Transfusion Medicine and Hemotherapy

Transfus Med Hemother 2009;36:449–459

9 Human Immunoglobulins

9.1 Preparation

9.1.1 Quality Criteria

9.2 Active Constituents

9.2.1 Normal Immunoglobulins for Subcutaneous/Intramuscular Injection or for Intravenous Injection

9.2.2 Specific Immunoglobulin Preparations (Hyperimmunoglobulins)

9.3 Physiological Function

9.4 Storage, Shelf Life and Package Sizes

9.5 Range of Application, Dosage

9.5.1 Indications for Subcutaneous or Intramuscular Injection of Normal Immunoglobulins

9.5.2 Indications for Intravenous Injection of Normal Immunoglobulins
- 9.5.2.1 Primary Immunodeficiency Diseases
- 9.5.2.2 Secondary Immunodeficiency Diseases
- 9.5.2.3 High-Dose ivIg Treatment in Certain Autoimmune Diseases and Diseases of Unknown Etiology

9.5.3 Licensed Indications with Conditional Recommendation or No Recommendation due to New Scientific Data

9.5.4 Indications for Specific (Enriched) Immunoglobulins

9.5.5 Absolute and Relative Contraindications

9.6 Adverse Reactions

9.7 Documentation

9.8 References

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9.1 Preparation

Human immunoglobulins are manufactured from human plasma using various procedures (enzymatic and/or chemical treatment as well as chromatographic techniques) [33, 95, 103, 118]. Donor selection, gentle separation procedures and effective steps for inactivation or elimination of enveloped and non-enveloped viruses are important parameters concerning quality, tolerance and safety. Immunoglobulin preparations for subcutaneous or intramuscular (sc/imIg) and intravenous (ivIg) application differ with respect to manufacturing, protein content and tolerance: in each case the prescribed mode of application must therefore be strictly observed.

9.1.1 Quality Criteria

Immunoglobulins are produced from a pool of donations from at least 1,000 healthy donors. The product must not transmit infections and must, at a protein concentration of 50–120 g/l (ivIg) or 160 g/l and 165 g/l (scIg), contain defined antiviral and antibacterial antibodies at a concentration at least three-fold (ivIg) or ten-fold (scIg) above that of the starting material [95]. Furthermore, ivIg preparations must have a defined distribution of mmunoglobulin G (IgG) subclasses as well as display Fc functions of native immunoglobulins. The proportion of monomeric and dimeric IgG molecules must amount to at least 90%, the proportion of polymers and aggregates may not exceed 3%. IvIg products must contain at least 0.5 U anti-HBs antibodies/g of immunoglobulin [95].

9.2 Active Constituents

The effective components of human immunoglobulin preparations are specific antibodies which may be used for prophylactic or therapeutic indications.

Immunoglobulin preparations are available in lyophilized form or in stabilized solution and contain as stabilizers albumin and amino acids (glycine, proline, isoleucine) as well as diverse sugars (glucose, sucrose, sorbitol, maltose) and nicotinamide in part at high concentrations [33, 41].

9.2.1 Normal Immunoglobulins for Subcutaneous/Intramuscular Injection or for Intravenous Injection

The quality criteria for immunoglobulins (scIg, imIg and ivIg) are set by the European Pharmacopeia. Most of the preparations currently available contain more than 90% monomeric IgG1–4 and only insignificant amounts of IgM and IgA molecules. A preparation enriched with IgM for special indications contains both 12% IgM and IgA as well as 76% IgG. Currently, several ivIg preparations are available with very low IgA concentration that are predominantly used in patients with manifest clinically relevant antibodies against IgA molecules [25]. As an alternative, subcutaneously administered immunoglobulins can be given in such cases without increased risk of anaphylactic reactions [32, 54].

9.2.2 Specific Immunoglobulin Preparations (Hyperimmunoglobulins)

These preparations have concentrations of the specific antibody that are many times higher than normal immunoglobulin preparations. They are produced from plasma of selected or immunized donors with higher serum concentrations of specific antibodies (table 9.1).

9.3 Physiological Function

Human immunoglobulins can be divided into 5 immunoglobulin classes: IgM, IgD, IgA, IgG, IgE. IgA is composed of two

Table 9.1. Specific immunoglobulins (according to [95] and further references)

Specificity	Preparations	Protein concentrations, g/l	Minimum content of specific antibody, IU/ml*
Anti-D (Rh_0)	imIg ivIg	100–180**	500–1,000 (= 100–200 µg) 500–750 (= 100–150 µg)
CMV	ivIg	50; 100	50
HBV	imIg ivIg	100–180 100	200 50
Rabies	imIg	100–180	150
Tetanus	imIg	100–180	100
VZV	imIg ivIg	100–180 100	100 25

*WHO standard; for lyophilized preparations after dissolving according to instructions.
**Varying concentrations according to manufacturer.

(IgA1, IgA2) and IgG of four subclasses (IgG1, IgG2, IgG3, IgG4). Certain antibody specificities occur preferentially in single classes or subclasses (e.g. antibodies against bacterial polysaccharides in IgG2, antibodies against proteins preferentially in IgG1 and IgG3, neutralizing antibodies against bacterial toxins in the IgM class). 90% of IgA is secreted by mucous membranes. Commercially available IgG preparations contain >90% monomeric IgG1–4, low amounts of IgA and IgM and no IgE and IgD.

Because of pool size (donations from >1,000–80,000 healthy individual donors) commercial immunoglobulin preparations contain antibodies to a large number of relevant antigens and toxins of a great variety of pathogens in our environment. In addition there are regulative antibodies (e.g. anti-idiotypes) and also certain autoantibodies in small concentrations. Thus every IgG batch extracted from a pool of over 1,000 donors contains the 'antibody repertoire of the human species'. A protective effect of immunoglobulin preparations against experimental infections has been demonstrated for all commercially available preparations. Because of considerable variation in the experimental approach, a comparison regarding efficacy between different preparations is impossible. Immunoglobulins selectively neutralize toxins and viruses and 'opsonize' bacteria. They strengthen unspecific defense mechanisms and can also modulate the immune response and lead to a temporary blockade of Fc receptors in the RES [9, 19, 23, 33, 62, 65, 90, 121].

Application of therapeutic doses of ivIg causes a steep rise of serum concentrations, followed by a decrease within 6–12 h to about half the peak concentration (due to distribution into the extravascular space). Plasma levels thereafter decrease slowly over a period of 2–4 weeks to initial levels. Circulating antibodies appear around 20 min after administration of imIg and scIg; maximum antibody titers are reached after about 4 days [33].

9.4 Storage, Shelf Life and Package Sizes

imIg, scIg and ivIg are available in various package sizes in order to allow dose adjustment according to individual indications in children and adults. Shelf life and storage temperature must be declared by the manufacturer.

9.5 Range of Application, Dosage*

9.5.1 Indications for Subcutaneous or Intramuscular Injection of Normal Immunoglobulins

sc/imIg can be injected as substitutes for specific immunoglobulins subcutaneously or intramuscularly (see 9.5.4).

For continuous substitution in children and adults with primary and secondary immunodeficiency diseases, subcutaneous administration represents an important and effective alternative to substitution with ivIg (see sections 9.5.2.1 and 9.5.2.2) [22, 33, 46, 48, 55, 67].

Dosage of subcutaneous immunoglobulins: Initially an subcutaneous 'loading dose' of 0.2–0.5 g/kg body weight may be required. The maintenance dose is 0.1–0.15 g/kg body weight/week. Empirically the necessary weekly dose amounts to approximately one quarter of the monthly dose when undergoing ivIg substitution. One or more subcutaneous infusions can be administered in parallel on the abdomen and/or thigh. After appropriate training patients are able to perform self-administered infusion therapy with or without assistance from a special infusion pump [46]. In comparison with intravenous administration, many mostly younger and working patients with antibody deficiency syndrome perceive subcutaneous self-administered infusion to provide a higher quality of life [47, 48, 67].

9.5.2 Indications for Intravenous Injection of Normal Immunoglobulins

Provided there is no reference to the contrary, indications in this chapter are licensed for prophylactic or therapeutic administration of immunoglobulins. Indications for prophylactic or therapeutic administration are substitution therapy with ivIg in patients with known impairment of antibody formation and modulation of the humoral immune response in certain autoimmune diseases and some diseases of unknown etiology.

In individual cases recommendations are given for indications in the 'off-label use'. In this context the comments in section 0.4 on legal issues involved in the 'off-label use' are referred to.

9.5.2.1 Primary Immunodeficiency Diseases

Long-term ivIg substitution with a dose adjusted for serum IgG concentrations has proved as efficient treatment in Bruton's X-linked agammaglobulinemia (XLA), severe combined immunodeficiency (SCID and variants), variable immunodeficiency syndromes (common variable immunodeficiency, CVID), and various forms of hyper-IgM syndrome as the incidence of severe infections and their sequelae are significantly reduced. In other rare immunodeficiency diseases (Wiskott-Aldrich syndrome, ataxia telangiectasia, IgG-subclass deficiency etc.), ivIg substitution therapy is indicated only in selected cases presenting with recurrent severe infections and in proven insufficient antibody formation following vaccination (diphtheria, tetanus, *Haemophilus influenzae* B, pneumococci) [18, 19, 49, 118, 134].

Even in patients with isolated IgG-subclass deficiency or in patients with specific antibody deficiency (e.g. against pneu-

* See section 0.4.

mococci) the substitution with immunoglobulins is reasonable only if the patients concerned show a propensity to contract infections and/or a failure to form antibodies following vaccination.

Depending on the time when the immunodeficiency became clinically manifest and was diagnosed, therapy is initiated and usually continued for life [129].

Dosage of ivIg: ivIg 0.4–0.8 g/kg body weight initially. Maintenance dose is 0.4–0.6 g/kg body weight at 2- to 10-week intervals, depending on the serum concentration and the clinical picture. The patient's clinical course is definitive in determining the maintenance dose. The trough level that is aimed for, of 6 to 9 g/l IgG before the next infusion, serves as reference value which however is not reached in some patients with high IgG catabolism. In particular, it has to be considered that patients with established organ damage (e.g. bronchiectasis) have higher requirements of immunoglobulins and therefore need a higher trough level. In addition, severe acute infections may increase the demand in immunoglobulins.

In primary immunodeficiency diseases, accompanied by antibody deficiencies and an increased susceptibility to infections, a continuous therapy with ivIg or scIg *shall* be performed.	**1 C+**

9.5.2.2 Secondary Immunodeficiency Diseases

9.5.2.2.1 Antibody Deficiency Syndromes in Patients with Malignant Lymphoma and Multiple Myeloma and in Chronically Immunosuppressed Patients (Including Patients after Allotransplantation)

A clinically relevant antibody deficiency syndrome may be defined in patients with malignant lymphoma, multiple myeloma, certain malignancies and in chronically immunosuppressed patients by the occurrence of at least three severe bacterial infections per year of the respiratory, digestive and/or urinary tract, or by the occurrence of one septicemia. Studies with various doses concur that the prophylactic treatment with ivIg significantly reduces the number of severe bacterial infections [6, 21, 33, 45, 108, 137].

Dosage: Depending on the preparation, 0.2–0.4 mg ivIg/kg body weight at 3- to 4-week intervals is administered as medium to long-term infection prophylaxis.

In the context of allogeneic bone marrow transplantation ivIg is used in cases of hypogammaglobulinemia as prophylaxis against infections and in order to lower the incidence of acute graft-versus-host disease (GVHD) [110, 133]. IvIg therapy is not indicated to alleviate chronic GVHD in patients with normal serum Ig levels [1, 39, 119, 131].

Dosage in hypogammaglobulinemia following bone marrow transplantation: 0.5 g ivIg/kg body weight/week from day –7 up to 3 months post transplantionem.

Substitution with ivIg *shall* be performed in patients with chronic lymphocytic leukemia (CLL) and multiple myeloma with a secondary antibody deficiency syndrome and a clinically relevant susceptibility to infections.	**1 A**
Substitution with ivIg *should* be performed in patients who are chronically immunosuppressed, patients after stem cell transplantation and patients with malignancies who develop a secondary antibody deficiency syndrome with a clinically relevant susceptibility to infections.	**1 C**

9.5.2.2.2 HIV Infection in Infants and Small Children

In contrast to HIV infection in adults, severe bacterial infections are more frequently observed in HIV infection in children. Several controlled studies have shown that the rate and severity of infections can be significantly reduced by ivIg therapy [123]. The survival rate in the patients concerned, however, was not improved [84, 85, 114]. Meanwhile standardized highly active antiretroviral combination therapy (HAART) [120] is preventing vertical transmission of infection from HIV-positive mothers to their newborns in up to 99%. Therefore, ivIg therapy in HIV-infected infants and small children is only indicated as supportive measure in individual cases that have an increased susceptibility to bacterial infections and an antibody deficiency despite HAART [128].

Dosage: Depending on the preparation, 0.2–0.4 mg ivIg/kg body weight are administered every 3–4 weeks.

HIV-infected infants and small children who have an increased susceptibility to bacterial infections despite HAART *shall* be treated with ivIg.	**1 A**

9.5.2.3 High-Dose ivIg Treatment in Certain Autoimmune Diseases and Diseases of Unknown Etiology

The mechanism of action of ivIg treatment in autoimmune diseases is not yet entirely understood. The neutralization of antigen and super-antigen (including autoantigens), the Fc receptor blockade [62, 90], enhanced catabolism and anti-idiotype regulation of autoantibodies [11, 69] are documented.

9.5.2.3.1 Indications

Autoimmune thrombocytopenic purpura (ITP; M. Werlhof): The use of ivIg is recommended prior to invasive treatment (e.g. surgery, tooth extraction) [122] for children [12, 16, 17] as well as for adults showing therapy refractoriness and clinically relevant thrombocytopenic bleeding. The response rate of ivIg therapy in cases of ITP is 90% in children and 70–80% in adults. The duration of the response is several days to weeks. Only in rare cases is the therapy curative.

Dosage: day 1: ivIg 0.8–1.0 g/kg body weight, repeated once up to day 3, or 0.4 g/kg body weight daily on consecutive days 2–5 [6]. Therapy may be repeated in episodic recurrences of the disease in patients responding to therapy.

Prior to invasive treatment, patients with ITP *shall* be treated with high doses of ivIg.	**1 A**

Fetal and neonatal alloimmunothrombocytopenia (FNAIT), prenatal therapy:
This rare form of immunothrombocytopenia develops if the mother forms alloantibodies against paternal platelet antigens of the fetus. The children are born with thrombocytopenia and can develop petechial bleeding during delivery, at worst intracranial hemorrhage (see section 2.9). In case of a corresponding family history and confirmed alloantibodies, the mother should be given 1 g ivIg/kg body weight/week as antenatal therapy of FNAIT [6], starting in the 20th–30th week of gestation. The additional administration of prednisolone (1 mg/kg body weight) appears to reduce the incidence of intracranial hemorrhage. However, this attempted therapy is associated with severe adverse reactions [14, 63]. Platelet transfusions are recommended post delivery to treat neonatal alloimmunothrombocytopenia (see section 2.9).

Dosage: 1 g ivIg/kg body weight/week starting in the 20th–30th week of gestation, depending on the severity of thrombocytopenia. The treatment must be discussed and coordinated with specialized neonatal centers.

Female patients with confirmed FNAIT can be treated prenatally with high doses of ivIg. *Note:* Because this indication is not licensed, the application would be done in the 'off-label use'. The legal issues involved in this are pointed out in section 0.4.	**2 C**

Posttransfusional purpura (PTP):
In this very rare adverse event following blood transfusion ivIg is considered the therapy of choice, if necessary following administration of corticosteroids [6, 72, 86, 87].

Dosage: ivIg 1 g/kg body weight on 2 consecutive days, or 0.4 g/kg body weight daily on 5 consecutive days.

Patients with PTP *shall* be treated with high doses of ivIg. *Note:* Because this indication is not licensed, the application would be done in the 'off-label use'. The legal issues involved in this are pointed out in section 0.4.	**1 C+**

Guillain-Barré syndrome (GBS):
IvIg and repeated plasma exchange have shown similar success rates in older studies [26]. In the rare event of recurrences of the disease repeated treatment is indicated [26, 28]. IvIg therapy is regarded as equivalent to or rather better and more cost-effective than plasma exchange therapy [57, 100, 116, 124].

Dosage: ivIg 0.4 g/kg body weight for 3–7 days.

Patients with GBS *shall* be treated with ivIg for 3–7 days.	**1 A**

Kawasaki syndrome:
IvIg combined with acetylsalicylic acid has been recommended during acute phases [73, 89, 91].

Dosage: IvIg 1.6–2.0 g/kg body weight portioned into several doses for 2–5 days, or 2.0 g/kg body weight as a single dose.

Patients with Kawasaki Syndrome *shall* be treated with high doses of ivIg for 2–5 days.	**1 A**

Aplastic anemia and pure red cell aplasia:
IvIg therapy is generally not recommended in patients with aplastic anemia. An attempt could be made with ivIg therapy in refractory patients with the immunologically induced form of aplasia (pure red cell aplasia), in particular if this is parvovirus B19 associated [6].

Dosage: ivIg 0.5 g/kg body weight/week for 4 weeks.

In refractory patients with aplastic anemia, in whom an immunosuppressive therapy has failed, an attempt could be made to administer ivIg with some prospect of success. *Note:* Because this indication is not licensed, the application would be done in the 'off-label use'. The legal issues involved in this are pointed out in section 0.4.	**2 C**

Toxic epidermal necrolysis (Lyell syndrome):
In a portion of patients with Lyell syndrome ivIg therapy has been shown to be very successful. High doses of ivIg are said to block Fas-mediated keratinocyte death in vitro and in vivo [20, 88, 97, 104, 125].

Dosage: ivIg 0.2–0.75 g/kg body weight for 5 days.

In patients with Lyell syndrome in whom an immunosuppressive therapy has failed an attempt can be made to administer ivIg with some prospect of success. *Note:* Because this indication is not licensed, the application would be done in the 'off-label use'. The legal issues involved in this are pointed out in section 0.4.	**2 C+**

Sepsis and septic shock:
In three meta-analyses (based on 55 studies) on polyvalent ivIg therapy in bacterial sepsis and septic shock [5, 71, 74],

a significant reduction of mortality was shown for the group of ivIg-treated patients. Although it is not yet possible to make reliable statements regarding benefit because of the low patient numbers involved in the studies, the authors conclude that ivIg might become a promising additional therapy in bacterial sepsis of adults as well as of children. The effect was even more pronounced when using polyvalent ivIg preparations enriched for IgM [71]. A significant benefit was also achieved when treating sepsis in neonates with ivIg [61, 94], but not as infection prophylaxis in premature infants and neonates [13, 36, 69, 92, 93, 130]. Larger multicenter prospective studies are required for confirmation of these statements. The guideline by the German Sepsis Society [101] as well as the guideline by the International Sepsis Campaign [30] arrive at a recommendation deviating from this; however, they did not include the most recent publications.

IvIg *can* be administered along with simultaneous antibiotic therapy for the selective treatment of sepsis or septic shock in adults, children and neonates.	**2 B**

Relapsing multiple sclerosis (MS):
Long-range ivIg therapy (long-term interval therapy) of this type of MS was shown to improve symptoms and reduce the number of relapses [2, 3, 26, 31, 37, 70, 77, 112, 113, 115, 116]. In patients with high relapse rates and clinical disease progression ivIg therapy is indicated especially during pregnancy and lactation, in childhood and also if IFN-β, Copaxone and nataluzimab are contraindicated. In refractory patients treated with a licensed therapy option (non-responders) therapy escalation is indicated [3, 15, 40, 50, 51, 53].

Dosage: Dosage is not standardized. IvIg 0.15–0.4 g/kg body weight once per month or every 2 months over 1 or 2 years.

In patients with rapidly progressing relapsing multiple sclerosis and with a contraindication for, or a treatment resistance to, licensed immunosuppressive or immunomodulatory drugs, an attempt should be made with ivIg in the context of a prospective therapeutic concept (e.g. therapy escalation) [116]. *Note:* Because this indication is not licensed, the application would be done in the 'off-label use'. The legal issues involved in this are pointed out in section 0.4. A scientific account on this application of ivIg is being prepared by the circle of experts 'Off-Label Use'* in neurology/psychiatry located at the German Federal Institute for Drugs and Medical Devices (BfArM) (*www.bfarm.de*).)	**2 A**

* See next page.

Chronic inflammatory demyelinating polyneuropathy (CIDP):
The application of ivIg is considered to be the first-line, short-term treatment of choice in CIDP. Long-term interval treatment has also been shown to have some beneficial effects [28, 56, 58, 82, 102, 116]. Preliminary investigations have shown a comparable efficacy of subcutaneous (scIg) and intravenous immunoglobulin (ivIg) administration [75].

Dosage: Initially ivIg 0.2–1 g/kg body weight, long-term treatment: 0.2–0.4 g/kg body weight every 4–8 weeks.

In patients with CIDP an induction therapy with ivIg shall be performed in the framework of an overall therapeutic concept.	**1 A**
In patients with CIDP who have shown refractoriness with a licensed therapy ivIg should also be applied as long-term interval therapy. *Note:* Because this indication is not licensed, the application would be done in the 'off-label use'. The legal issues involved in this are pointed out in section 0.4. A scientific account on this application of ivIg is being prepared by the circle of experts 'Off-Label Use'[1*] in neurology/psychiatry located at the BfArM (*www.bfarm.de*).)	**2 A**

Multifocal motor neuropathy with conduction blocks (MMN):
There is no licensed therapy for treating MMN with conduction blocks. The treatment of MMN using ivIg has a distinct effect on the clinical symptoms. This effect decreases with the duration of the disease [38, 76] and may probably be improved by higher doses [28, 126].

Dosage: 0.4 g/kg body weight for 5 days, followed by a long-term interval therapy that is adjusted to the individual case with a dose determined by titration depending on the clinical picture.

Patients with MMN should initially be treated with ivIg therapy. *Note:* Because this indication is not licensed, the application would be done in the 'off-label use'. The legal issues involved in this are pointed out in section 0.4. A scientific account on this application of ivIg is being prepared by the circle of experts 'Off-Label Use'* in neurology/psychiatry located at the BfArM (*www.bfarm.de*).)	**2 A**

Myasthenia syndrome:
The classification of the autoimmune myasthenia syndrome is still under debate. In most patients with myasthenia gravis and Lambert-Eaton myasthenic syndrome (LEMS) the administration of ivIg is effective, representing an alternative to plasmapheresis. In doing this, the overall therapeutic concept has to be taken into account adjusted to the individual case. There are no controlled trials on the long-term therapy [102].

Acute exacerbation of myasthenia gravis (AChR-positive or MusK-positive) or so-called seronegative myasthenia gravis show a response to ivIg therapy [44, 135]. Similarly ivIg therapy has the same effect as plasmapheresis in the case of a myasthenic crisis requiring obligatory intubation. However, ivIg has a more favorable profile regarding adverse reactions [43]. A beneficial effect has also been confirmed by trials in cases of LEMS, a syndrome that has a far lower incidence [7]. A reliable total dose of ivIg is considered to be 1 g/kg body weight [116].

Dosage: 0.4 g/kg body weight for 5 days.

In patients with seronegative and antibody-positive myasthenia gravis and in patients with LEMS ivIg should be used in cases of acute exacerbation. *Note:* Because this indication is not licensed, the application would be done in the 'off-label use'. The legal issues involved in this are pointed out in section 0.4. A scientific account on this application of ivIg is being prepared by the circle of experts 'Off-Label Use'* in neurology/psychiatry located at the BfArM (*www.bfarm.de*).)	**2 A**

Additional immunologically mediated diseases:
In a number of additional diseases, favorable outcomes on using ivIg have been reported, mostly in the form of case reports, e.g. autoimmune hemolytic anemia (AIHA), autoimmune neutropenia, Evans syndrome, Morbus hemolyticus neonatorum, hemolytic transfusion reactions, hemolytic uremic syndrome, heparin-induced thrombocytopenia type II, HIV-associated thrombocytopenia, various forms of vasculitis, bullous dermatosis, uveitis, rheumatoid arthritis, systemic lupus erythematosus (SLE; e.g. during pregnancy). Representative prospective randomized trials confirming the efficacy of ivIg are still lacking [6, 9, 10, 15, 26, 28, 29, 69, 102, 105, 116, 128].

In case of refractoriness to a licensed treatment protocol successful therapeutic attempts have been documented with ivIg as add-on therapy in several case reports for the following clinical pictures: stiff-person syndrome [27, 28], opsoclonus-myoclonus syndrome, postpolio syndrome and Alzheimer's syndrome [102, 116]. Due to insufficient data, we refrain from making definite therapeutic recommendations. Because this indication is not licensed, the application would be done in the 'off-label use'. The legal issues involved in this are pointed out in section 0.4.

9.5.3 Licensed Indications with Conditional Recommendation or no Recommendation due to New Scientific Data

Substitution of immunoglobulins in preterm infants, especially prior to week 32 of gestation:
The largest prospective multicenter study [36] with over 2,400 premature infants has shown that the number and severity of infections could not be reduced by ivIg as prophylaxis. In addition to humoral immunodeficiency, premature infants exhibit cellular immune defects which cannot be corrected by administration of ivIg [8, 36]. This is also confirmed by more recent meta-analyses [92, 93].

IvIg should *not* be used as infection prophylaxis in preterm infants, even though this indication is licensed.	**2 A**

Prophylaxis and therapy of cytomegalovirus (CMV) infections:
Clinically manifest CMV infections are frequent complications after bone marrow or organ transplantation. Following the introduction of effective virostatic drugs, the prophylactic or therapeutic use of ivIg or CMV-Ig in treating CMV-derived organic diseases (e.g. CMV pneumonitis) has no longer advantages over an antiviral therapy alone. This also applies for CMV-antibody-negative recipients of a CMV-positive transplant [68, 78–80, 99, 132, 136].

According to the current state of scientific knowledge regarding prophylaxis and treatment of CMV infections, ivIg or CMV-Ig therapy *cannot* be recommended without simultaneous administration of virostatic drugs. This indication is not licensed.	**2 C**

*The circle of experts 'Application of Medical Products Beyond the Limits of Their Approved Indications' was created by decree of the German Federal Ministry of Health and Social Security (BMGS) dated September 17, 2002. By decree dated August 31, 2005 the circles of experts 'Off-Label Use' located at the German Federal Institute for Drugs and Medical Devices (BfArM) were extended to further medical disciplines. At present there are three circles of experts covering the medical disciplines oncology, infectious diseases with focus on HIV/AIDS and neurology/psychiatry. According to article 1 paragraph 2 of the establishing decree by the BMGS dated August 31, 2005, the circles of experts 'Off-Label Use' have the following tasks:

a) Submission of assessments regarding the state of scientific knowledge in medicine and technology on the application of approved medical products for indications and areas of indications for which they are not approved according to the German Medicinal Products Act (Arzneimittelgesetz; AMG). The assessments must be reappraised at reasonable intervals and, if necessary, adapted to the development of the state of scientific knowledge.
b) Inform the BMGS and the Federal Joint Committee according to article 91 SGB V (Code of Social Law, Book V) about the state of scientific knowledge in medicine and technology on the application of approved medical products for indications and areas of indications for which they are not approved according to the AMG.

Table 9.2. Prophylactic application of specific immunoglobulins for RhD

Target group/indications/mode of exposition	Preparation	Current evaluation of indication
Rh(D)-negative (dd) women		
After delivery of an Rh-positive child	anti-D imIg	prescribed post partum prophylaxis
During pregnancy	anti-D imIg	ante partum prophylaxis
In abortion, after interruption, ectopic pregnancy, amniocentesis, chorion biopsy or cord puncture, in bleeding during pregnancy, after forced inversion, after removal of a hydatid mole, in placenta praevia	anti-D imIg	prescribed prophylaxis
Rh(D)-incompatible RBC transfusion; granulocyte transfusion Prophylaxis for immunization against D in Rh-negative (dd) recipients of Rh-positive (D+) RBC or granulocyte concentrates	anti-D ivIg	individual cases, for prevention of anti-D formation, especially for women of reproductive age; not applicable in emergency transfusion
Rh (D)-positive platelet transfusion in Rh(D)-negative (dd) women	anti-D ivIg	individual cases, for prevention of anti-D formation, especially for women of reproductive age; not applicable in emergency transfusion
ITP	anti-D ivIg anti-D s.c. [83]	second-line therapy after ivIg; ineffective after splenectomy [17, 106]; *caution:* hemolysis, hemoglobinuria [42]!

Recurrent miscarriage:
Regarding the issue of immunomodulatory effect on recurrent miscarriage (>3 miscarriages) by administration of ivIg and other measures, there is a large number of reports [98], including a meta-analysis [96] and guidelines [59]. Though positive effects have been reported for individual cases, no significant benefit of ivIg has been confirmed to date. Therefore, the application is not recommended. Additionally, the indication is not licensed.

Hemophilia complicated by inhibitor formation or confirmed spontaneous or induced factor VIII autoantibodies:
In general ivIg therapy is not recommended in patients with hemophilia complicated by inhibitor formation [6]. However, in individual cases ivIg therapy was reported to have been successful [109, 121]. All of the more recent trials and consensus reports recommend ivIg therapy at best as a standby therapy that could be tried after corticosteroids and immunosuppressive drugs have failed [6, 24, 102].

Dosage: ivIg 0.4 g/kg body weight for 2–5 days.

In patients with hemophilia complicated by inhibitor formation a therapy attempt using ivIg is not recommended unless conventional immunosuppressive therapy has failed or in emergency situations. **1 C**

Note: Because this indication is not licensed, the application would be done in the 'off-label use' (the legal issues involved in this are pointed out in section 0.4).

Application of ivIg in refractory recipients of platelet concentrates:
Regarding the simultaneous application of ivIg and platelets in refractory platelet recipients, the reader is referred to section 2.8.

9.5.4 Indications for Specific (Enriched) Immunoglobulins

Regarding specific immunoglobulins, the reader is referred to the current publications by the German Standing Vaccination Committee (Ständige Impfkommission; STIKO) [cf. 34, 35]. Statements on the application of specific immunoglobulins for RhD prophylaxis can be found in table 9.2.

9.5.5 Absolute and Relative Contraindications

- Administration of ivIg or imIg is contraindicated in selective IgA deficiency and clinically relevant, verified antibodies to IgA. However, these patients can safely be substituted with scIg or, after blocking of the antibodies, with ivIg [4, 32, 54, 107].
- In transient hypogammaglobulinemia during childhood, substitution with Ig preparations is not indicated provided that such children form normal amounts of antibodies following vaccination [19].
- Simultaneous parenteral administration of specific immunoglobulins and attenuated live vaccines (measles, rubella, mumps, chicken pox, yellow fever) can lead to impair-

ment of active antibody formation. A minimum interval of 2 weeks between Ig application and vaccination must be observed. Guidelines for dosage and manufacturers' informations are to be followed carefully, especially on administration of specific immunoglobulins.

Note: Underdosing of sc/imIg or ivIg without precise indication is always contraindicated, as this does not lead to effective antibody concentrations. Specifically the intramuscular administration of immunoglobulins as substitution therapy is considered to have become obsolete as the dose necessary for treatment is not achieved (example: 10 ml 16% sc/imIg ≈ 1.6 g IgG, i.e. ≤2% of the total body pool of 1 g/kg body weight in adults).

9.6 Adverse Reactions

See chapter 11.

So-called aseptic meningitis [52, 111, 127] with headache, stiff neck, vomiting and fever occasionally occurring after too rapid infusion or too high doses of ivIg does not constitute a contraindication to further infusion therapy. But an interruption of therapy is recommended as pachymeningitis was also observed to occur under ivIg administration [81]. A slower rate of infusion is recommended and/or switching to a lower-dose ivIg preparation; another possibility is to switch the ivIg preparation. It is not yet clear whether this represents a variant of the drug-induced aseptic meningitis (DIAM) [66] or whether the Fc concentration or other immunological mechanisms are more likely explanations [60].

Additional rare adverse reactions are to be expected like embolic incidents (cerebral infarction) or renal tubular necrosis [28]. There is also the possibility of ivIg-derived acute polyneuroradiculitis in chronic inflammatory demyelinizing polyneuropathy [64].

9.7 Documentation

According to article 14 German Transfusion Act (Transfusionsgesetz; TFG), there is an obligation to perform a patient- as well as product-related batch documentation for human immunoglobulins.

9.8. References

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