 3.2.1., Table 2).

Infusion-related side effects
With earlier preparations, 10 to15 % of the infusions caused mild to moderate reactions, whereas with the current products, this rate has dropped to approximately 1 %. In a large prospective audit of adverse reactions involving 13,508 infusions in 459 patients with primary antibody deficiency, Brennan et al. (2003) found that the frequency of adverse effects was 0.8 %. Most of these reactions were thought to be related to the rate of infusion and to improve rapidly when the latter was reduced. The incidence of adverse reactions was greater if the infusions were administered in case of an infection, which suggests that the formation of immune-complexes composed of exogenous IVIG and bacterial antigens may be responsible for some infusion-related reactions.
Nevertheless, the potential clinical side effects of IVIG infusions include: chills, headache, low-grade fever, nausea, vomiting, arthralgia, moderate low back pain, and lower blood pressure. These reactions are frequently related to the rate of infusion, and can easily be mastered by reducing the latter or temporarily interrupting the infusion. Finally, there will also be symptomatic medical treatment provided.

That the rate of infusion plays a significant part in the appearance of immediate adverse reactions was shown in a study of healthy volunteers (Bagdasarian et al., 1998), where a direct link was found to exist between a high rate of infusion and the release of vasoactive agents and cytokines such as thromboxane B2 and interleukin-6. It is reassuring to note that there are no severe reactions to IVIG in these cohorts, which is in keeping with the fact that anaphylactoid or anaphylactic reactions to current IVIG products are rare. Potential complications can often be prevented by injecting the product slowly at first and by carefully monitoring the patients for symptoms during the infusion as well as during the first 30 minutes that follow it. In addition, patients should be carefully hydrated before the IVIG infusion is initiated. The concomitant use of diuretics should be avoided (Brannagan et al., 1996). These complications are less frequently observed when the IVIG is administered subcutaneously.

Rare, but more severe potential adverse effects include:

- *Allergic reaction due to IgA deficiency with anti-IgA antibodies*

The presence of anti-IgA antibodies (1:1,000) can be associated with allergic reactions, although anaphylaxis is very rare. It is therefore recommended to screen patients with serum IgA deficiency (< 0.05 g/L) for the presence of anti-IgA antibodies and to use IgA-depleted IVIG preparations for patients with a high number of anti-IgA antibodies. It has been reported that

these patients can tolerate Ig that contain IgA and are administered subcutaneously, and that they may even lose their anti-IgA antibodies (Munks et al., 1998; Sundin et al., 1998; Eijkhout et al., 2003).

- *Renal impairment*

Between 1981 and 1998, the FDA received over 120 reports of acute renal dysfunction induced by IVIG. Most of these cases were caused by the sucrose in some IVIG preparations. Patients with pre-existing renal impairment and/or diabetes are at a higher risk of developing this complication. The awareness that sucrose triggers renal impairment has prompted manufacturers to use an alternative non-sucrose carbohydrate stabiliser (Levy & Pusey, 2000).

In patients with risk factors (such as pre-existing decreased renal function, diabetes mellitus, hypovolemia, concomitant use of potential nephrotoxic drugs, and an elderly age), the use of IVIG products that do not contain sucrose may be considered. In that case, it is necessary to provide adequate hydration.

Dosage-related complications

- *Thrombo-embolic events*

There is clinical evidence in support of the fact that there is a link between the administration of IVIG and the occurrence of thrombo-embolic events such as acute myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis. This is assumed to be related to a relative increase in blood viscosity. It is therefore necessary to exercise caution when prescribing and infusing IVIG in patients with pre-existing risk factors for thrombo-embolic events, or pre-existing hyperviscosity (e.g. paraproteinaemia or polyclonal hypergammaglobulinemia) (Paran et al., 2005).

- *Haemolysis*

Acute immune-mediated haemolytic anaemia (direct Coombs test positive) is rare and may be linked to a passive transmission of anti-blood group antibodies. Consequently, the passive transmission of antibodies combined with the use of high-dose IVIG may cause acute Coombs positive haemolytic anaemia (Thomas et al., 1993; Daw et al., 2008). According to the current guidelines of the European Pharmacopoeia (EDQM, 2008b), anti-blood group antibody titres in IVIG should not exceed 1/64. Yet most manufacturers strive to ensure that antibody titres do not exceed 1/8.

- *Aseptic meningitis*

This complication is characterised by signs and symptoms of meningism and fever. It can occur within 24 hours after completing the administration of high-dose IVIG. This complication has been reported in up to 10 % of patients receiving a high dose of IVIG. Cerebrospinal fluid analysis reveals the presence of leukocytosis (neutrophilic or eosinophilic) with negative cultures. The symptoms usually disappear spontaneously within 3 – 5 days without leaving any after-effects. Underlying migraine is a risk factor, which suggests that IgG crossing the blood-brain barrier may be responsible for endothelial irritation in the meninges (Sekul et al., 1994).

- *IVIG in patients with mixed cryoglobulinaemia*

Infusing IVIG in patients with mixed cryoglobulinaemia or B-cell lymphoma associated with IgM paraproteins exhibiting rheumatoid factor activity entails a high risk of the IgM component forming immune-complexes with the infused IgG, thus causing renal failure and cutaneous vasculitis (Odum et al., 2001). The use of IVIG in these patients should therefore be avoided.

Miscellaneous
Immunoglobulins may impair the efficacy of live attenuated virus vaccines, such as measles, rubella, mumps and varicella, for 6 – 12 weeks after the treatment. In addition, the momentary rise in antibodies that are passively transferred into the patient's blood may result in misleading positive results during serological testing. Clinical experience with IVIG suggests that no harmful effects are to be expected as regards the course of pregnancy or the foetus and the neonate.

3.2.3. IVIG-MECHANISMS OF ACTION

As a result of their investigation of natural (vs. acquired) autoantibodies, Dr. Kazatchkine and Dr. Kaveri advocate the use of IVIG in new indications. They examined the positive effect of IVIG in patients with autoantibodies to coagulation factor VIII (Bayry et al., 2005).

Dr. Kaveri's laboratory is particularly involved in studying the interactions between dendritic cells, T-cells and B-cells. Dendritic cells send signals to T-cells and to B-cells. T-cells are essential for the proper functioning of the B-cells. Following a detailed study of the signals exchanged by the cells involved in the immune response, the use of IVIG can be recommended to treat autoimmune and systemic inflammatory disorders (Bayry et al., 2005). They examined the regulatory controls of natural autoantibody production. Autoantibodies to thyroglobulin and DNA can be found in normal controls, but their levels vary in cycles, which is not the case in "autoimmune patients", e.g. those suffering from Hashimoto's disease (Kazatchkine & Kaveri, 2001). It is possible to perform a multiparametric study of antibody repertoires using microarray techniques (Negi et al., 2007).

A pool of IVIG provides a whole range of antibody repertoires from the general population. It contains:

- antibodies to non-self;
- antibodies to self (autoantibodies);
- antibodies to antibodies (anti-idiotypes).

This polyclonality makes IVIG effective in the treatment of certain autoantibody- and T-cell-mediated autoimmune diseases and certain systemic inflammatory conditions.

Modulation of the cytokine production
IVIG modulates the production of cytokines and cytokine antagonists. This is a major mechanism through which immunoglobulins produce anti-inflammatory effects in vivo in various neuromuscular disorders, such as inflammatory myopathies, demyelinating neuropathies, and myasthenia gravis (Ehrlich et al., 2008). IVIG was shown to selectively trigger the production of the interleukin-1 receptor antagonist (IL-1ra), the natural antagonist of IL-1, in cultures of purified monocytes, without affecting the production of the proinflammatory cytokines IL-1α, IL-1β, IL-6, and TNF-α. Although the underlying mechanisms responsible for the selective effect of IVIG are not fully established, it is clear that both F(ab′)2 and Fc portions of IgG are responsible for the observed effect, and that the production of IL-1ra and IL-8 was significantly enhanced when monocytes were cultured in the presence of autologous lymphocytes. Circulating levels of interleukin-1β decrease after IVIG treatment in patients with Guillain–Barré syndrome (Andersson et al., 1994). The anti-inflammatory effects of IVIG linked to the modulation of cytokine production are not restricted to monocytic cytokines. They are also largely dependent on the ability of IVIG to modulate the production of Th1 and Th2 cytokines.

Mitigation of complement-mediated damage
The interaction of IVIG with the complement prevents the C5b-9 membrane attack complex from being generated, thus avoiding complement-mediated tissue damage, by neutralising active complement components and diverting the complement attack from cellular targets. IVIG binds to the activated components C3b and C4b in a C1q-independent and C1q-dependent fashion. In doing so, it prevents these fragments from being deposited on the target surfaces of complement activation (Sharief et al., 1999). This mode of action of IVIG is relevant to the treatment of patients with severe dermatomyositis, Guillain-Barré syndrome, and myasthenia gravis. Thus, the effect of IVIG on dermatomyositis has been linked to a decrease in C5b-9 plasma levels and to significantly lower amounts of C3b and C5b-9 antigens deposited on the endomysial capillaries (Basta et al., 1991).

Fc-mediated blockade of the Fc receptors
IVIG is able to block Fcγ receptor function on the phagocytes temporarily by saturating, altering, or down-regulating the affinity of the Fc receptors, a process that may render the sensitised phagocytic cells unable to exert their phagocytic function (Basta & Dalakas, 1994). Also, some studies have suggested that IVIG could also be effective in ITP by up-regulating the FcγRIIB expression (Debre et al., 1993; Bussel, 2000). Thus, it has been shown on the basis of a transgenic murine model of ITP that the ability of IVIG to induce the expression of the inhibitory FcγRIIB on effector cells that otherwise trigger the clearance of the opsonised platelets allows it to mediate its protective effect.
Using experimental models, the Ravetch group showed that the beneficial effect of IVIG is mediated mainly by a fraction of antibodies with terminal sialic acid at the Asn297-linked glycan of the Fc region. Thus, an IVIG fraction enriched in sialic acid-containing antibodies was shown to possess FcγRIIB-dependent anti-inflammatory effects, whilst the enzymatic removal of the sialic acid residues suppressed the protective effect of IVIG. Furthermore, the Ravetch group reproduced the anti-inflammatory activities of sialylated Fc fragments of IVIG using a homogenous 2,6-sialylated fully recombinant human IgG1 Fc protein (Samuelsson et al., 2001; Anthony et al., 2008; Nimmerjahn & Ravetch, 2008).

Interaction of IVIG with the membrane molecules of antigen presenting cells
In addition to binding to immunoglobulin idiotypes, IVIG reacts with a number of membrane molecules of T-cells, B-cells and monocytes that are relevant to control autoreactivity and induce tolerance to self. Thus, IVIG has been shown to contain antibodies to variable and constant regions of the human αβ T-cell receptor (Marchalonis et al., 1992), cytokines and cytokine receptors (Svenson et al., 1998), CD5 (Vassilev et al., 1993), CD4 (Hurez et al., 1994), HLA class I molecules (Kaveri et al., 1996), RGD adhesion motif (Vassilev et al., 1999), the chemokine receptor CCR5 (Bouhlal et al., 2001), CD40 and Fas (Prasad et al., 1998).

IVIG inhibits dendritic cell differentiation and maturation *in vitro*, and takes away the ability of mature dendritic cells to secrete IL-12 upon activation, whilst enhancing IL-10 production (Bayry et al., 2003). IVIG induces the down-regulation of the co-stimulatory molecules associated with the modulation of cytokine secretion. This results in the inhibition of auto- and alloreactive T-cell activation and proliferation. It was further observed that IVIG interferes with the differentiation of dendritic cells in systemic lupus erythematosus patients, which has been linked to an inhibited expression of HLA and CD80/CD86 on the dentridic cells. Immature dendritic cells that had been treated with IVIG also displayed a reduced ability to ingest nucleosomes (Bayry et al., 2003b).

Recent results underline the fact that IVIG has an agonistic effect on the differentiation of defective dendritic cells when it is administered at low doses that are similar to the replacement doses used to treat immunodeficiencies. In contrast, it has an inhibitory effect on dendritic cells at the high doses used to treat autoimmune and inflammatory diseases (Bayry et al., 2004).

Prospects
There has been considerable progress made in understanding the mechanisms through which IVIG has an immunomodulatory effect in autoimmune and inflammatory diseases. IVIG has a complex mode of action, which involves the modulation of Fc receptor expression and function, interference with the activation of the complement and the cytokine network, the production of anti-idiotypic antibodies, the regulation of cell growth, and effects on the activation, differentiation and effector functions of T- and B-cells.

We still do not know enough about how IVIG should be administered for optimal immunomodulation: should plasma immunoglobulin levels be kept high for lengthy periods of time or should the immune system be intermittently spiked with high doses of immunoglobulins?

IVIG is frequently used to treat autoimmune and inflammatory diseases, though there is insufficient evidence to document its efficacy. As a result, controlled trials are of vital importance, especially as regards diseases in which IVIG constitutes a promising but unproved treatment.

However, it should be remembered that some of these situations occur so infrequently that studies of this order might be impossible to carry out. Lower levels of evidence should therefore be agreed upon to allow the use of IVIG in certain rare disorders (Provan et al., 2007).

3.2.4. INDICATIONS FOR THE USE OF POLYCLONAL IMMUNOGLOBULINS

The aim was to review the available data regarding the use of IVIG and to formulate recommendations on its clinical use.

The following items need to be taken into account for clarification purposes:

- In addition to its licensed indications (see Table 3), IVIG is also increasingly being used in a number of off-label situations, often for rare or orphan disorders. The level of evidence in support of the use of IVIG in this context is frequently limited to non-comparative studies or expert opinions. The increasing demand, the scarce supplies, and high costs curtail the use of IVIG. Still, these rare indications should not be forgotten;
- Optimal use of immunoglobulins requires expert knowledge and advice. The decision to initiate Ig treatment should be taken by a specialist with sufficient expertise and experience in this field.

3.2.4.1. Immunodeficiencies (primary, secondary, stem cell transplantation)

Primary immunodeficiency (PID)
Primary immunodeficiencies are common, but in many individuals, mild or moderate drops in Ig levels will not result in an increased risk of infections and will therefore require no treatment (Bonilla & Geha, 2003). Still, patients with severe hypogammaglobulinaemia suffer from recurrent bacterial infections that especially affect the respiratory and gastro-intestinal tract and the skin. Primary immunodeficiency syndromes are most frequently caused by B-cell disorders, but can also originate from a T-cell defect, or a combination of T- and B-cell defects. The most common primary immunodeficiencies include: common variable immunodeficiency (CVID), IgG subclass deficiency, X-linked agammaglobulinaemia (XLA), severe combined immunodeficiency (SCID) (Pirofsky & Kinzey, 1992). Case definitions for these conditions as well as European statistics can be found on the website of the *European Society for Immunodeficiencies* (www.ESID.org).

Defining an IgG level under which immunoglobulins should be given (IV or SC) does *not* constitute the main criterion for treatment. The lower limit of what is looked upon as a "normal" level varies from one laboratory to another; a mean normal value cannot be given. The mention "*2 sd below the laboratory mean value*" is obsolete. Adults with IgG levels < 3.5 g/L generally

suffer from recurrent infections. This is an indicative value and clinical criteria as defined in the Belgian PID Group's 10 warning signs should be followed (Farber et al., 2001). It is recommended to seek the advice of a clinical immunologist.

Slight deficiencies are common, but in many individuals mild or moderate drops in Ig levels will not result in an increased risk of infections. They will therefore not require immunoglobulins, but conjugated polysaccharide vaccines, aggressive antibiotic use, sometimes rotating antibiotic prophylaxis, surgical repair of anatomical defects, anti-allergy measures, and changed activities (increased physical activity, sometimes physiotherapy) (Stiehm, 1999).

In 1952, Bruton was the first to show that monthly Ig injections effectively reduce the infectious complications in XLA patients (Bruton, 1952). Since then, there has been ample evidence in support of the fact that substitution with polyvalent immunoglobulins can be life-saving. In addition, valuable information about the optimal dose and administration interval has become available. Most infections can be mastered by administering IgG that allow for levels of 5.5 to 6.5 g/L serum to be reached. IVIG doses vary between 300 – 800 mg/kg and dosing intervals will generally not exceed 3 to 5 weeks (Darabi et al., 2006).

Secondary/acquired immunodeficiency

Cancer patients, especially those with haematological malignancies, are prone to infections due to the underlying disease, neutropenia, mucosal damage, but also due to hypogammaglobulinaemia that is related to the underlying malignancy or to the antineoplastic treatment. The population with the highest risk for hypogammaglobulinaemia are patients with chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM), as these disorders are frequently associated with a lower production of polyclonal immunoglobulins. In addition, the antineoplastic treatment can be an additional cause of hypogammaglobulinaemia in these disorders. The use of IVIG in patients with CLL and MM is supported by randomised clinical trials. In 4 randomised trials, the use of IVIG reduced the number of serious bacterial infections compared to CLL patients with hypogammaglobulinaemia and/or a history of infection who had either received no treatment at all or had been administered a placebo (CGSICLL, 1988; Griffiths et al., 1989; Boughton et al., 1995; Molica et al., 1996).

Also in the case of MM, a 6 – 12 month IVIG treatment has been shown to have a beneficial effect in reducing the risk of serious infectious complications (Chapel et al., 1994). According to the cited references, additional smaller studies and the clinical consensus, the use of IVIG is recommended for infection prophylaxis in adults with CLL or MM associated with hypogammaglobulinaemia and a recent life-threatening infection or recurrent episodes of clinically significant infections that require the use of antibiotics. It is reasonable to believe that they are caused by low levels of polyclonal Ig (Anderson et al., 2007).

A proposal for a more restricted use of IVIG in CLL and MM can be found in the report of the European Medicines Agency (EMA, 2008). For MM, the suggested wording is: "*plateau phase MM patients with hypogammaglobulinaemia and recurrent bacterial infections who have failed to respond to pneumococcal immunisation*".

For CLL, the EMA (2008) suggests a rephrasing of the British Committee for Standards in Haematology: "*CLL patients with hypogammaglobulinaemia and recurrent bacterial infections, especially those in whom prophylactic antibiotics have failed*". Yet it should be kept in mind that these key studies are over 10 years old. During the last decade, the treatment of CLL, MM and related disorders has changed dramatically. Especially as regards CLL, the antineoplastic drug fludarabine and the monoclonal antibody rituximab have improved patient prognosis, but both drugs can also induce prolonged hypogammaglobulinaemia (Cabanillas et al., 2006; Nishio et al., 2007). In addition, fludarabine is sometimes also used in combination with rituximab in other lymphoproliferative disorders.

This evolution is not taken into account in the EMA (2008) report, nor in the UK guidelines (Provan et al., 2007). It follows that strictly limiting the access to IVIG to CLL and myeloma in a plateau phase would discriminate patients with other lymphoproliferative disorders who develop symptomatic hypogammaglobulinaemia after receiving the same immunosuppressive regimen as CLL and MM patients. In addition, it is well known that serious hypogammaglobulinaemia can occur in MM patients who have not yet reached a plateau phase.

Patient selection and the discrimination of patients in need should be avoided. In this respect, the Canadian guidelines for secondary immunodeficiency (Anderson et al., 2007) are much more in line with current clinical reality. They recommend the use of IVIG for:
"infection prophylaxis in adults with malignant hematological disorders associated with secondary hypogammaglobulinaemia and either:
- a recent life-threatening infection, which is reasonably thought to be caused by low levels of polyclonal Ig;
- recurrent episodes of clinically significant infections necessitating the use of antibiotics and which are reasonably thought to be caused by low levels of polyclonal immunoglobulins".

Adopting this recommendation will not result in a significant increase of the IVIG consumption, the vast majority of patients with secondary immunodeficiency being MM and CLL patients. From a more global perspective, other indications in the field of haematology can be disregarded (see the sections on stem cell transplantation, IgG subclass deficiency).

Stem cell transplantation

Autologous stem cell transplantation

The generalised prophylactic use of IVIG after autologous stem cell transplantation has been abandoned (Wolff et al., 1993).

Allogeneic stem cell transplantation
Immunodeficiencies caused by a myeloablative regimen can lead to serious infections, including opportunistic infections like CMV, and can be complicated by acute and/or chronic graft-versus-host disease (GvHD). A pilot study showed that administering IVIG during the first year after transplantation had a beneficial effect on the risk of interstitial pneumonia, serious bacterial infections, mortality and the risk of developing acute graft-versus-host disease (Sullivan et al., 1990). This study led to the widespread use of IVIG after allogeneic transplantations, until another prospective, multicentre, and randomised study that was carried out in France between 1998 and 2000 re-examined the prophylactic role of several doses of IVIG compared to a placebo from day 7 before the transplantation until day 100 afterwards (Cordonnier et al., 2003). In contrast to the study by Sullivan et al. (1990), this more recent research did not find any significant reduction in the risk of interstitial pneumonia, infection rate, or transplant-related mortality. The most plausible explanation for the difference between both studies is the more widespread prophylactic and pre-emptive use of newer and highly effective antiviral and antifungal agents. In addition, little evidence has remained to support the use for IVIG to prevent GvHD. Although a limited subset of patients could benefit from the prophylactic use of high doses of IVIG to prevent acute GvHD (Abdel-Mageed et al., 1999; Winston et al., 2001), the use of these high doses is associated with an increased risk of veno-occlusive disease of the liver (Cordonnier et al., 2003).

In sum, current evidence no longer supports the generalised prophylactic use of IVIG after conventional allogeneic transplantation. Yet in the last paragraph of their paper, Cordonnier et al. (2003) state the following: *"our study does not question the indication of immunoglobulins in hypogammaglobulinaemic stem-cell transplant patients, as recommended by the Centers for Disease Control and Prevention".*

Finally, there has been a significant shift in recent years from myeloablative to non-myeloablative conditioning regimens (or so called Reduced-Intensity Conditioning (RIC) transplants). Conditioning regimens in RIC transplants are less myelosuppressive but are highly immunosuppressive. For this purpose, the same lympholytic agents as described in the section on CLL (fludarabine, rituximab) as well as others, such as anti-thymocyte globulin and low-dose irradiation, are most commonly used. The use of these agents can also promote prolonged post-transplant hypogammaglobulinaemia. Although there is no prospective, randomised trial yet in support of this point of view, it would be very difficult to justify that individual patients who contract either a life-threatening bacterial infection or repeated serious bacterial infections that are clearly related to a state of secondary hypogammaglobulinaemia, should have no access to IVIG until their immune system has recovered. The most logical approach would be to shift from a generalised prophylactic use in transplant patients towards an individual use in selected patients with serious infectious complications caused by secondary hypogammaglobulinaemia. Such an approach is supported by the Canadian guidelines (Anderson et al., 2007), the UK guidelines (Provan et al., 2007) and the EMA directives (2008). The approval for administering IVIG to patients with secondary immunodeficiencies can be reviewed every 6 or 12 months.

Other immunodeficiencies

Isolated IgG subclass deficiency
At present, there is no evidence that would support the recommendation that isolated IgG subclass deficiency or selective IgA deficiency should be added to the established indications.

Anti-polysaccharide antibody deficiency
This disorder can lead to recurrent infections that are as severe as those found in CVID. It is genetically related to certain forms of CVID and can evolve into CVID over time. Immune deficiencies are not static, and a careful clinical follow-up by a specialist in immunology is recommended, as least once a year. Some anti-polysaccharide deficiencies may require IVIG replacement. Yet the patient benefits most from physiotherapy, rotating antibiotics, and the judicious use of conjugated vaccines. It is necessary to take into account the patient's personal and family history, as well as the evolution of the clinical situation. There can also be a link with autoimmune diseases, as in full-blown CVID.

Transient hypogammaglobulinaemia of infancy
This is a physiological situation that results from the progressive loss of maternal IgG transmitted during pregnancy. The IgG levels reach a nadir between 4 and 6 months after birth. The onset of Ig synthesis in babies is slow. It takes a few months to reach "normal" IgG levels. In exceptional cases, this situation can drag on. A diagnosis can be made by testing for antibodies to vaccines: they will be normal in the case of transient hypogammaglobulinaemia. This case does not require the use of IVIG.

Neonatal sepsis (prevention or treatment)
At present, neonatal sepsis cannot be considered a confirmed indication for IVIG, since antibiotics are a valid alternative.

<u>Recommendation regarding immunodeficiencies</u>

The use of IVIG is recommended for primary and secondary immunodeficiencies with:

- recurrent episodes of clinically significant infections that require the use of antibiotics, which are reasonably thought to be caused by low levels of polyclonal Ig, or
- a recent life-threatening infection, which is reasonably thought to be caused by low levels of polyclonal Ig.

3.2.4.2. Immunomodulation

Immune thrombocytopenia (ITP) [3]
ITP is a disorder characterised by accelerated platelet destruction following the appearance of platelet reactive autoantibodies. Acute and chronic ITP can affect both children and adults. Acute ITP usually disappears within 6 months, whereas chronic ITP can drag on for years. The use of IVIG successfully raises platelet counts in about 75 % of patients, 50 % of whom will reach normal platelet counts. However, these responses are temporary, and there is little evidence for any lasting effect. A prospective study (Colovic et al., 2003) showed no difference in the efficacy of a 5-day treatment with 0.4 g/kg/d and that of a 2-day treatment with 1 g/kg/d. The IVIG-mechanism of action in ITP remains largely unknown, but is believed to involve a blockade of the Fc receptors on the reticulo-endothelial cells and the presence of anti-idiotype antibodies.

For the indication of IVIG in the treatment of ITP, we refer to the guidelines of the American Society of Hematology (ASH, 1997) and those of the British Society of Haematology (BCSH, 2003). In sum, IVIG is recommended for adults with ITP and severe or life-threatening bleeding, or when there is a risk of bleeding (prior to surgery, during pregnancy, before labour). As regards children with ITP, IVIG should be reserved for when the platelet count drops below 20,000/µL (ASH, 1997), for emergency treatment of serious bleeding symptoms, or for children who undergo procedures that are likely to induce blood loss (BCSH, 2003). HIV and ITP during pregnancy are not looked upon as separate entities.

Foetal/neonatal alloimmune thrombocytopenia (NAIT)
NAIT can be looked upon as a particular form of immune-mediated thrombocytopenia which can occur in a foetus when the mother produces alloantibodies against a platelet antigen on foetal platelets, leading to platelet destruction when the maternal anti-platelet antibodies cross the placenta. Babies may develop thrombocytopenia that results in petechiae or bleeding, with a risk of intracranial haemorrhage in severe cases. The most common maternal antibodies are directed against the human platelet alloantigen (HPA-1a). The risk of recurrence in subsequent pregnancies is 100 % if the father is homozygous for the responsible antigen, and 50 % if he is heterozygous. Administering antigen-negative platelets is a first-line treatment for this condition in newborns, but administering IVIG is standard as regards the antenatal treatment for this extremely rare condition with potentially fatal consequences (Bussel et al., 1996; Birchall et al., 2003).

Post-transfusion purpura (PTP)
This is a disorder that is similar to immune-mediated platelet destruction. It too responds well to IVIG that is administered to patients who are negative for the HPA-1 platelet antigen and develop antibodies after platelet transfusion (Mueller-Eckhardt & Kiefel, 1988). Taking into account its pathogenesis, these patients can be treated according to the recommendations for “immune-mediated thrombocytopenia”.

HIV/AIDS

**** Children with HIV***
The use of IVIG to prevent bacterial infections in children with HIV was approved on the basis of the placebo-controlled randomised NICHHD trial (1991) and several smaller studies that preceded it. However, these studies were carried out before the Highly Active Anti-Retroviral Therapy (HAART) became routinely used. A subsequent randomised, double-blind study that compared IVIG to a placebo administered to children infected with HIV and treated with zidovudine cast doubt on the use of IVIG in preventing bacterial infections in patients on HAART and on appropriate antimicrobial prophylaxis (Spector et al., 1994). It follows that the use of IVIG is no longer justified in this indication.

[3] The abbreviation “ITP” is currently being used to refer to "immune thrombocytopenia" rather than “idiopathic thrombocytopenic purpura”. As regards the latter, it is replaced by “primary ITP”.

**** HIV-associated thrombocytopenia***

Primary HIV-associated thrombocytopenia is the most common cause of thrombocytopenia in patients with HIV infection, and thrombocytopenia will be the initial manifestation of HIV infection in up to 10 % of cases. Primary HIV-associated thrombocytopenia is related to the direct infection of bone marrow precursor cells with HIV, which leads to the production of anti-platelet antibodies. This in turn results in decreased platelet survival. Several randomised controlled trials have shown that IVIG is effective in the treatment of HIV-associated thrombocytopenia (Jahnke, 1994). Taking into account the immune-mediated mechanism, these patients could have access to IVIG on the basis of the "ITP" criteria and do not necessarily have to be considered as a separate entity.

Haemolytic disease of the newborn (HDN)

HDN occurs when maternal IgG antibodies to foetal red cell antigens cross the placenta and bind to foetal red cell antigens, leading to haemolysis. Before birth, this can lead to hydrops foetalis and, in the most severe cases, to the death of the infant. After birth, it can lead to hyperbilirubinaemia, which can affect the basal nuclei of the brain in its most severe form.

According to a systematic review (Gottstein & Cooke, 2003) and the recommendations of the American Academy of Pediatrics (AAP, 2004), IVIG can be offered to patients with HDN to treat severe hyperbilirubinaemia if the total serum bilirubin is rising despite intensive phototherapy or the total serum bilirubin is within 2 – 3 mg/dL of the exchange level: "*In iso-immune haemolytic disease, administration of IVIG is recommended if the total serum bilirubin (TSB) is rising despite intensive phototherapy or the TSB is within 2-3 mg/dl of the exchange level"*. But this remains a controversial issue, with the 2007 UK guidelines also stating that neonatal hyperbilirubinaemia is not an indication for IVIG (Provan et al., 2007).

Kawasaki disease

Kawasaki disease is one of the most common types of childhood vasculitis. Although this is usually a self-limited condition, it can result in coronary artery aneurysm, arrythmias, myocardial infarction and heart failure. The current standard treatment is IVIG plus aspirin, which are administered as soon as Kawasaki disease is diagnosed. It has repeatedly been shown to be effective in preventing the development of coronary artery aneurysms in 85 % of patients. A Cochrane database meta-analysis of 16 randomised clinical trials comparing the use of IVIG with that of a placebo in Kawasaki disease found a definite and significant decrease in new coronary artery aneurysms with the use of IVIG (Oates-Whitehead et al., 2003).

Erythroblastopenia caused by a parvovirus B19 infection

Viral erythroblastopenia is caused by a parvovirus B19 infection. Giant pronormoblasts can be seen in the bone marrow, and the clinical picture can be associated with life-threatening anaemia. Immunocompromised patients with erythroblastopenia caused by a parvovirus B19 infection are uniformly responsive to IVIG (Mouthon et al., 2005).

Acquired von Willebrand disease (aVWD)

aVWD is an unusual bleeding disorder that is characterised by quantitative/qualitative abnormalities of the von Willebrand factor. It is mostly caused by the presence of an inhibitor antibody directed against the vWAg/FVIII complex. This disorder has been described in association with lymphoproliferative disorders, haematological malignancies and immune-mediated diseases. IVIG may be considered as a therapeutic option in case of emergency, when there is active bleeding or before an operation, and when other therapeutic measures have failed (Arkel et al., 1994; Nichols et al., 2008).

Miscellaneous
Although there have been cases in which IVIG could be shown to be clinically effective, there is too little evidence in support of extending their use to numerous other haematological disorders, such as immune-mediated erythroblastopenia (with the exception of parvovirus B19 infection), immune-mediated neutropenia, auto-immune haemolytic anaemia, thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia, acquired haemophilia, and haemophagocytic syndrome.

Recommendations regarding immunomodulation

The use of IVIG is recommended for:

- acute and chronic immune thrombocytopenia (ITP), including pregnancy-associated and HIV-associated immune-mediated thrombocytopenia, in case of
  - severe or life-threatening bleeding,
  - when bleeding is predictable (prior to surgery, during pregnancy, before labour);
- antenatal treatment in foetal-neonatal allo-immune thrombocytopenia (NAIT);
- haemolytic disease of the newborn (HDN) complicated by severe hyperbilirubinaemia if the total serum bilirubin is rising despite intensive phototherapy, or the total serum bilirubin is within 2-3 mg/dL of the exchange level;
- Kawasaki disease;
- erythroblastopenia induced by a parvovirus B19 infection in an immunocompromised patient;
- second-line treatment in the case of acquired von Willebrand disease (aVWD) when there is life-threatening bleeding.

3.2.4.3. Neurological disorders

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
The prevalence of CIDP is around 2/100,000. This disease usually progresses slowly and becomes severely disabling in 50 % of the patients. In the Cochrane review on CIDP treated with IVIG (van Schaik et al., 2002), 6 randomised controlled trials involving a total of 170 patients and using different IVIG preparations met the previously defined review criteria. Four of these tested IVIG against a placebo. According to these 4 trials, IVIG proved to be superior to the placebo, and showed a similar efficacy to plasma exchange and prednisolone. This was confirmed by Eftimof et al. (2009).

A recently published, double-blind, placebo-controlled study compared IVIG with a placebo during the initial treatment phase and an extension phase, each of which lasted 24 weeks. This study is the largest that has ever been reported on CIDP treatment. It shows the short-term and long-term efficacy and safety of IVIG and supports its use as a therapy for CIDP (Hughes et al., 2008).

Multifocal Motor Neuropathy (MMN)
Multifocal motor neuropathy is characterised by slowly progressive, predominantly distal, asymmetric limb weakness and wasting, especially in the arms, with muscle cramps and fasciculations, within an anatomic distribution of individual motor nerves, with minimal or no sensory involvement. It is a rare condition that affects no more than 1 or 2 individuals per 100,000. Unlike CIDP, multifocal motor neuropathy does not respond to steroids, even when they are administered intravenously at high doses, whereas the condition of almost 20 % of the patients has even been reported to worsen dramatically as a result of this treatment, as has also been the case with plasma exchange (Leger et al., 2007).

The conclusions from the Cochrane review on the use of IVIG to treat multifocal motor neuropathy (van Schaik et al., 2005) show that a statistically significant effect can be seen on muscle strength, that approximately one third of the patients are in remission for over 12 months, but that it does not have a significant effect on their disability (4 randomised controlled trials, 4 different IVIG products, one meta-analysis). The 2006 European Federation of Neurological Societies/ Peripheral Nerve Society (van Schaik et al., 2006) recommended the use of IVIG as a first-line treatment for MMN, but the diagnosis should be made by a specialist in neuromuscular disorders with specific expertise. If the initial IVIG treatment is effective, repeated infusions should be considered. The frequency of maintenance therapy should be determined by the individual response.

Myasthenia gravis (MG)
Myasthenia gravis is induced by autoantibodies against acetylcholine nicotinic postsynaptic receptors. Its prevalence is 1-10:100,000. There is currently no evidence from randomised controlled studies in support of the fact that IVIG improve the functional outcome or have a steroid sparing effect in the case of moderate or severe stable MG.

As regards the use of IVIG in the case of *MG exacerbation*, 3 randomised controlled trials have been performed, 2 of which were adequately powered. In Zinman et al. (2007), the efficacy of IVIG was determined in 51 MG patients with worsening muscle weakness by means of a randomised placebo-controlled double blind study. The Quantitative Myasthenia Gravis (QMG) score for disease severity, a validated clinical composite scale, was calculated by a masked observer at baseline and at days 14 and 28. A clinically significant improvement was observed in the QMG score of patients treated with IVIG at day 14 and persisted at day 28. The greatest improvement occurred in the more severely affected patients. A dose of 1 g/kg may be sufficient.

In *chronic MG*, there is insufficient evidence from randomised trials to determine whether IVIG is efficacious. More research is needed to determine whether IVIG reduces the need for corticosteroids, as suggested by two case series (Gajdos et al., 2007).

Guillain-Barré syndrome (GBS)
According to Feasby et al. (2007), IVIG is recommended as a treatment option for GBS within 2 weeks of its onset in patients with:

- symptoms of grade 3 severity (able to walk with aid) or worse;
- progressing symptoms with less than grade 3 severity.

A Cochrane database analysis (Hughes et al., 2006) concludes that there are no adequate comparisons with a placebo in adults. Randomised trials involving severely affected patients show that intravenous immunoglobulin started within two weeks from the onset of the disease speeds up recovery as much as plasma exchange. Administering intravenous immunoglobulin after plasma exchange does not confer any significant additional benefit.

In children, intravenous immunoglobulin probably speeds up recovery, as opposed to supportive care alone. More research is needed on mild disease and on treatment initiated more than two weeks after the onset of the condition. There are insufficient data as regards the recommendations on the optimal therapeutic strategy (Donofrio et al., 2009).

Multiple sclerosis (MS)
IVIG is recommended (Gray et al., 2003; Elovaara et al., 2008) for:

- patients with relapsing/remitting MS who fail, decline, or are not able to take standard immunomodulatory therapies;
- patients with relapsing/remitting MS who are pregnant or breast-feeding or in the immediate postpartum period;

- MS patients with severe, refractory, optic neuritis who have not recovered vision after 3 months of standard steroid therapy, or for whom corticosteroid therapy is contraindicated.

Even though IVIG is efficient against multiple sclerosis, there are currently more powerful therapies available for these patients (Sorensen et al., 2002).

Miscellaneous
As regards the use of IVIG in rare neurological conditions, Feasby et al. (2007) recommend that IVIG should be used in all of the following disorders: stiff person syndrome (cf. CEDIT, 2004), Lewis-Sumner syndrome, Birdshot retinopathy (cf. CEDIT, 2004), acute disseminated encephalomyelitis, opsoclonus-myoclonus, paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, and Rasmussen encephalitis. The decision to initiate IVIG treatment for these indications should be taken by a neurologist who is experienced in treating these disorders. Rigorous and careful follow-up is required in order to assess the treatment response.

There are insufficient data available to recommend the use of IVIG in the following conditions: adrenoleukodystrophy, amyotrophic lateral sclerosis, autism, critical illness neuropathy, diabetic neuropathy, intractable childhood epilepsy, neuropathy due to paraproteinaemia, POEMS syndrome, Rasmussen encephalitis (except in the case of short-term treatment), chronic fatigue syndrome, and numerous other disorders.

Recommendations regarding neurological disorders

The use of IVIG is recommended for:

- short-term and long-term treatment of chronic inflammatory demyelinating polyneuropathy (CIDP);
- first-line treatment of multifocal motor neuropathy (MMN);
- Guillain-Barré syndrome (GBS) with symptoms of grade 3 severity (able to walk with aid) or worse and patients with progressing symptoms of less than grade 3 severity;
- Myasthenia gravis (MG) exacerbation;
- Multiple sclerosis (MS) in case of optic neuritis.

3.2.4.4. Autoimmune inflammatory myopathies

Dermatomyositis (DM)
Autoimmune myositis can be subdivided into 4 main types: dermatomyositis, polymyositis, sporadic inclusion body myositis, and myositis with extramuscular involvement. DM is a complement-mediated microangiopathy affecting the skin and muscles, resulting in skin abnormalities, including subcutaneous calcifications, muscle weakness and disability.

According to Feasby et al. (2007), IVIG is recommended as an option, in combination with other agents, for patients with dermatomyositis who have not responded adequately to other immunosuppressants, like steroids. The IVIG trial conducted by Dalakas et al. (1993) indicated a positive effect of IVIG in patients with refractory DM, but the number of patients involved was very low (n = 15).
In juvenile DM, the long-term effects of corticosteroids should be avoided, which may perhaps justify a first line therapy in this age group (Feasby et al., 2007).

Miscellaneous

In other skin or skin-related disorders like scleromyxoedema (Blum et al., 2008) and autoimmune mucocutaneous blistering diseases like pemphigus (Daoud & Amin, 2006), IVIG can have a beneficial effect when other therapies have failed. However, the decision to initiate IVIG treatment should be taken by an expert in the treatment of these rare disorders.

Recommendation

The use of IVIG is recommended for steroid resistant dermatomyositis (DM).

Table 3. Summary of the main internationally recommended indications for the use of immunoglobulins that were available before the expert meeting.

Clinical indication	France (CEDIT, 2004)	United Kingdom (Provan et al., 2007)	Canada (Robinson et al. , 2007)	Australia (NBA, 2007)	Europe (EMA, 2008)
Immunodeficiency					
Primary immunodeficiency	yes	yes	yes	yes	yes
Chronic lymphocytic leukaemia and multiple myeloma	—	yes	yes	yes	yes
Secondary immunodeficiency in haematological malignancies	—	—	yes	yes	—
Immunodeficiency after haematopoietic stem cell transplantation	—	yes	yes	yes	yes
Immunomodulation					
Immune thrombocytopenia (acute and chronic, children and adults)	yes	yes	yes	yes	yes
Foetal/Neonatal alloimmune thrombocytopenia (antenatal use)	—	yes	yes	yes	—
Post-transfusion purpura	yes	yes	yes	yes	—
Adults and children with HIV	no	no	—	no*	yes
Haemolytic disease of the newborn	—	no	yes	yes	—
Kawasaki disease	yes	yes	yes	yes	yes
Erythroblastopenia caused by a parvovirus B19 infection	—	yes	yes	yes	—
Neurology					
Chronic inflammatory demyelinating polyneuropathy	yes	yes	yes	yes	yes
Multifocal motor neuropathy	yes	yes	yes	yes	yes
Myasthenia gravis (exacerbation)	yes	yes	yes	yes	yes
Guillain-Barré syndrome	yes	yes	yes	yes	—
Multiple sclerosis	no	yes	yes	yes	—
Autoimmune inflammatory myopathies					
(Steroid-resistant) dermatomyositis	yes	yes	yes	yes	yes

— not discussed; * children: exceptional

4. CONCLUSIONS

1. When there are no randomised controlled trials, the “orphan indications” must be discussed with clinical experts;
2. The clinical indications for immunoglobulins can be classified by order of priority in a rational manner (see Tables 4 and 5);
3. Subcutaneous immunoglobulin can be an alternative for intravenous immunoglobulin in the indications selected;
4. The different commercially available immunoglobulin preparations are not identical;
5. It is recommended that the indications for the use of immunoglobulins should be reviewed at least once every five years. This will allow for these products to be put to the best possible use, according to the latest developments in science and clinical medicine;
6. When a decision is made on whether or not to treat with Ig, all potential alternative treatments must be taken into consideration;
7. Even though immunoglobulins can be looked upon as safe products with usually moderate side effects, their safe and optimal use requires expertise and experience.

Table 4. Summary of the therapeutic roles of immunoglobulin treatment in certain disorders.

Indication	Therapeutic role
Established	
Primary immunodeficiencies	Essential
Immune deficiency caused by a malignant blood disorder, chronic lymphocytic leukaemia or multiple myeloma	In case of recurring infections; restricted to the duration of the humoral deficiency
Low levels of IgG in the serum following a haematopoietic stem cell transplantation	In case of recurring infections; restricted to the duration of the humoral deficiency
Immune thrombocytopenia – adults and children	Useful in acute and chronic situations, including pregnancy-associated and HIV-associated immune-mediated thrombocytopenia, in case of ▪ severe or life-threatening bleeding; ▪ when bleeding is predictable (prior to surgery, during pregnancy, before labour)
Foetal/neonatal alloimmune thrombocytopenia	Useful in case of antenatal treatment (treatment administered to the mother)
Alloimmune thrombocytopenia - treatment for newborns	When there are no compatible platelets available
Post-transfusion purpura	Essential
Acquired von Willebrand disease	Second-line treatment in case of grade 3 bleeding
Erythroblastopenia caused by a B19 parvovirus infection	Last resort option
Kawasaki Disease	Essential

Dermatomyositis resistant to corticosteroids	Last resort option
Juvenile dermatomyositis resistant to corticosteroids	Last resort option
Multifocal motor neuropathy	First-line treatment
Chronic inflammatory demyelinating polyneuropathy	Useful in acute situations
Guillain-Barré syndrome	Useful when accompanied by symptoms of grade 3 severity (able to walk with aid) or worse and patients with progressing symptoms of less than grade 3 severity
Myasthenia gravis	Useful in case of acute episodes
Haemolytic disease of the newborn (isoimmune haemolytic jaundice)	Useful if complicated by severe hyperbilirubinaemia if the total serum bilirubin is rising despite intensive phototherapy, or the total serum bilirubin is within 2-3 mg/dL of the exchange level
Multiple sclerosis	Useful in case of severe, refractory, optic neuritis in patients who have had not recovered vision after 3 months of standard steroid therapy, or for whom corticosteroid therapy is contraindicated; Useful in case of relapsing/ remitting MS in patients who are pregnant or breast-feeding or in the immediate postpartum period; Option in case of relapsing/ remitting MS in patients for whom standard immunomodulatory therapies fail, who decline or who are intolerant of these treatments.
Uncertain	
Autoimmune haemolytic anaemia	
Immune-mediated neutropenia	

Immune-mediated erythroblastopenia (with the exception of parvovirus B19 infection	
Thrombotic thrombocytopenic purpura	
Antiphospholipid syndrome	Treatment of severe cases
Haemophagocytic syndrome	
Heparin-induced thrombocytopenia	
Alloimmunisation to platelet transfusions	
Anti-polysaccharide antibody deficiency	
Isolated IgG subclass deficiency	In case of recurring infections
Scleromyxoedema	
Autoimmune mucocutaneous blistering diseases	
Stiff person syndrome	
Rasmussen encephalitis	Short-term treatment
Birdshot retinopathy	
Lewis-Sumner syndrome	
Acute disseminated encephalomyelitis	
Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)	
Opsoclonus-myoclonus	
Not recommended, no evidence in support of efficacy	
Other disorders	

Table 5. Overview of the recommendations regarding the established indications for Ig-treatment.

As regards the diagnoses that have not been included in this table, there were insufficient data available. The specific recommendations are discussed in detail in the argumentation of this advisory report and have been included in Table 4. Red indicates that the disorder has the highest level of priority (risk to life without treatment). Blue signifies that this is a disease for which the risk is moderate because there are other treatment options available.

Condition	Recommended?	
	Short-term	Long-term
Immunology		
Kawasaki disease	yes	no
Primary immunodeficiencies	selected	yes
Haematology		
Neonatal alloimmune thrombocytopenia (treatment to the mother)	yes	no
Neonatal alloimmune thrombocytopenia (treatment to the newborn)	selected	no
Immune thrombocytopenia – adults	selected	no
Immune thrombocytopenia – paediatric (< 16 years)	selected	no
Erythroblastopenia caused by a B19 parvovirus infection	selected	no
Post-transfusion purpura	yes	no
Acquired von Willebrand disease	selected	no
Haemolytic disease of the newborn (isoimmune haemolytic jaundice)	selected	no
Haemato-oncology		
Chronic lymphocytic leukaemia	no	selected
Multiple myeloma	no	selected
Immunodeficiency caused by a malignant blood disorder	selected	selected
Low levels of IgG in the serum following a haematopoietic stem cell transplantation	selected	selected
Neurology		
Guillain-Barré syndrome	selected	no
Chronic inflammatory demyelinating polyneuropathy	selected	selected
Multifocal motor neuropathy	selected	selected
Myasthenia gravis	selected	selected
Multiple sclerosis	selected	no
Dermatology		
Dermatomyositis	selected	selected
Paediatrics		
Immune thrombocytopenia – paediatric (< 16 years)	selected	no
Haemolytic disease of the newborn (isoimmune haemolytic jaundice)	selected	no
Adult rheumatology		
Dermatomyositis	selected	selected
Paediatric rheumatology		
Kawasaki disease	yes	no
Juvenile dermatomyositis	selected	selected
Transplantation		
Low levels of IgG in the serum following a haematopoietic stem cell transplantation	selected	selected

5. REFERENCES

- AAP. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2004;114:297-316.
- Abdel-Mageed A, Graham-Pole J, Del Rosario ML, Longmate J, Ochoa S, Amylon M, et al. Comparison of two doses of intravenous immunoglobulin after allogeneic bone marrow transplants. Bone Marrow Transplant 1999;23:929-32.
- AFSSAPS. Agence française de sécurité sanitaire des produits de santé. Proposition de hiérarchisation des indications des immunoglobulines humaines intraveineuses (IgIV) en situation de tension forte sur les approvisionnements pour le marché français. MED08/B13. Paris: AFSSAPS; 2008.
- APIIEG. Asia Pacific Immunoglobulins In Immunology Expert Group. Consensus Recommendations for the use of Immunoglobulin Replacement Therapy in Immune Deficiency. Second Edition. Singapoure: APIIEG; 2009.
- Anderson D, Ali K, Blanchette V, Brouwers M, Couban S, Radmoor P, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. Transfus Med Rev 2007;21(Suppl 1):S9-56.
- Andersson U, Bjork L, Skansen-Saphir U, Andersson J. Pooled human IgG modulates cytokine production in lymphocytes and monocytes. Immunol Rev 1994;139:21-42.
- Anthony RM, Nimmerjahn F, Ashline DJ, Reinhold VN, Paulson JC, Ravetch JV. Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. Science 2008;320:373-6.
- Arkel YS, Lynch J, Kamiyama M. Treatment of acquired von Willebrand syndrome with intravenous immunoglobulin. Thromb Haemost 1994;72:643-4.
- ASH. The American Society of Hematology ITP Practice Guideline Panel. Diagnosis and treatment of idiopathic thrombocytopenic purpura: recommendations of the American Society of Hematology. Ann Intern Med 1997;126:319-26.
- Bagdasarian A, Tonetta S, Harel W, Mamidi R, Uemura Y. IVIG adverse reactions: potential role of cytokines and vasoactive substances. Vox Sang 1998;74:74-82.
- Basta M, Dalakas MC. High-dose intravenous immunoglobulin exerts its beneficial effect in patients with dermatomyositis by blocking endomysial deposition of activated complement fragments. J Clin Invest 1994;94:1729-35.
- Basta M, Fries LF, Frank MM. High doses of intravenous Ig inhibit in vitro uptake of C4 fragments onto sensitized erythrocytes. Blood 1991;77:376-80.
- Bayry J, Lacroix-Desmazes S, Carbonneil C, Misra N, Donkova V, Pashov A, et al. Inhibition of maturation and function of dendritic cells by intravenous immunoglobulin. Blood 2003;101:758-65.
- Bayry J, Lacroix-Desmazes S, Delignat S, Mouthon L, Weill B, Kazatchkine MD, et al. Intravenous immunoglobulin abrogates dendritic cell differentiation induced by interferon-alpha present in serum from patients with systemic lupus erythematosus. Arthritis Rheum 2003b;48:3497-502.
- Bayry J, Lacroix-Desmazes S, Kazatchkine MD, Galicier L, Lepelletier Y, Webster D, et al. Common variable immunodeficiency is associated with defective functions of dendritic cells. Blood 2004;104:2441-3.
- Bayry J, Lacroix-Desmazes S, Hermine O, Oksenhendler E, Kazatchkine MD, Kaveri SV. Amelioration of differentiation of dendritic cells from CVID patients by intravenous immunoglobulin. Am J Med 2005;118:1439-40.
- BCSH. British Committee for Standards in Haematology. General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol 2003;120: 574-96.
- Berger M, Cupps TR, Fauci AS. Immunoglobulin replacement therapy by slow subcutaneous infusion. Ann Intern Med 1980;93:55-6.
- Birchall JE, Murphy MF, Kaplan C, Kroll H. European collaborative study of the antenatal management of feto-maternal alloimmune thrombocytopenia. Br J Haematol 2003;122:275-88.

- Blum M, Wigley FM, Hummers LK. Scleromyxedema: a case series highlighting long-term outcomes of treatment with intravenous immunoglobulin (IVIG). Medicine (Baltimore) 2008;87:10-20.
- Bonilla FA, Geha RS. Primary immunodeficiency diseases. J Allergy Clin Immunol 2003;111(Suppl 2):S571-81.
- Boughton BJ, Jackson N, Lim S, Smith N. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clin Lab Haematol 1995;17:75-80.
- Bouhlal H, Hocini H, Quillent-Gregoire C, Donkova V, Rose S, Amara A, et al. Antibodies to C-C chemokine receptor 5 in normal human IgG block infection of macrophages and lymphocytes with primary R5-tropic strains of HIV-1. J Immunol 2001;166:7606-11.
- Boulis A, Goold S, Ubel PA. Responding to the immuglobulin shortage: a case study. J Health Polit Policy Law 2002;27:977-1000.
- Brannagan TH, Nagle KJ, Lange DJ, Rowland LP. Complications of intravenous immunoglobulin treatment in neurologic disease. Neurology 1996;47:674-7.
- Brennan V, Salome-Bentley N, Chapel HM. Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin. Clin Exp Immunol 2003;133:247-51.
- Bresee JS, Mast EE, Coleman PJ, Baron MJ, Schonberger LB, Alter MJ, et al. Hepatitis C virus infection associated with administration of intravenous immune globulin. A cohort study. JAMA 1996;276:1563-7.
- Bruton OC. Agammaglobulinemia. Pediatrics 1952;9:722-8.
- Burnouf T. Modern plasma fractionation. Transfus Med Rev 2007;21:101-17.
- Bussel JB. Fc receptor blockade and immune thrombocytopenic purpura. Semin Hematol 2000;37:261-6.
- Bussel JB, Berkowitz RL, Lynch L, Lesser ML, Paidas MJ, Huang CL, et al. Antenatal management of alloimmune thrombocytopenia with intravenous gamma-globulin: a randomized trial of the addition of low-dose steroid to intravenous gamma-globulin. Am J Obstet Gynecol 1996;174:1414-23.
- Cabanillas F, Liboy I, Pavia O, Rivera E. High incidence of non-neutropenic infections induced by rituximab plus fludarabine and associated with hypogammaglobulinemia: a frequently unrecognized and easily treatable complication. Ann Oncol 2006;17:1424-7.
- CEDIT. Comité d'évaluation et de diffusion des innovations technologiques. Recommandations de bon usage des immunoglobulines intraveineuses polyvalentes dans les indications reconnues par le Comité d'experts IgIV de l'Assistance Publique - Hôpitaux de Paris. Paris: CEDIT;2004.
- CGSICLL. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. N Engl J Med 1988;319:902-7.
- Chapel HM, Lee M, Hargreaves R, Pamphilon DH, Prentice AG. Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma. Lancet 1994;343:1059-63.
- Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol 2000;20:94-100.
- Cohn E, Strong L, Hughes W. Preparation and properties of serum and plasma proteins IV: A system for the separation into fractions of the protein and lipoprotein components of biological tissues and fluids. J Am Chem Soc 1946;68:459-75.
- Colovic M, Dimitrijevic M, Sonnenburg C, Suvajdzic N, Donfrid M, Bogdanovic A. Clinical efficacy and safety of a novel intravenous immunoglobulin preparation in adult chronic ITP. Hematol J 2003;4:358-62.
- Cordonnier C, Chevret S, Legrand M, Rafi H, Dhedin N, Lehmann B, et al. Should immunoglobulin therapy be used in allogeneic stem-cell transplantation? A randomized, double-blind, dose effect, placebo-controlled, multicenter trial. Ann Intern Med 2003;139:8-18.

- Dalakas MC, Illa I, Dambrosia JM, Soueidan SA, Stein DP, Otero C, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med 1993;329:1993-2000.
- Daoud YJ, Amin KG. Comparison of cost of immune globulin intravenous therapy to conventional immunosuppressive therapy in treating patients with auto-immune mucocutaneous blistering diseases. Int Immunopharmacol 2006;6:600-6.
- Darabi K, Abdel-Wahab O, Dzik WH. Current usage of intravenous immune globulin and the rationale behind it: the Massachusetts General Hospital data and a review of the literature. Transfusion 2006;46:741-53.
- Daw Z, Padmore R, Neurath D, Cober N, Tokessy M, Desjardins D, et al. Hemolytic transfusion reactions after administration of intravenous immune gamma globulin: a case series analysis. Transfusion 2008;48:1598-601.
- Debre M, Bonnet MC, Fridman WH, Carosella E, Philippe N, Reinert P, et al. Infusion of Fc gamma fragments for treatment of children with acute immune thrombocytopenic purpura. Lancet 1993;342:945-9.
- Donofrio PD, Berger A, Brannagan TH 3rd, Bromberg MB, Howard JF, Latov N, et al. Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM ad hoc committee. Muscle Nerve 2009;40:890-900.
- EDQM. The European Directorate for the Quality of Medicines & Health Care. Human anti-D immunoglobulin for intravenous administration. European Pharmacopoeia 2008;6:monograph 1527.
- EDQM. The European Directorate for the Quality of Medicines & Health Care. Human normal immunoglobulin for intravenous administration. European Pharmacopoeia 2008b;6(Suppl 6.6):monograph 0918.
- Eftimov F, Winer JB, Vermeulen M, de Haan R, van Schaik IN. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2009;Issue 1:CD001797.
- Ehrlich JR, Tang L, Caiazzo RJ, Jr., Cramer DW, Ng SK, Ng SW, et al. The "reverse capture" autoantibody microarray : an innovative approach to profiling the autoantibody response to tissue-derived native antigens. Methods Mol Biol 2008;441:175-92.
- Eijkhout HJ, Van den Broek PJ, Van der Meer JW. Substitution therapy in immunodeficient patients with anti-IgA antibodies or severe adverse reactions to previous immunoglobulin therapy. Neth J Med 2003;61:213-7.
- Elovaara I, Apostolski S, van Doorn P, Gilhus NE, Hietaharju A, Honkaniemi J, et al. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases. Eur J Neurol 2008;15:893-908.
- EMA. European Medicines Agency. Report of EMEA expert meeting on the revision of the Core SPC and Note for Guidance for Human Normal Immunoglobulin for Intravenous Administration (IVIg). EMEA/CPMP/BPWP/361857/2006. London: EMA; 2008.
- Enk A, Fierlbeck G, French L, Girolomoni G, Hertl M, Jolles S, et al. Guidelines on the use of high-dose intravenous immunoglobulin in dermatology. Eur J Dermatol 2009;19:90-8.
- Erdman DD, Anderson BC, Török TJ, Finkel TH , Anderson LJ. Possible transmission of parvovirus B19 from intravenous immune globulin. J Med Virol 1997;53:233-6.
- Farber CM, Benoit Y, Boven K, De Baets F, Ferster A, Hoyoux C, et al. Déficits immunitaires primaires : diagnostic, prise en charge, quelques perspectives. Rev Med Brux 2001;22:73-82.
- Feasby T, Banwell B, Benstead T, Bril V, Brouwers M, Freedman M, et al. Guidelines on the use of intravenous immune globulin for neurologic conditions. Transfus Med Rev 2007;21(Suppl 1):S57-107.
- Gajdos P, Chevret S, Toyka KI. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev 2007;Issue 4:CD002277.
- Galeotti C, Maddur MS, Kazatchkine MD, et al. Immunoglobulines intraveineuses dans les maladies auto-immunes et inflammatoires: au-dela d'une simple substitution. Transfus Clin Biol 2009;16:75-9.
- GAO. United States General Accounting Office. Plasma Product Risks and Manufacturer's Compliance. GAO/T-HEHS-98-242. Washington: GAO; 1998.

- Gardulf A, Bjorvell H, Gustafson R, Hammarstrom L, Smith CI. The life situations of patients with primary antibody deficiency untreated or treated with subcutaneous gammaglobulin infusions. Clin Exp Immunol 1993;92:200-4.
- Gottstein R, Cooke RW. Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. Arch Dis Child Fetal Neonatal Ed 2003;88:F6-10.
- Gray O, McDonnell GV, Forbes RB. Intravenous immunoglobulins for multiple sclerosis. Cochrane Database Syst Rev 2003;Issue 4:CD002936.
- Griffiths, Brennan V, Lea J, Bunch C, Lee M, Chapel H. Crossover study of immunoglobulin replacement therapy in patients with low-grade B-cell tumors. Blood 1989;73:366-8.
- Hayakawa F, Imada K, Towatari M, Saito H. Life-threatening human parvovirus B19 infection transmitted by intravenous immune globulin. Br J Haematol 2002;118:1187-9.
- Healey CJ, Sabharwal NK, Daub J, Davidson F, Yap PL, Fleming KA, et al. Outbreak of acute hepatitis C following the use of anti-hepatitis C virus--screened intravenous immunoglobulin therapy. Gastroenterology 1996;110:1120-6.
- Hughes RA, Donofrio P, Bril V, Dalakas MC, Deng C, Hanna K, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol 2008;7:136-44.
- Hughes RA, Raphaël JC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. Cochrane Database Syst Rev 2006;Issue 1:CD002063.
- Hurez V, Kaveri SV, Mouhoub A, Dietrich G, Mani JC, Klatzmann D, et al. Anti-CD4 activity of normal human immunoglobulin G for therapeutic use. Ther Immunol 1994;1:269-77.
- Jahnke L, Applebaum S, Sherman LA, Greenberger PA, Green D. An evaluation of intravenous immunoglobulin in the treatment of human immunodeficiency virus-associated thrombocytopenia. Transfusion 1994;34:759-64.
- Kaveri S, Vassilev T, Hurez V, Lengagne R, Lefranc C, Cot S, et al. Antibodies to a conserved region of HLA class I molecules, capable of modulating CD8 T cell-mediated function, are present in pooled normal immunoglobulin for therapeutic use. J Clin Invest 1996;97:865-9.
- Kazatchkine MD, Kaveri SV. Immunomodulation of auto-immune and inflammatory diseases with intravenous immune globulin. N Engl J Med 2001;345:747-55.
- KCE. Belgian Health Care Knowledge Centre. How to ensure self-sufficiency of stable plasma derivatives in Belgium? Brussels: KCE; 2009. KCE reports 120.
- Kistler P, Nitschmann H. Large scale production of human plasma fractions. Eight years experience with the alcohol fractionation procedure of Nitschmann, Kistler and Lergier. Vox Sang 1962;7:414-24.
- Kumar A, Teuber SS, Gershwin ME. Intravenous immunoglobulin: striving for appropriate use. Int Arch Allergy Immunol 2006;140:185-98.
- Lawlor E, Power J, Garson J, Yap P, Davidson F, Columb G, et al. Transmission Rates of Hepatitis C Virus by Different Batches of a Contaminated Anti–D Immunoglobulin Preparation. Vox Sang 1999;76:138-43.
- Leger JM, Vargas S, Lievens I. Efficacy of intravenous immunoglobulin in multifocal motor neuropathy. Ann N Y Acad Sci 2007;1110:248-55.
- Lever AM, Webster AD, Brown D, Thomas HC. Non-A, non-B hepatitis occurring in agammaglobulinaemic patients after intravenous immunoglobulin. Lancet 1984;2:1062-4.
- Levy JB, Pusey CD. Nephrotoxicity of intravenous immunoglobulin. Q J Med 2000;93:751-5.
- Lin MW, Kirkpatrick PE, Riminton DS. How intravenous immunoglobulin is used in clinical practice: audits of two Sydney teaching hospitals. Intern Med J 2007;37:308-14.
- Llewelyn CA, Hewitt PE, Knight RS, Amar K, Cousens S, Mackenzie J, et al. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Lancet 2004;363:417-21.
- Marchalonis JJ, Kaymaz H, Dedeoglu F, Schluter SF, Yocum DE, Edmundson AB. Human autoantibodies reactive with synthetic autoantigens from T-cell receptor beta chain. Proc Natl Acad Sci USA 1992;89:3325-9.
- Molica S, Musto P, Chiurazzi F, Specchia G, Brugiatelli M, Cicoira L, et al. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study. Haematologica 1996;81:121-6.

- Mouthon L, Guillevin L, Tellier Z. Intravenous immunoglobulins in auto-immune- or parvovirus B19-mediated pure red-cell aplasia. Auto-immun Rev 2005;4:264-9.
- Mouthon L, Guilpain P. Immunoglobulines et physiopathologie: des indications actuelles aux indications potentielles. La Revue de médecine interne 2007;28(Hors Série 1):11-7.
- Müller-Breitkreutz K. Results of viral marker screening of unpaid blood donations and probability of window period donations in 1997. EPFA Working Group on Quality Assurance. Vox Sang 2000;78:149-57.
- Mueller-Eckhardt C, Kiefel V. High-dose IgG for post-transfusion purpura-revisited. Blut 1988;57:163-7.
- Munks R, Booth JR, Sokol RJ. A comprehensive IgA service provided by a blood transfusion center. Immunohematology 1998;14:155-60.
- NBA. National Blood Authority of the Australian Government. Criteria for the Clinical Use of Intravenous Immunoglobulin (IVIg) in Australia. Canberra: NBA; 2007.
- Negi VS, Elluru S, Sibéril S, Graff-Dubois S, Mouthon L, Kazatchkine MD, et al. Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. J Clin Immunol 2007;27:233-45.
- NICHHD. The National Institute of Child Health and Human Developments Intravenous Immunoglobulin Study Group. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. N Engl J Med 1991;325:73-80.
- Nichols WL, Hultin MB, James AH, Manco-Johnson MJ, Montgomery RR, Ortel TL, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). Haemophilia 2008;14:171-232.
- Nicolay U, Kiessling P, Berger M, Gupta S, Yel L, Roifman CM, et al. Health-related quality of life and treatment satisfaction in North American patients with primary immunedeficiency diseases receiving subcutaneous IgG self-infusions at home. J Clin Immunol 2006;26:65-72.
- Nimmerjahn F, Ravetch JV. Anti-inflammatory actions of intravenous immunoglobulin. Annu Rev Immunol 2008;26:513-33.
- Nishio M, Fujimoto K, Yamamoto S, Endo T, Sakai T, Obara M, et al. Delayed redistribution of CD27, CD40 and CD80 positive B cells and the impaired in vitro immunoglobulin production in patients with non-Hodgkin lymphoma after rituximab treatment as an adjuvant to autologous stem cell transplantation. Br J Haematol 2007;137:349-54.
- Oates-Whitehead RM, Baumer JH, Haines L, Love S, Maconochie IK, Gupta A, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev 2003;CD004000.
- Ochs HD, Gupta S, Kiessling P, Nicolay U, Berger M. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J Clin Immunol 2006;26:265-73.
- Odum J, D'Costa D, Freeth M,Taylor D, Smith N, MacWhannell A. Cryoglobulinaemic vasculitis caused by intravenous immunoglobulin treatment. Nephrol Dial Transplant 2001;16:403-6.
- Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(Suppl 4):S525-53.
- ORBCON. Ontario Regional Blood Coordination Network. Ontario Intravenous Immune Globulin (IVIG) Utilization Management Guidelines. Ottawa: ORBCON; 2009.
- Paran D, Herishanu Y, Elkayam O, et al. Venous and arterial thrombosis following administration of intravenous immunoglobulins. Blood Coagulation and Fibrinolysis 2005;16:313-8.
- Paran D, Herishanu Y, Elkayam O, Shopin L, Ben-Ami R. Venous and arterial thrombosis following administration of intravenous immunoglobulins. Blood Coagulation and Fibrinolysis 2005;16:313-8.
- Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. Lancet 2004;364:527-9.

- Peden A, McCardle L, Head MW, Love S, Ward HJT, Cousens SN, et al. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. Haemophilia 2010;16:296-304.
- Pendergrast JM, Sher GD, Callum JL. Changes in intravenous immunoglobulin prescribing patterns during a period of severe product shortages, 1995-2000. Vox Sang 2005;89:150-60.
- Pirofsky B, Kinzey DM. Intravenous immune globulins. A review of their uses in selected immunodeficiency and auto-immune diseases. Drugs 1992;43:6-14.
- Prasad NK, Papoff G, Zeuner A, Bonnin E, Kazatchkine MD, Ruberti G, et al. Therapeutic preparations of normal polyspecific IgG (IVIg) induce apoptosis in human lymphocytes and monocytes: a novel mechanism of action of IVIg involving the Fas apoptotic pathway. J Immunol 1998;161:3781-90.
- Provan D, Nokes TJC, Agrawal S, Winer J, Wood P. Clinical guidelines for the use of intravenous immunoglobulin. London: Department of Health; 2007.
- Provan D, Nokes TJC, Agrawal S, Winer J, Wood P. Clinical Guidelines for Immunoglobulin Use. Second Edition. London: Department of Health; 2008.
- Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation. Cochrane Database Syst Rev 2008;Issue 4:CD006501.
- Radosevich M, Burnouf T. Intravenous immunoglobulin G: trends in production methods, quality control and quality assurance. Vox Sang 2010;98:12-28.
- Razvi S, Schneider L, Jonas MM, Cunningham-Rundles C. Outcome of intravenous immunoglobulin-transmitted hepatitis C virus infection in primary immunodeficiency. Clin Immunol 2001;101:284-8.
- Robinson P, Anderson D, Brouwers M, Feasby TE, Hume H; IVIG Hematology and Neurology Expert Panels. Evidence-based guidelines on the use of intravenous immune globulin for hematologic and neurologic conditions. Transfus Med Rev 2007;21(Suppl 1):S3-8.
- Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science 2001;291:484-6.
- Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high dose intravenous immunoglobulin treatment: frequency and risk factors. Ann Intern Med 1994;121:259-62.
- Sharief MK, Ingram DA, Swash M, Thompson EJ. I.v. immunoglobulin reduces circulating proinflammatory cytokines in Guillain-Barre syndrome. Neurology 1999;52:1833-8.
- SHC. Superior Health Council. Advisory report on the risk of blood transfusion transmitted vCJD. Brussels:SHC; 2005. Advisory no 8048-5.
- Shehata N, Palda V, Bowen T, Haddad E, Issekutz TB, Mazer B, et al. The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline. Transfus Med Rev 2010;24(Suppl 1):S28-50.
- Shehata N, Palda VA, Meyer RM, Blydt-Hansen TD, Campbell P, Cardella C, et al. The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. Transfus Med Rev 2010b;24(Suppl 1): S7-S27.
- Sorensen PS, Fazekas F, Lee M. Intravenous immunoglobulin G for the treatment of relapsing-remitting multiple sclerosis: a meta-analysis. Eur J Neurol 2002;9:557-63.
- Spector SA, Gelber RD, McGrath N, Wara D, Barzilai A, Abrams E, et al. A controlled trial of intravenous immune globulin for the prevention of serious bacterial infections in children receiving zidovudine for advanced human immunodeficiency virus infection. Pediatric AIDS Clinical Trials Group. N Engl J Med 1994;331:1181-7.
- Stiehm ER. therapy of immunodeficiency diseases. In: Ochs HD, Smith CIE, Puck JM, eds. Primary immunodeficiency diseases: a molecular and genetic approach. New York: Oxford University Press; 1999:448–58.
- Stiehm ER, Casillas AM, Finkelstein JZ, Gallagher KT, Groncy PM, Kobayashi RH, et al. Slow subcutaneous human intravenous immunoglobulin in the treatment of antibody immunodeficiency: use of an old method with a new product. J Allergy Clin Immunol 1998;101:848-9.
- Strobel E, Schöniger M. False-positive hepatitis serology after administration of immunoglobulins. Dtsch Med Wochenschr 2006;131:1325-7.

- Sullivan KM, Kopecky KJ, Jocom J, Fisher L, Buckner CD, Meyers JD, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. N Engl J Med 1990;323:705-12.
- Sundin U, Nava S, Hammarstrom L. Induction of unresponsiveness against IgA in IgA-deficient patients on subcutaneous immunoglobulin infusion therapy. Clin Exp Immunol 1998;112:341-6.
- Svenson M, Hansen MB, Ross C, Diamant M, Rieneck K, Nielsen H, et al. Antibody to granulocyte-macrophage colony-stimulating factor is a dominant anti-cytokine activity in human IgG preparations. Blood 1998;91:2054-61.
- Thomas MJ, Misbah SA, Chapel HM, Jones M, Elrington G, Newsom-Davis J. Hemolysis after high-dose intravenous Ig. Blood 1993;82:3789.
- van Schaik IN, Bouche P, Illa I, Leger JM, Van den Bergh P, Cornblath DR, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Eur J Neurol 2006;13:802-8.
- van Schaik IN, van den Berg LH, de Haan R, Vermeulen M. Intravenous immunoglobulin for multifocal motor neuropathy. Cochrane Database Syst Rev 2005;Issue 2:CD004429.
- van Schaik IN, Winer LH, de Haan R, Vermeulen M. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2002;Issue 2:CD001797.
- Vassilev T, Gelin C, Kaveri SV, Zilber MT, Boumsell L, Kazatchkine MD. Antibodies to the CD5 molecule in normal human immunoglobulins for therapeutic use. Clin Exp Immunol 1993;92:369-72.
- Vassilev TL, Kazatchkine MD, Van Huyen JP, Mekrache M, Bonnin E, Mani JC, et al. Inhibition of cell adhesion by antibodies to Arg-Gly-Asp (RGD) in normal immunoglobulin for therapeutic use. Blood 1999;93:3624-31.
- Waller C. Historical perspective on blood & plasma products, the stakeholders and the issues. Pharmaceuticals Policy and Law (2005,2006);7:7-19.
- Winston DJ, Antin JH, Wolff SN, Bierer BE, Small T, Miller KB, et al. A multicenter, randomized, double-blind comparison of different doses of intravenous immunoglobulin for prevention of graft-versus-host disease and infection after allogeneic bone marrow transplantation. Bone Marrow Transplant 2001;28:187-96.
- Wolff SN, Fay JW, Herzig RH, Greer JP, Dummer S, Brown RA, et al. High-dose weekly intravenous immunoglobulin to prevent infections in patients undergoing autologous bone marrow transplantation or severe myelosuppressive therapy. A study of the American Bone Marrow Transplant Group. Ann Intern Med 1993;118:937-42.
- Wroe SJ, Pal S, Siddique D, Hyare H, Macfarlane R, Joiner S, et al. Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report. Lancet 2006;368:2061-7.
- Yap PL. The viral safety of intravenous immune globulin. Clin Exp Immunol 1996;104(Suppl 1):35-42.
- Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. Neurology 2007;68:837-41.
- Zou S, Fang CT, Schonberger LB. Transfusion transmission of human prion diseases. Transfus Med Rev 2008;22:58-69.

6. COMPOSITION OF THE WORKING GROUP

All experts joined the working group *in a private capacity.* The names of the members and experts of the Superior Health Council are indicated with an asterisk*.

The following experts were involved in drawing up this advisory report:

BAELE Philippe	(anaesthesiology – UCL);
BENOIT Yves	(paediatric haemato-oncology – UGent);
COENE José	(transfusion – Dienst voor het Bloed, Rode Kruis - Vlaanderen);

DE BACKER Daniel	(intensive care – ULB);
DENEYS Véronique*	(transfusion – Service du Sang, Croix-Rouge de Belgique, UCL);
DELFORGE Michel	(haematology – KUL);
DE PAEP Rudy*	(intensive care – UZA);
FARBER Claire-Michèle	(immunodeficiencies – ULB);
FERRANT Augustin*	(clinical haematology – UCL);
LAMBERMONT Micheline*	(transfusion – ULB ; Service du Sang, Croix-Rouge de Belgique);
LATINNE Dominique*	(haematological biology – UCL);
MATHYS Esther	(blood and blood products, virology – IPH);
MUYLLE Ludo*	(blood, tissues and cells – UA; UZA; FAMHP);
PEERLINCK Kathelijne	(coagulation and blood vessel disorders – KUL);
SELLESLAG Dominik	(internal medicine, haematology – AZBrugge);
SZABO Bertrand	(transfusion – Cliniques Reine Astrid Malmédy);
THOMAS Isabelle*	(virology – IPH);
TOUNGOUZ Michel*	(immunology, haematology, transfusion – ULB);
VANDEKERCKHOVE Bart*	(clinical biology, cell therapy – UGent).

This working group was initially chaired by Mr. Michel TOUNGOUZ, then by Mrs. Véronique DENEYS; the scientific secretary was Mr. Roland HÜBNER.

About the Superior Health Council (SHC)

The Superior Health Council is a federal body that is part of the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC takes no decisions on the policies to follow, nor does it implement them. It does, however, aim at giving guidance to political decision-makers on public health matters. It does so on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, members of scientific institutions), 200 of whom are appointed experts of the Council. These experts meet in multidisciplinary working groups in order to write the advisory reports.

These advisory reports are submitted to the Board. Once they have been endorsed, they are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.css-hgr.be). Some of them are also communicated to the press and to target groups among healthcare professionals.

The SHC is also an active partner in developing the EuSANH network (European Science Advisory Network for Health), which aims at drawing up advisory reports at the European level.

In order to receive notification about the activities and publications of the SHC, you can subscribe to the mailing-list and/or an *RSS-feed* via the following link: http://www.css-hgr.be/rss.

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