Therapeutic immunoglobulins in clinical practice

Efficacy, pharmacoeconomic aspects and safety of therapeutic use of immunoglobulins for diverse indications in the Netherlands

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Abbreviations

CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
CLL	chronic lymphatic leukaemia
CVID	common variable immunodeficiency
EMA	European medicines agency
GBS	Guillain-Barré syndrome
IgA	immunoglobulin A
IgG	immunoglobulin G
ISNO	interuniversitair steunpunt neuromusculair onderzoek, Dutch Neuromuscular Research Centre
ITP	immune thrombocytopenic purpura
IVIg	intravenous immunoglobulin
MMN	multifocal motor neuropathy
NNT	Number needed to treat
PC	platelet count
RCT	randomized controlled trial
SAS	Stichting voor Afweerstoornissen, patient organization immunodeficiencies
SCIg	subcutaneous immunoglobulin
VSN	Vereniging Spierziekten Nederland, patient organization neuromuscular diseases
WID	Werkgroep Immuundeficientie, Working group on immunodeficiencies
XLA	x-linked agammaglobulinemia

Summary

Introduction
Immunoglobulins have been included in the "Beleidsregel Dure Geneesmiddelen" since January 2002 for the treatment of various (rare) disorders. Mechanism of action of therapeutic immunoglobulins is either immunomodulation, in disorders like Kawasaki Disease, immune-mediated thrombocytopenic purpura (ITP) and Guillain-Barré syndrome, or replacement in disorders with a shortage of endogenous IgG (hypogammaglobulinemia).This report details efficacy, safety and pharmacoeconomic aspects of therapeutic use of immunoglobulins in the Netherlands.

Methods
A systematic literature review was performed for clinical efficacy, safety and pharmacoeconomic evaluations for the following four indications: Kawasaki Disease, ITP, Guillain-Barré syndrome and immunodeficiency. In addition, we conducted interviews with expert professionals and patient organizations, and made an inventory of existing national guidelines on the use of immunoglobulins.

Therapeutic efficacy
Kawasaki Disease: treatment with IVIg was shown to be effective in preventing long-term complications. A short course of 2 g/kg IVIg is first-line treatment in clinical practice. There is no national guideline.
ITP: treatment with IVIg is very efficient in quickly raising platelet count, but after a few days response is equal to that of prednisone. In clinical practice, a short course of IVIg (2 g/kg) is reserved for patients who suffer from severe bleeding or need to undergo surgical intervention. A national guideline exists for adults with ITP, not for children.
Guillain-Barré Syndrome: IVIg is as effective as plasma exchange in improving disability, but is easier to administer and causes less complications. The national CBO guideline considers a short course of IVIg as standard treatment (2 g/kg).
Hypogammaglobulinemia: replacement therapy with IVIg is effective in reducing the number of bacterial infections. There is no national guideline. Patients with primary hypogammaglobulinemia and frequent infections are treated with chronic IVIg treatment at an average of 300-400 mg/kg once every 3-4 weeks.
Other indications: multifocal motor neuropathy and chronic inflammatory demyelinating polyradiculoneuropathy are rare neuromuscular diseases that are treated long-term with high-dose IVIg maintenance therapy (up to 17 g/week). Foetal and neonatal alloimmune thrombocytopenia can be prevented by treatment of the pregnant woman with 0,5 g/kg IVIg during 10 weeks of pregnancy. For most of the other indications of IVIg, treatment will be likely to be incidental in treatment failure of standard care (e.g. dermatomyositis, multiple sclerosis).

Safety
Safety and tolerability of immunoglobulins is generally good. Frequent adverse events are (mild) headache and fever.

Pharmacoeconomic considerations
There are only a limited number of pharmacoeconomic evaluations for therapeutic immunoglobulins, and none of the Dutch situation. Cost prognosis estimates confirm that the largest cost is from chronic IVIg treatment in patients with neuromuscular disease (MMN, CIDP) and hypogammaglobulinemia.

Current studies & missing data
Five Dutch studies that include IVIg have been identified and are detailed. Missing data include especially national guidelines on a number of disorders, pharmacoeconomic evaluations relevant for the Dutch situation, data on prevalence of some rare disorders and off-label use of IVIg.

Conclusion
Therapeutic immunoglobulins are used in a range of settings, either for supplementation or immunomodulation, and either as a short course or as maintenance therapy. This makes it complicated to get a good overview of its use in daily practice.

Samenvatting in het Nederlands

Introductie
Immuunglobulines staan sinds januari 2002 op de “Beleidsregel Dure Geneesmiddelen” voor de behandeling van diverse (zeldzame) aandoeningen. Therapeutische immuunglobulines werken door immuunmodulatie, in aandoeningen zoals de ziekte van Kawasaki, ITP en Guillain-Barré syndroom, of door suppletie in aandoeningen met een deficiëntie van endogeen IgG (hypogammaglobulinemie). Dit rapport beschrijft effectiviteit, veiligheid en farmacoeconomische aspecten van therapeutische immuunglobulines in Nederland.

Methode
Een systematisch literatuuronderzoek naar Klinische effectiviteit, veiligheid en farmacoeconomische evaluatie werd uitgevoerd voor de volgende vier indicaties: ziekte van Kawasaki, ITP, Guillain-Barré syndroom en immuundeficiëntie. Daarnaast werden interviews uitgevoerd met professionele experts en patiëntenorganisaties, en werd informatie verzameld over landelijke richtlijnen.

Klinische effectiviteit
Ziekte van Kawasaki: het is bewezen dat behandeling met IVIg het risico op lange-termijn complicaties sterk verlaagt. Eenmalige toediening van 2 g/kg IVIg is standaard therapie in de dagelijkse praktijk. Er bestaat geen nationale richtlijn.
ITP: behandeling met IVIg geeft een snelle stijging van het aantal bloedplaatjes, maar na een paar dagen is er geen verschil met bv prednison. In de klinische praktijk wordt een eenmalige toediening van IVIg (2 g/kg) beperkt tot patiënten met ernstige bloedingen of die een chirurgische ingreep moeten ondergaan. Er is een nationale richtlijn voor volwassenen, niet voor kinderen.
Guillain-Barré Syndroom: IVIg is net zo effectief als plasmaferese ter verbetering van de neurologische uitval, maar is makkelijker toe te passen en geeft minder bijwerkingen. De nationale CBO richtlijn beschouwt eenmalige toediening van IVIg als standaard behandeling (2 g/kg).
Hypogammaglobulinemie: suppletie met IVIg is effectief in het vermindering van het aantal bacteriële infecties. Er is geen nationale richtlijn. Patienten met primaire hypogammaglobulinemie en frequente infecties worden chronisch behandeld met IVIg (300-400 mg/kg per 3-4 wkn).
Andere indicaties: multifocal motor neuropathy (MMN) en chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) zijn zeldzame neuromusculaire aandoeningen die chronisch behandeld worden met hoge dosis IVIg (12-17 g/week of meer). Foetale en neonatale alloimmune thrombocytopenia kan worden voorkomen door behandeling van de zwangere vrouw met 0,5 g/kg IVIg gedurende 10 wkn. Voor de meeste andere indicaties is gebruik van IVIg in het algemeen incidenteel bij falen van standaardbehandeling (bv dermatomyositis, multiple sclerosis).

Veiligheid
Immuunglobulines zijn veilig in het dagelijks gebruik. Veelvoorkomende bijwerkingen zijn (milde) hoofdpijn en koorts.

Farmacoeconomische overwegingen
Er bestaan slechts een beperkt aantal farmacoeconomische studies, en geen specifiek voor de Nederlandse situatie. De grootste kostenpost zijn de patiënten die chronisch behandeld worden met IVIg voor chronische neuromusculaire ziekten of hypogammaglobulinemie.

Lopende studies en ontbrekende data
Er zijn vijf lopende studies met IVIg in Nederland geïdentificeerd. Onder de ontbrekende data vallen met name het ontbreken van nationale richtlijnen voor IVIg bij een aantal aandoeningen, farmacoeconomische evaluaties die relevant zijn voor de Nederlandse situatie, prevalentie van sommige van de zeldzame aandoeningen en het off-label gebruik van IVIg.

Conclusie
Therapeutische immuunglobulines worden gebruikt in een gevarieerd setting, voor suppletie van een deficiëntie of voor immuunmodulatie, en als een korte kuur of levenslang. Deze variatie maakt het lastig om een goed overzicht te krijgen van het algemeen gebruik in de dagelijkse praktijk.

1. Introduction

1.1 Background

Immunoglobulins have been included in the "Beleidsregel Dure Geneesmiddelen" since January 1, 2002, for a number of indications. There is an increase in use of immunoglobulins and of costs associated with this. ZonMW has commissioned this report on the pharmacotherapeutic value, efficacy and effective implementation of this therapy. In preparation, we used a combination of systematic literature review, examination of existing guidelines and treatment algorithms, interviews with clinical experts, patient organizations and pharmacy.
The disorders in which immunoglobulins are used are very diverse. Efficacy, mode of treatment, treatment algorithms and pharmacoeconomic aspects are very different for these various indications, which makes an overall consideration of immunoglobulin treatment complicated. We will treat these disorders separately in the current report.

1.2 Content of immunoglobulin preparations

Therapeutic immunoglobulin preparations consist of normal, polyclonal, polyspecific immunoglobulins prepared from plasma pools of thousands of healthy donors. They contain mainly IgG (>95%), with all IgG subclasses represented. Most products contain no IgM and very small amounts of IgA [1]. IgM is removed because it can rapidly form large complexes leading to a variety of adverse reactions. IgA is removed as much as possible because patients with IgA-deficiency (a frequent component of e.g. common variable immunodeficiency (CVID)) may develop anti-IgA antibodies that may provoke anaphylactic reactions to IgA-containing blood products.

1.3 Existing preparations of immunoglobulin

Historically, immunoglobulin administration was done intramuscularly. Since some 20 years now, intravenous immunoglobulin (IVIg) administration has replaced this i.m. route as a less painful alternative, allowing administration of larger quantities with fewer side effects. Another option is subcutaneous administration (SCIg). Most frequent reason to choose SCIg is to avoid the need for intravenous access (especially in children or adults with difficulty of i.v. access); it is practically only used in replacement therapy. It also is safe in patients with adverse reactions to IVIg [2]. Disadvantage of SCIg is the smaller volume and therefore need for more frequent administration. IVIg is still the dominant form of therapy in The Netherlands.
In The Netherlands, the two major pharmaceutical companies in the immunoglobulin market are Sanquin and Baxter.
Sanquin (Amsterdam) produces immunoglobulin preparations from at least 1000 Dutch blood donors. Most prescribed is the IVIg preparation Nanogam®, a ready-made solution. The product Gammaquin® can be given i.m. or s.c.. Baxter produces the preparations Kiovig® for i.v. use, Gammagard S/D® for i.v. use (a powder to be reconstituted) and Subcuvia® for i.m. or s.c. use.
Another preparation on the Dutch market is Flebogammadif®, for i.v. use, produced by the company Grifols. These preparations differ only slightly in the percentage of IgG and IgA in the content and stabilizers used.
Octagam®, an IVIg preparation by Octapharma GmbH, was recalled from the European market in September 2010 on the advice of EMA, because of an unexpected increase in reports of thromboembolic reactions, including stroke, myocardial infarction and pulmonary embolism in patients receiving the medicine. This increase was thought to be related to problems with the medicine's manufacturing process (www.ema.europa.eu)

1.4 Mode of action of therapeutic immunoglobulin

1.4.1 Replacement

The mechanism of action of immunoglobulins in case of substitution in patients with hypogammaglobulinemia is easily understood. Missing IgG is replaced by IgG from blood donors, and because the immunoglobulin preparation is generated from a pool of thousands of donors it is likely that it will contain a sufficient amount of common pathogen-specific IgG antibodies [3]. It is assumed that it is preferable to use an immunoglobulin preparation that has been obtained from donors from the same population as the hypogammaglobulinemic patient, with presumably similar exposure to microorganisms. This has not been formally tested.

1.4.2 Immunomodulation

The immunomodulatory mechanisms of Ig infusions are less clear, and have not been fully elucidated [3]. IgG can exert both inflammatory and anti-inflammatory activity, depending on its concentration. At low-dose, IVIg has inflammatory characteristics, through complement activation or binding of the Fc fragment of IgG to IgG specific receptors (FcγR) on innate immune effector cells. But at high concentrations, IVIg has an anti-inflammatory effect. This results from multiple effects on innate as well as adaptive immunity, which are still under investigation [3]. This anti-inflammatory effect is used in several immune-mediated disorders (section 1.5).

1.5 Therapeutic indications and disease characteristics

1.5.1 Kawasaki Disease

Kawasaki disease is a childhood vasculitis with a relatively high incidence. In Western countries, the incidence is estimated at 8-18 children younger than 5 years per 100.000. In Japan, the incidence is much higher (112 per 100.000). [4]

It is an acute-onset systemic vasculitis of unknown etiology, occurring primarily in babies and young children (85% < 6 years of age). It especially affects middle-sized vessels such as coronary arteries. Kawasaki disease manifests itself by fever and signs of acute inflammation such as polymorphous exanthema, conjunctivitis, diffuse redness of the oropharyngeal mucosa, strawberry-tongue, cervical lymphadenopathy or painful edema and/or erythema of hands and feet. Diagnosis is made on the basis of clinical criteria.

If left untreated, these symptoms will persist for a medium of 12 days, after which they often spontaneously disappear. However, in 15-25% of untreated patients Kawasaki disease will lead to formation of aneurysms in the coronary arteries, which may result in childhood myocardial ischemia and infarction due to thrombosis and stenosis of coronary arteries. When patients are treated adequately, this risk of formation of coronary aneurysms is reduced to <5%. [4].

1.5.2 Immune-mediated Thrombocytopenic Purpura (ITP)

Primary immune-mediated thrombocytopenic purpura (ITP), or idiopathic thrombocytopenic purpura, is a disorder characterized by an acquired isolated thrombocytopenia (thrombocyte count <100x10^9/l), in the absence of an associated disease or cause. It is thought to be caused by increased destruction of thrombocytes by auto-antibodies, faults in the production of thrombocytes, T-cell mediated immune processes or a combination of these. It can occur in children as well as in adults, with an equal distribution among men and women (except for the age 30-60 years, when it is more common in women). It can be divided into acute ITP, persisting ITP (3- 12 months duration) or chronic ITP (more than 12 months) [5].

Clinical symptoms can vary greatly. Some patients are asymptomatic, others may present with mild petechiae, purpura or mucosal bleeding. In a small percentage of patients, life-threatening severe gastrointestinal or intracerebral bleeding can occur. In adults, this risk is estimated to be 0,0162-0,0389 cases per patient year [5].

1.5.3 Guillain-Barré Syndrome (GBS)

Guillain-Barré syndrome (GBS) is an acute neurological disease, that is usually preceded by a 'minor' upper airway tract infection or diarrhea. It is characterized by rapidly progressive ascending symmetrical muscle weakness, which usually starts in the legs and can progress to the arms. Muscles of face, eyes and breathing can become paralyzed as well. There are often also disturbances of sense and pain. The maximum severity of disease is reached within four weeks of start of symptoms. After a stable phase of days to months, improvement is seen. Recovery can take weeks to many months and sometimes even years. Symptoms, severity and speed of recovery are extremely variable. The pathogenesis is unknown. Life-threatening complications due to respiratory insufficiency or difficulty swallowing can occur, sometimes within 24 hours of onset of symptoms. Patients with GBS are admitted to hospital, about 25% need admission to intensive care for respiratory support. IVIg is first line treatment of GBS.
GBS is the most frequent cause of acute muscle weakness in the Western world. Incidence in the Netherlands is 1.3 per 100.000 per year, which means that about 200 persons per year get GBS (CBO guideline Guillain-Barré syndrome 2010).

1.5.4 Hypogammaglobulinemia / Immunodeficiency

A reduced concentration of IgG in the blood can occur as a primary immunodeficiency or secondary to other conditions.
It occurs as primary immunodeficiency when there is a B-cell deficiency, for example in X-linked agammaglobulinemia, Wiskott-Aldrich syndrome or severe combined immunodeficiency; this will manifest itself at a young age. The most common primary immunodeficiency in adults is common variable immunodeficiency (CVID). There are also more subtle immunodeficiencies in which there is a lack of a specific subclass of IgG, or where a specific anti-polysaccharide response is insufficient. Treatment is indicated when the patient suffers from frequent infections.
Hypogammaglobulinemia can occur as a secondary phenomenon in for example chronic lymphatic leukemia (CLL), other forms of leukemia or after stem cell transplantation. Pre-term babies often have a relative shortage of IgG in the first weeks/months of life.

1.5.5 Other indications or off-label use

1.5.5.1 Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Chronic inflammatory demyelinating polyneuropathy (CIDP, also known as chronic inflammatory demyelinating polyradiculoneuropathy) is an acquired disorder of peripheral nerves and nerve roots. The classic form of CIDP is fairly symmetric and motor involvement is greater than sensory, with weakness in both proximal and distal muscles. Cranial nerve and bulbar involvement occur in 10 to 20 percent of patients. Most patients with CIDP exhibit a slowly progressive course, but a relapsing-remitting course is noted in at least one-third. Pathogenesis is unknown, but it is considered to be immunologically based. Estimated prevalence is 0,8 and 8,9 per 100,000 [6].

1.5.5.2 Multifocal motor neuropathy (MMN)

Multifocal motor neuropathy is a rare, probably immune mediated disorder characterised by slowly progressive, asymmetric, distal weakness of one or more limbs with no objective loss of sensation. It may cause prolonged periods of disability. The treatment options for multifocal motor neuropathy are sparse. Patients with multifocal motor neuropathy do not usually respond to steroids or plasma exchange, and may even worsen with these treatments. Many uncontrolled studies have suggested a beneficial effect of intravenous immunoglobulin [7]. A recent national cross-sectional descriptive study identified 97 patients with MMN in the Netherlands [8].

1.5.5.3 Other neuromuscular disease

Other neurological diseases in which IVIg treatment, usually in short courses, can be given are: acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), myasthenia gravis (MG), opsoclonus-myoclonus and stiff person syndrome. In most of these diseases, treatment with IVIg is reserved for patients with a poor prognosis and/or poor response to other immunomodulatory treatment [9]. These indications will not be discussed in more details in the current report.

1.5.5.4 Dermatomyositis / polymyositis

Dermatomyositis and polymyositis are both inflammatory myopathies, systemic autoimmune disorders characterised by inflammation of skin and muscle. The CBO guideline (2005) on these disorders recommends prednisone as first line treatment, but it lists IVIg as alternative treatment in case of failure or progression of disease.

1.5.5.5 Fetal and neonatal alloimmune trombocytopenia (FNAIT)

Fetal and neonatal alloimmune trombocytopenia (FNAIT) is a disease characterised by fetal or neonatal severe trombocytopenia. It is analogous to fetal or neonatal anemia due to red cell (Rhesus) alloimmunisation in pregnancy. Maternal-paternal incompatibility for antigens on platelets leads to production of antibodies against fetal platelets during pregnancy. The most feared complication is intracranial hemorrhage in the child. Many of these children suffer life-long handicaps, cerebral palsy, cortical blindness and mental retardation due to the bleeding [10].
It occurs in an estimated 1:1000-2000 pregnancies. It is usually only caught in time for treatment when there has been a previous child born with trombopenia or hemorrhaging, since there is no screening program for this disorder. [11]

1.5.5.6 Autoimmune Haemolytic Anaemia (AIHA)

Autoimmune haemolytic anaemia (AIHA) is a rare disorder caused by autoantibodies that bind to antigens on the red blood cell surface and initiate red cell destruction. There are clear similarities in the pathogenesis of AIHA and ITP. AIHA is relatively uncommon, with an estimated incidence of 1-3 cases per 100.000 population per year. IVIg is not recommended for routine use in acute or chronic treatment of AIHA, but it may be considered as an option for treatment of life-threatening AIHA [12].

1.5.5.7 Organ Transplantation

Administration of IVIg is among the immunomodulatory therapies that are being used to overcome antibody-mediated graft rejection after solid organ transplantation. There is only limited evidence for this use; only in certain forms of transplant rejection in kidney transplantation is there evidence for a beneficial effect [13]. It is not used in routine care as far as we are aware, but only in very specific cases.

1.5.5.8 Other

The list of disorders in which IVIg has been tried or recommended on the basis of case reports or small studies is much longer. Kivity et al. recently published an extensive overview of all these indications[14].

2. Methods

2.1 Systematic review of literature

We limited our systematic review to populations that are mentioned in the Dutch Pharmacotherapeutic Formulary (Farmacotherapeutisch kompas): patients with immunodeficiency (both primary and secondary immunodeficiency syndromes), patients with Kawasaki disease, patients with idiopathic thrombocytopenic purpura (ITP), and patients with Guillain Barré syndrome. As in current practice HIV is no longer used as indication for IVIg, we excluded studies including HIV populations.
In this review we searched for evidence on the effectiveness, efficiency and safety of IVIg in the above mentioned patient groups. The full review, including references, figures and tables will be attached in a separate document, the results and conclusions from the review are included in this report.

2.1.1 Research questions (PICO)

For Kawasaki disease, the primary outcome measure is the number of patients with coronary abnormalities. For ITP, the primary outcome measure is the number of patients with bleeding events. A secondary outcome measure is platelet counts (number of patients that reached predefined level). A platelet count (PC) lower then $20x10^9$/L is associated with a high risk of complications. We therefore extracted data concerning response rates using a PC>20 or $30x10^9$/L where possible. For immunodeficiency, the primary outcome measure for effectiveness is the number of (respiratory) infections. For efficiency and safety no specific outcome measures were defined.

We selected studies in which IVIg was compared to no treatment or a placebo (in case of immunodeficiency), or an alternative active treatment (ITP: corticosteroids or Anti-D; Kawasaki: aspirin). Studies in which different formulations of IVIg were compared or different ways of administration of immunoglobulin (for example IVIg versus subcutaneous administration) were not included in this review.

This resulted in the following research questions (PICO):

- Does treatment with IVIg decrease the rate of cardiovascular complications in patients with Kawasaki Disease as compared to alternative interventions (such as aspirin)?
- Does treatment with IVIg decrease the risk of bleeding in patients with ITP as compared to alternative interventions (such as corticosteroids)?
- Does treatment with IVIg increase response defined in increased platelet counts in patients with ITP as compared to alternative interventions (such as corticosteroids)?
- Does treatment with IVIg decrease the rate of infections in patients with immunodeficiency syndromes?
- Is treatment with IVIg safe?
- What are the costs and effects of treatment with IVIg as compared to alternative interventions in abovementioned populations?

Secondarily, we selected studies in which the effectiveness of different doses of IVIg were compared.

2.1.2 Search methods for identification of studies

We searched in Medline (OVID), EMBASE (OVID), and the Cochrane database of controlled clinical trials for relevant studies on the effectiveness of IVIg. For economic evaluations, we searched Medline (OVID), EMBASE (OVID) and the NHS Economic Evaluation Database (via Cochrane Library). Searches were performed in December 2010.

We also performed hand searching for relevant studies in references.

2.1.3 Types of studies

We searched for randomized clinical trials (RCTs). However, it was expected that no RCT might be available for some indications. Therefore, if no RCTs were found, we extended our search to non-randomized trials in which IVIg was compared to no treatment, placebo, or another intervention (two or more cohorts; before-after study).

2.1.4 Types of participants

For each population, a search strategy was developed. A detailed description of the search is provided in the separate detailed document on the systematic review. We identified two relevant and recent Cochrane reviews. One review reported on the effectiveness of IVIg in patients with Guilain Barré syndrome. The other review reported on prophylactic use of IVIg in neonates. A search revealed that no new trials were published after these Cochrane reviews. Therefore, in this systematic review, we will summarize these two Cochrane reviews.

2.1.5 Selection, data collection and analysis

Two persons independently selected potentially relevant studies, based on title and abstract. The same two persons independently read full text reports and extracted data. In the systematic review of clinical effectiveness, selection and appraisal were conducted by a methodologist and physician. In the review of cost effectiveness, selection was conducted by a methodologist and an HTA expert. Data extraction forms were used to collect relevant data.
Assessment of risk of bias, randomization, blinding of patients, physicians, and study personnel, comparability of groups at baseline; and the completeness of follow up. For cost-effectiveness, quality criteria were: a full economic evaluation (measuring both costs and effectiveness, unless there clinical equivalence in which case a cost-minimization analysis was accepted), explicit time horizon, sensitivity analysis, and discounting.
Because of the high heterogeneity in included studies, no meta-analysis was performed and hence, data were synthesized qualitatively.

2.1.6 Search and selection

The references to the selected literature can be found in the separate document of the systematic review, attached to this report.

2.1.6.1 Kawasaki Disease

The literature search for clinical effectiveness of IVIg in Kawasaki Disease yielded 43 hits. Based on title and abstract 16 potentially relevant studies were selected. Three publications were not available in the Netherlands. After reading full text reports, 7 studies were excluded (2x other research question; 3x not a RCT; 1x other intervention was evaluated, 1 comparison between different preparates of IVIg). Manual search yielded 3 extra studies.

Four studies reported on the effectiveness of IVIg as compared to alternative interventions. In 6 studies, a comparison of different doses of IVIg was made (one study reported on 2 trials, 1x IVIg versus alternative treatment, 1x different doses of IVIg).

2.1.6.2 Immune thrombocytopenic purpura (ITP)

The literature search for clinical effectiveness of IVIg in ITP yielded 59 hits. After reading title and abstract 23 potentially relevant references were selected. Of these 23 articles, 2 articles were not available in the Netherlands. Five studies were excluded after reading full text reports (4x not RCT; 1x insufficient information on methods or results to assess quality).

In 14 of the 19 included studies the effectiveness of IVIg was compared to an alternative treatment (12 children with acute ITP, 3x children with chronic ITP, 4x adults with ITP). In 5 studies different doses of IVIg were compared. The results are reported separately for 1) children with acute ITP, 2) children with chronic ITP and 3) adults with ITP.

2.1.6.3 Guillain-Barré syndrome

In 2010, a systematic review on IVIg or patients with Guillain-Barré was published by the Cochrane collaboration (Hughes 2010). For this review, RCTs published until June 2009 had been searched. Since June 2009 no new RCTs have been published.

2.1.6.4 Hypogammaglobulinemia / Immunodeficiency

For patients with primary immunodeficiency syndromes, no RCTs for IVIg treatment were found. We therefore expanded our search to include clinical trials. The expanded literature searches yielded 202 references. Based on title and abstract 34 potentially relevant studies were selected. After reading the full text reports, 26 studies were excluded (7x report on new IVIg preparations in which no comparison was made; 6x comparison between two or more preparations of IVIg; 2x double publication of same study, 2x IVIg compared to intramuscular or subcutaneous immunoglobulin, 4x (review / no original study / no RCT), 2x other research question; 1x other population, 1x insufficient information on period during with infections are measured in pretreatment period, 1x patients who crossed over were counted in both groups (doubled), 1x no relevant outcome measure.)
Of the 8 included studies, 5 studies report on the effectiveness of IVIg as compared to no treatment or a placebo (2x in primary immunodeficiency syndromes; 3x in secondary immunodeficiency syndromes). Three studies report on a comparison of different doses of IVIg.

2.2 Interviews with experts and patients, and inventory of practice guidelines

2.2.1 Kawasaki Disease

Interview with dr Esther P.A.H. Hoppenreijs, Department of General Pediatrics and Pediatric Rheumatology Clinic, Radboud University Nijmegen Medical Centre. Local guideline Kawasaki Disease by Department of Pediatric Immunology and Pediatric Cardiology, based upon the 2004 Guideline of the American Heart Association [4].

2.2.2 Immune thrombocytopenic purpura (ITP)

On the subject of ITP in adults: interview with dr. Vera M.J. Novotny, Department of Hematology, Radboud University Nijmegen Medical Centre, co-author of the “Dutch guideline for the diagnosis and management of immune thrombocytopenic purpura in adults” and member of the Working Group Non-Oncological Hematology of the Dutch Society for Hematology.
On the subject of ITP in children: interview with dr. Paul Brons, Pediatric Oncologist / Pediatric Hematologist, Department of Pediatrics, Radboud University Nijmegen Medical Centre.
As guidelines used in clinical practice: the “Nederlandse richtlijn voor de diagnose en behandeling van immuun trombocytopenische purpura bij volwassenen”, from the Nederlands Tijdschrift voor Geneeskunde, 2010, 7:59 and the “International consensus report on the investigation and management of primary immune thrombocytopenia” (Provan et al., Blood 2010, 115:168-186).

2.2.3 Guillain-Barré syndrome and other neurological indications

Interview with Prof. Dr. Baziel G.M. van Engelen, professor for neuromuscular diseases at the Department of Neurology of the Radboud University Nijmegen Medical Centre, and board member of the Dutch Neuromuscular Research Centre (Interuniversitair Steunpunt Neuromusculair Onderzoek, ISNO). Also, interview with Anja Horemans, from the Patient Organisation for Muscular Diseases in the Netherlands (Vereniging Spierziekten Nederland, VSN). National CBO guideline on Guillain Barré syndrome, 2010.

2.2.4 Hypogammaglobulinemia

This is the area of expertise of two of the authors of this report, prof.dr. Jos W.M. van der Meer and dr. Marcel van Deuren, Department of General Internal Medicine, section Infectious Diseases, Radboud University Nijmegen Medical Centre and members of the Dutch National Working group on Immunodeficiency. Also interview with Dr. Adilia Warris, Department of Pediatric Immunology, Radboud University Nijmegen Medical Centre and also member of the Dutch National Working group on Immunodeficiency. And interview with Geert-Jan van Moorsel, from the Dutch Patient Foundation for Immunodeficiencies (Stichting voor Afweerstoornissen). There are no Dutch guidelines on treatment of hypogammaglobulinemia.

2.2.5 Other indications

Fetal/neonatal alloimmune thrombopenia: Interview with Dr Dick Oepkes, Department of Gynaecology at Leiden University Medical Centre (LUMC). Other indications: literature search, CBO guidelines and interview with the above mentioned experts (sections 2.2.1 – 2.2.5).

2.2.6 Pharmacy

Interview with Dr. Remco de Jong, head of the Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre, who also supplied data on cost and expenditure on IVIg.

3. Therapeutic efficacy per indication

NB References mentioned in the sections detailing the systematic literature review can be found in the accompanying document of this systematic review.

3.1 Kawasaki Disease

3.1.1 Results of systematic literature review for efficacy in Kawasaki Disease

3.1.1.1 Comparison of IVIg with alternative treatment

See table 9.4.1. in the Systematic Review for full details of included studies. In three trials, treatment with ASA (aspirin) was compared with treatment with the combination of IVIg and aspirin. Furusho (1984) compared IVIg 400 mg/kg for 3 days plus aspirin with aspirin alone in 85 children with Kawasaki disease. In a next trial, Furusho compared a lower dose of IVIg alone (200 mg/kg, 5 days) with aspirin alone and the combination of IVIg and aspirin. Newburger (1986) compared IVIg 400 mg/kg during 4 days plus aspirin with aspirin alone in 168 children.

Furusho (1984) reported a lower percentage of patients with coronary artery lesions after 30 days in patients treated with the combination of IVIg and aspirin treatment as compared to patients treated with aspirin alone (15% and 42% respectively, Number Needed To Treat, NNT, is 4). After 60 days, the percentage of patients with coronary arterial lesion was lower in both treatment groups, but the difference between the group remained (7.5% and 31% respectively, NNT 4).
In the study of Furusho (1991), the percentage of patients with coronary arterial lesions were slightly lower in patients treated with IVIg alone (7.8%) than in patients treated with the combination of IVIg and aspirin (10.2%, IVIg versus combination NNT=42) or with aspirin alone (19,1%, IVIg versus aspirin NNT=8.8), but differences were not statistically significant.
Newburger (1986) also found a lower percentage of patients with coronary abnormalities in patients treated with the combination of aspirin and IVIg as compared to treatment with aspirin alone (4% versus 18%, NNT 7).

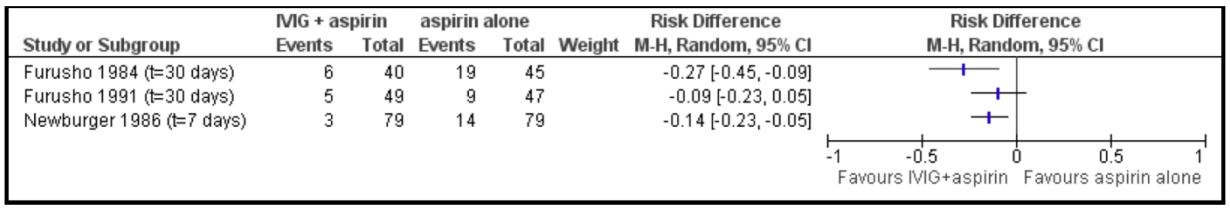

Figure 3-1. Clinical efficacy in Kawasaki Disease. Intravenous immunoglobulin (IVIg) plus aspirin compared to aspirin alone. Outcome parameter: coronary artery lesions.

Hashino reported the results of a trial on IVIg versus methylprednisolone in 17 children. After 7 days, the percentage of patients with coronary artery abnormalities was slightly lower in patients treated with IVIg (63%) than in patients treated with methylprednisolone (78%, NNT 6.7, N.S.).

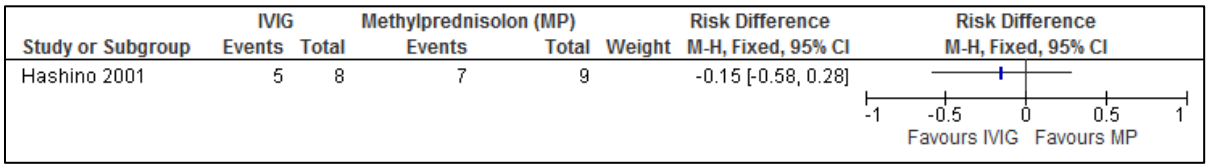

Figure 3-2. Clinical efficacy in Kawasaki Disease. Intravenous immunoglobulin (IVIg) compared to methylprednisolone (MP). Outcome parameter: coronary artery lesions.

3.1.1.2 Comparison of Dose

In six trials, treatment of children with Kawasaki with different doses of IVIg were compared (see table 9.5.1. of the Systematic Review).
Furusho (1991) compared treatment with 100, 200 or 400 mg/kg/day, for 5 days. No clear dose response relation was found. Thirty days after onset of the disease, the number of patients with coronary abnormalities was slightly lower, but not statistically significant, in patients receiving 200 mg IVIg (6%) as compared to 100mg (14%) or 400 mg (11%).
In four trials, a dose of 400 mg/kg on 4 or 5 consecutive days was compared with a dose of 1 or 2 g/kg once. In these trials, no clear dose-response relations was founds. Sato (1999) compared 2g/kg IVIg once with 400 mg/kg IVIg for 5 days in 145 children. After 7 days, 1.4% of the children treated with IVIg 2g and 9.6% of the children treated with IVIg 400 mg had an aneurysm (statistically significant difference; NNT 12). Newburger (1991) compared a single dose of 2g/kg with 400 mg/kg IVIg for 4 days in 549 children. After two weeks, the number of children with aneurysm was statistically significant lower in patients treated with 2 g/kg IVIg as compared to children receiving 400 mg (4,5% versus 9%, NNT=22). After 7 weeks, however, the number of children with aneurysms was no longer significantly different between the two groups (2g: 4%, 400mg: 7%,NNT=30 N.S.)
Barron (1990) and Liang (2004) found no differences in coronary abnormalities between IVIg 2 g/kg once or IVIg 400 mg/kg for 5 days.

3.1.1.3 Conclusions of systematic review for efficacy in Kawasaki Disease

In children with Kawasaki Disease, the proportion of children with coronary aneurysms was lower after a short term treatment with IVIg (4 or 5 days) and aspirin as compared to treatment with aspirin alone. A single high dose of IVIg (1 or 2 g/kg) was more effective than a lower dose (400 mg/kg) on 4 or 5 consecutive days in avoiding the occurrence or persistence of coronary aneurysms.

3.1.2 Therapeutic regimen in clinical practice in Kawasaki Disease

Intravenous immunoglobulin is first-line treatment in Kawasaki Disease in clinical practice. The child with Kawasaki Disease is admitted to a paediatric department, and IVIg 2 g/kg is given in a single dose in 16-24 hours. This IVIg regimen is combined with aspirin. This is usually seen to be very effective in clinical practice, with disappearance of fever within 1 day. An alternative regimen suggested only in case of concomitant cardiac failure is to divide the high dose IVIg (2 g/kg) over 2 or 5 days, to decrease the fluid burden.
If fever persists or relapses more than 36 hours after the end of IVIg infusion - considered as sign of persisting vasculitis - another single dose of 2 g/kg IVIg is administered.
Treatment of Kawasaki Disease is done by paediatricians in university medical centres as well as in peripheral smaller hospitals, although usually in the latter case there is at least telephone consultation with an academic paediatrician.

3.2 Immune thrombocytopenic purpura (ITP)

ITP can present itself in a very different way in children and in adults, warranting different treatment strategies. There is also a difference in the acute and chronic forms of ITP, including treatment. Therefore, these different forms of ITP will be discussed separately.

3.2.1 Systematic review of literature for ITP

3.2.1.1 Children with acute ITP

No trials were found that reported the number of bleedings as an outcome measure.
Ten RCTs on IVIg in acute ITP in children were included (Table 9.4.2. of the Systematic Review). In eight RCTs, treatment with IVIg was compared to treatment with corticosteroids; In three RCTs IVIg was (also) compared to treatment with anti-D.

3.2.1.1.1 IVIg versus corticosteroids

In three studies, short term response (PC>20 x 10^9/L within 2 or 3 days) was slightly better in patients treated with IVIg than in patients treated with high dose methylprednisolone (Erduran 2003, Rosthoj 1996, Ancona 2002). Ancona compared IVIg 1 g/kg (2 doses) with methylprednisolone 30 mg/kg (3 doses). Erduran compared IVIg 1 g/kg for 2 days with high dose methylprednisolone (3 days 30 mg/kg/day + 4 days 20 mg/kg/day). Rosthoj (1996) compared IVIg 1 g/kg for 2 days with high dose methylprednisolone (30 mg/kg for 2 days). For full details, see table 9.4.2. of the Systematic Review. NNT ranged between 3-8. However, after a few days, the differences between the two interventions diminished (Erduran 2003). In the trial of Erduran (2003) the time until response was statistically significant shorter in patients treated with IVIg as compared to patients treated with methylprednisolone.

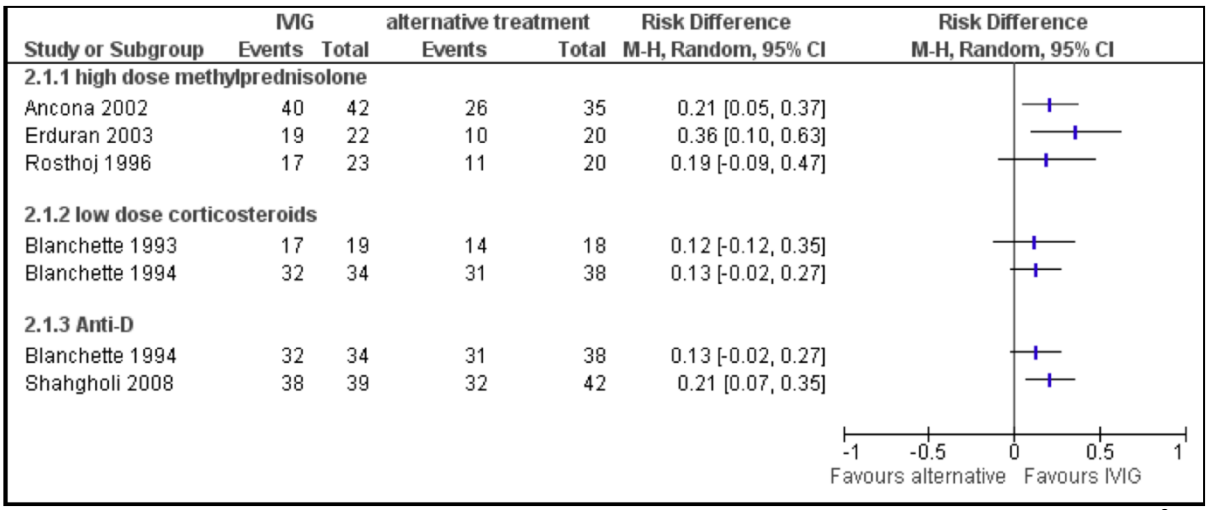

Figure 3-3. Children with acute ITP. Outcome parameter: short term response in platelet count (>20x10^9/L in 2 or 3 days)

Two trials reported the number of patients with complete response (PC>100 or 150 x 10^9/L) after 1-12 months of follow up (Albayrak 1994, Ozsoylu 1993). Albayrak reported slightly higher response for IVIg, not statistically significant (NNT 20). Özsoylu reported higher response for patients treated with methylprednislone (NNT 6.7, N.S.).

In three RCTs, IVIg was compared to long-term treatment with a low dose of corticosteroids. Blanchette (1993) compared IVIg (1g/kg, 2 days) with low dose prednisolone (initial dose 4 mg/kg/day; total 17 days treatment) or no treatment in 53 patients. Blanchette (1994) compared IVIg 1 g/kg for 2 days, IVIg 0.8 g/kg once, low dose prednisolone (initial dose 4 mg/kg; treatment 21

days) and Anti-D (25 µg/kg for 2 days). Imbach compared treatment with IVIg 0.4 g/kg on 5 days with oral corticosteroid (60 mg/m^2 for 21 days).

In the trial of Blanchette (1994), the number of days with PC< 20x10^9/L was lower in patients treated with IVIg 0.8 g/kg as compared to patients treated with prednisolone. In patients treated with IVIg 1.0 g/kg, the results were comparable to patients treated with prednisolone. Blanchette (1993) reported no difference in median number of days with an low platelet count (PC<20 x10^9/L) between patients treated with IVIg and patients treated with corticosteroids.

Imbach (1985) only reported the number of patients with complete response (PC>100 x 10^9/L) after 12 months of follow up. A slightly higher response rate was found in patients treated with IVIg as compared to patients treated with corticosteroids, but this difference not statistically significant (NNT 17).

3.2.1.1.2 IVIg vs anti-Rhesus D immunoglobulin treatment (anti-D treatment)

In the three RCTs, the percentage of patients with a short term response was higher when treated with IVIg as compared to anti-D (NNT between 3.3 and 12.5). Shahgholi (2008) compared IVIg 1 g/kg for 2 days with a single dose of Anti-D (75 µg/kg) in 81 children. Tarantino compared a single dose of IVIg 0.8 g/kg with a single dose of Anti-D 75 µg/kg or Anti-D 50 µg/kg. Blanchette (1994) compared IVIg 1 g/kg for 2 days, IVIg 0.8 g/kg once, low dose prednisolone (initial dose 4 mg/kg; treatment 21 days) and Anti-D (25 µg/kg for 2 days).

In the trial of Shahgholi (2008), the rate of patients with short-term response was significantly higher in patients receiving IVIg then in patients receiving anti-D (NNT 4.8). In the RCT of Blanchette (1994) response rate after 72 hour was 94% in patients receiving IVIg 1 g/kg, 97% in patients receiving IVIg 0.8 g/kg and 82% in patients receiving Anti-D. In the trial of Tarantino (2006) IVIg was better than Anti-D 50µg once (NNT ~ 3.3) and slightly better than Anti-D used in a dose of 75µg once (NNT ~13). After 7 days, the percentage responders was comparable for IVIg and Anti-D 50µg. The results were only graphically reported.

3.2.1.1.3 Dose response

In two RCTs, different doses of IVIg were compared (table 9.5.2. of the Systematic Review). Benesch (2003) compared IVIg 1g/kg/day for two days with 0.3 g/kg/day for two days in 34 children with acute ITP. The number of patients who responded (PC<20x10^9/L) 72 hour after the first infusion was slightly lower in patients receiving the low dose (76% versus 88%, NNT 8, N.S.).
Warrier (1997) reported the data of two small trials. In the first trial IVIg 400 mg/kg for 2 days was compared with IVIg 1 g/kg for 2 days in children between 5 and 12 years of age. In the second trial, a dose of 250 mg/kg for 2 days was compared with a dose of 500 mg/kg for 2 days in children younger than 5 years of age. All doses were equally effective. Within 10 days, all children treated with 250 mg/kg, 400 mg/kg or 1g/kg responded (PC>30x10^9/l). Of the patients receiving 500 mg 5 out of 6 children responded (83%).

3.2.1.1.4 Conclusion on effectiveness in children with acute ITP

No trials were found in which the number of bleeding events was reported as outcome measure.
In children with acute ITP, the short term response (PC>20 x 10^9/L within 2 or 3 days) might be better for patients treated with IVIg (1 g/kg for 2 days) as compared to patients treated with high dose methylprednisolone (30 mg/kg for 2-3 days), low dose corticosteroids or anti-D. However, after a few days, the differences between the interventions diminished.

3.2.1.2 Children with chronic ITP

In three RCTs, the effectiveness of IVIg in children with chronic ITP was investigated, for full details see table 9.4.3. of the Systematic Review. In one study (El Alfy, 2006b) the data of two RCTs on the effect of interventions on the number of severe bleedings were reported shortly. The number of

severe bleedings ranged between 8.6 (IVIg 0.8 g/kg once) and 10.1 (oral methylprednisolone 4mg/kg 4 days) However, the information on methods and results was minimal.

El Alfy (2006 a), compared IVIg (250 mg/kg ,2 days) with anti D (50 µg/kg every 3-4 weeks) in 34 children. Response was defined as a platelet count above $50x10^9$/L or doubling the baseline platelet count. The number of children with response seemed slightly better after 3 days in patients treated with IVIg as compared to children treated with anti-D (37% versus 33%, NNT8 N.S). After 28 days the number of patients with response was similar in both treatment groups (IVIg: 38%, Anti-D 39%, NNT 72, N.S).

Hedlund (2003) compared IVIg (800 mg/kg once + retreatment if PC<$30x10^9$/L) and dexamethasone. After 3 days, the number of patients who partial responded (PC>$30x10^9$/L) seemed higher in patients treated with IVIg then patients treated with dexamethasone (87% versus 67%, NNT=5, N.S.). At long term (at least 3 months without therapy) the percentage of complete response (PC>$150x10^9$/L) was similar for IVIg and dexamethasone (12,5% and 13% respectively, NNT 120).

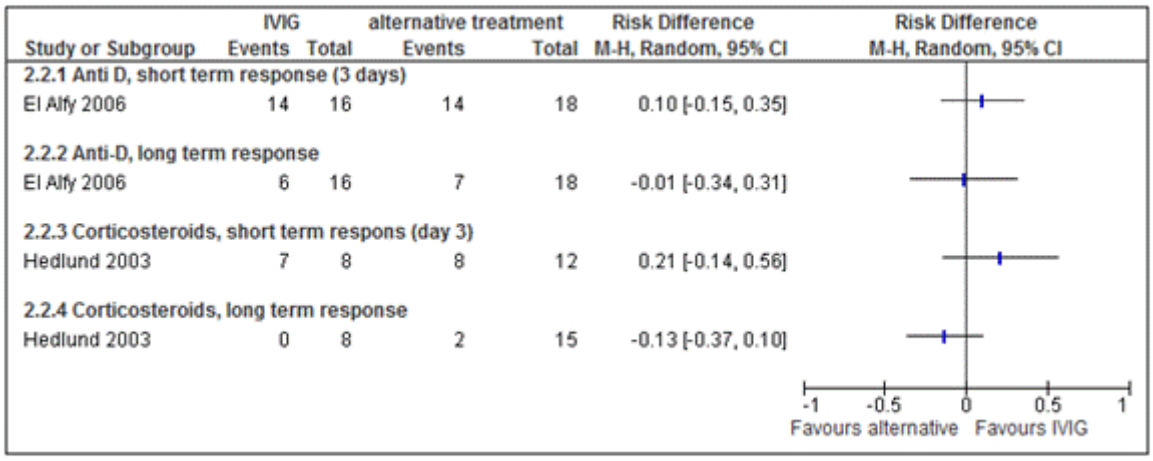

Figure 3-4. Children with chronic ITP. Outcome parameter: platelet count >20-$30x10^9$/L.

In conclusion, in children with chronic ITP, the number of patients who responded after treatment with IVIg (at long term) was similar to treatment with anti-D or dexamethason.

3.2.1.3 Adults with ITP

Two trials were identified in which IVIg was used for the treatment of adults with ITP. In these trials, different comparators and levels of platelet counts were used to define clinical response. For full details, see table 9.4.4. of the Systematic Review.

Godeau (2002) compared IVIg (0,7 g/kg, 3 days) with methylprednisolone in 122 patients. The short term response (PC>$20x10^9$/L at day 5) was slightly higher in patients treated with IVIg compared to patients treated with methylprednisolone, but not statistically significant (89% versus 80%, NNT 11). In neither treatment groups, patients died or had severe life threatening hemorrhagic events.

Jacobs (1994) compared treatment with IVIg (400 mg/kg, 5 days) with oral prednisolone or a combination of IVIg and oral prednisolone in 43 adults with symptomatic ITP. After 2 years, the percentage of patients with complete response (PC>$100x10^9$/L) was 29% in patients treated with prednisolone alone, 23% in patients treated with IVIg and 7% in patients treated with the combination (IVIg versus prednisolone NNT=16, N.S.).

In two RCTs, different doses of IVIg were compared (table 9.5.3. of the Systematic Review). In 1993, Godeau compared treatment with 1 g/kg IVIg for 2 days with 2 g/kg IVIg for 2 days. Reinfusions were given as long as platelet counts were below $50x10^9$/l. The number of patients with response (PC>$150x10^9$/l) 90 days after last booster seemed higher in patients receiving 2g/kg than in patients

receiving 1 g/kg (44% versus 11%, NNT 3, N.S.) The follow up period varied between patients and ranged from 5 to 75 months.

In 1999, Godeau compared treatment of 1 g/kg IVIg with 0.5 g/kg as initial treatment. In both groups patients received a reinfusion if they did respond to the first infusion. After 8 days, number of patients who responded (PC>80x10^9/l) was slightly lower in patients who received 1 g/kg initially. (78% versus 88%, NNT=10, N.S.)

In conclusion, in adults with ITP two RCTs showed no difference in platelet counts at long term (1-2 year) between 3-5 days of IVIg treatment with either high-dose methylprednisolon, low dose oral prednisone, or anti –D.

3.2.2 Therapeutic regimen in clinical practice in ITP

3.2.2.1 Children with ITP

In children with acute ITP, the current first-line approach is watchful waiting. Treatment is not determined by the platelet count but by the occurrence (or threat) of severe bleeding. In case of severe bleeding, first-line treatment is IVIg. Dose recommended is 0.8-1 g/kg for 1 day. In case of life-threatening situations, a combination of IVIg and steroids is recommended.
At present, an active trial is recruiting children with acute ITP to investigate whether earlier treatment with IVIg will reduce the risk of developing chronic ITP (see section 7.2).
In chronic ITP, IVIg is only used short-term in cases of severe bleeding. There is no national guideline on ITP in children.

3.2.2.2 Adults with ITP

In adults with ITP, treatment with IVIg is reserved for special circumstances only; first-line treatment when treatment is necessary consists of steroids. In clinical practice, it has been noticed that the effect of one IVIg treatment course lasts 2-4 weeks, and therefore is no real option for curative or chronic treatment. The Dutch guideline [5] recommends that IVIg may be considered in the following circumstances:

- Severe bleeding (at very low platelet count): steroids are given in combination with IVIg
- Bleeding risk in pregnant patients with low platelet count.
- When a surgical procedure is necessary in a patient with low platelet count.
- To raise platelet count sufficiently to be able to perform a splenectomy in case of failure of steroids.
- Acute ITP following a recent or active infection with EBV, CMV, Rubella, VZV or HIV: in this case IVIg as first line treatment can induce complete remission

Dosage used is IVIg 1 g/kg per day for days (so 2 g/kg total). For this indication, IVIg is usually given during a hospital admission.

3.3 Guillain-Barré syndrome (GBS)

3.3.1 Systematic review of literature

In the Cochrane review [6], randomized and quasi randomized trials published until June 2009 were included. The primary outcome was improvement in disability grade. Five trials were included in which IVIg treatment was compared to plasma exchange, which was considered to be standard-of-care. Primary outcome was the disability grade after four weeks (GBS scale, scores ranges from 0-6, 0=healthy). The meta analysis included data from 273 patients treated with IVIg and 263 patients treated with plasma exchange. The difference in change in a 7-grade disability scale after four weeks was not statistically significant between IVIg and plasma exchange (mean difference -0.02, 95%CI[-0.25;0.20]).
In conclusion, treatment with IVIg and plasma exchange were equally effective as measured with the change on a disability scale.

3.3.2 Therapeutic regimen in clinical practice in GBS

In clinical practice, the recent CBO guideline on GBS is followed. This states that IVIg is the treatment of choice for GBS, unless the patient has a known allergy for plasma products or a known IgA deficiency with circulating antibodies against IgA. It is preferred above plasmapheresis, despite equal effectiveness, because of more severe potential complications of plasmapheresis and more specialized care needed.
The IVIg treatment should be given as early as possible, and at least within the first two weeks of onset of muscle weakness. The recommended regimen is 400 mg/kg per day for 5 days (total 2 g/kg). The CBO guideline offers recommendations on which patients are most likely to benefit from IVIg treatment, and which patients do not need this standard treatment. If a GBS patient shows a relapse with progression of muscle weakness after initial improvement or stabilisation after IVIg treatment (this is estimated to occur in approximately 10% of patients), the CBO guideline recommends a new IVIg treatment of 400 mg/kg per day for 5 days.
Treatment of Guillain-Barré syndrome is given in academic medical centres as well as regional hospitals. Treatment in regional hospitals has increased since IVIg treatment has replaced plasmapheresis, because the latter treatment was often only available in academic medical centres.

3.4 Hypogammaglobulinemia

3.4.1 Systematic review of literature for hypogammaglobulinemia

3.4.1.1 Primary immunodeficiency

Two before-after studies were found in which the frequency of infections during a period on IVIg treatment was compared to the period before starting IVIg (full details: see table 9.4.5 in Systematic Review).

Abdou (2009) investigated the effectiveness of IVIg (400 mg/kg each month) in 10 patients with immunoglobulin subclass deficiency. The number of infections during 12 months of treatment were compared to the number of infections during a 12-month period prior to start of IVIg. Gracia (2004) reported on IVIg (200-300 mg/kg each 3 weeks) in 24 patients with CVID (newly diagnosed). The number of infections during a 2-year period of treatment were compared to 2-year prior to the start of IVIg.

Both studies reported a decrease in number of infections per year. Abdou reported a decrease in the mean number infection per year from 7.9 to 3.1 ($p<0.01$). In the study by Gracia, the rate of mild infections decreased from 4.9 infections per year to 2.2 infections per year ($p=0.01$). The annual rate of serious infections decreased from 0.48 to 0.047. Pulmonary function, measured by FEV1 % predicted, did not differ between the period on IVIg treatment and before starting IVIg.

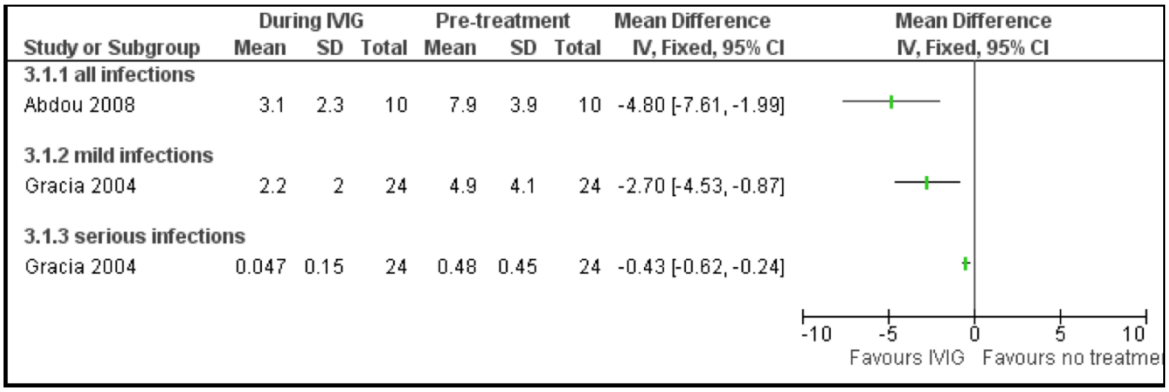

Figure 3-5. Studies in primary immunodeficiency (CVID and subclass deficiency). Outcome parameter: annual rate of infections.

In three cross-over trials, different doses for IVIg were compared in primary immunodeficiency (table 9.5.4. of the Systematic Review). In a Dutch collaborative study, Eijkhout (2001) compared standard IVIg dose (300 or 400 mg/kg) with a high dose of IVIg (600 or 800 mg/kg) in 43 children and adults with primary hypogammaglobulinemia. The mean number of immunodeficiency related infections was lower in patients treated with high dose IVIg as compared to patients treated with a standard dose (on average 2.5 and 3.5 infections per patient respectively, $p=0.004$). Roifman compared 200 mg/kg IVIg with 600 mg/kg in 12 patients with antibody deficiency and chronic pulmonary disease. Pruzanski compared 200 mg/kg, 400 mg/kg and 600 mg/kg in 21 adults with CVID. Pruzanski (1996) and Roifman (1987) found comparable outcomes in the number of infections per patient between patients treated with a high or a low dose of IVIg.

In conclusion, in patients with primary immunodeficiency, treatment with IVIg may decrease the annual number of infections per patient with approximately 50 percent as compared to no treatment. The mean number of immunodeficiency related infections appears lower in patients treated with high dose IVIg as compared to patients treated with a standard dose.

3.4.1.2 Secondary immunodeficiency

Three RCTs reported on the effectiveness of IVIg in secondary immunodeficiency (for full details, see table 9.4.6. in the Systematic Review). Two trials reported on the use of IVIg in patients with chronic lymphocytic leukemia. In the third trial, IVIg was used in low weight neonates.

Two RCTs reported on IVIg versus placebo in patients with chronic lymphocytic leukemia (CLL) (Anonymous 1988, Boughton 1995). In the trial of Cooperative Group for the Study of Immunoglobulin in CLL (Cooperative Group CLL 1998), 81 patients with CLL and at risk for infections were treated with IVIg (400 mg/kg every 3 weeks) or a placebo for 1 year. In the study of Boughton (1995) 42 patients with CLL started with IVIg (18 g every 3 weeks) or a placebo.

In the study of the Cooperative Group, the number of bacterial infections per patient was lower in patient treated with IVIg as compared to patients receiving a placebo (0.56 and 1.05 infections per patient respectively, p=0.01). Bougthon reported a statistically significant lower risk of three or more serious infections in patients treated with IVIg as compared to placebo (21% and 56% respectively, NNT 2.9).
In conclusion, in patients with CLL, treatment with IVIg decreased the annual rate of infections per patient as compared to treatment with a placebo.

	IVIG			placebo			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
4.1.1 Bacterial infections							
CLL group 1988	23	0	41	42	0	40	Not estimable
4.1.2 Serious bacterial infections							
CLL group 1988	18	0	41	31	0	40	Not estimable

Figure 3-6 IVIg in CLL patients. Outcome parameter: annual rate of infections.

We identified one RCT with neonates with secondary immunodeficiency (Baker 1992) . Most trials, however, evaluated the prophylactic use of IVIg in neonates. In 2010, a systematic review on this subject by was published Cochrane collaboration (Ohlsson 2010). As the study of Baker was included in the Cochrane review, we only describe this review. In the Cochrane review, sixteen RCTs in which IVIg was compared to either a placebo or no treatment, were included (update of earlier version, last search until December 2009). Outcome measures included the number of patients with sepsis, the number of patients with any serious infection, and mortality. When the results of these trials were combined in a meta-analysis, a reduction in the number of patients with a serious infections was found for IVIg (absolute risk difference = 0.04 (NNT=24)). There were no differences in mortality.
In conclusion, the prophylactic use of IVIg in preterm and/or low birth neonates reduces the proportion of patients with a serious infection as compared no treatment or a placebo.

3.4.2 Therapeutic regimen in clinical practice for hypogammaglobulinemia

3.4.2.1 Primary immunodeficiency

Although there is a Dutch National Working group on Primary Immunodeficiency (Werkgroep Immuundeficiëntie, WID), which is striving for consensus regarding diagnosis and treatment, there are no Dutch guidelines on IVIg supplementation in primary immunodeficiency. Treatment with IVIg is lifelong. Treatment regimen is chosen on an individual basis. A usual starting dose is 300-400 mg/kg once every 28 days. Aim is to reduce the number of infections the patient experiences.FDA and EMA guidelines mention in their guidance documents for the pharmaceutical industry for the

development of immunoglobulin preparations an aim of less than 0.5 acute bacterial infections per year.
A dose adjustment can be made in case of residual infections either by increasing the dose or by increasing the frequency of infusions. It was generally recommended to aim for a trough IgG concentration (the concentration just before the next infusion) of at least 5 g/L. Recently, it has been shown that a higher trough level, up to 10 g/L, can still further reduce the number of infections: incidence of pneumonia was shown to be 0.113 (CI 0.042-0.3) at a trough level of 5 g/L and 0.023 (CI 0.008-0.0068) at trough level 10 g/L [15]. More recent recommendations therefore increase the optimal trough level to 7 g/L [16].
Immunoglobulins are most often administered intravenously, although in young children and in patients with problematic intravenous access, as well as in those experiencing serious side effects of IVIg, the subcutaneous route may be chosen. The first administration of IVIg these patients should be given at the day-care unit of a hospital. Thereafter home-based treatment with help of specialized care can be instituted for most patients (section 5.3). Most patients prefer home-based treatment.
In patients with more subtle decrease of IgG, for example IgG subclass deficiency or a specific anti-polysaccharide defect, it has not been proven that IVIg is superior to prophylactic use of antibiotics; a study is currently recruiting patients to test this (section 7.4).

3.4.2.2 Secondary immunodeficiency

IVIg is not part of the standard care in patients with CLL. It is only considered in CLL patients who have documented hypogammaglobulinemia and proven increased susceptibility to respiratory infections. The same is true in daily practice for IVIg in premature neonates: it is not a routine part of treatment, but will be given in fragile patients with frequent infections and hypogammaglobulinemia.

3.5 Other indications / off label use

3.5.1 Multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and other neuromuscular disease

A 2009 Cochrane review on IVIg for ***CIDP*** included seven RCTs, including 287 participants. The authors concluded that IVIg improves disability for at least 2-6 weeks compared with placebo, with a NNT of 3. During this period it has similar efficacy to plasma exchange and oral prednisolone. In one large trial, benefit of IVIg persisted for 24 and possibly 48 weeks [7].
A Cochrane review on IVIg for ***MMN*** from that same year included 4 RCTs, with a total of 34 patients – there was therefore limited evidence, but these studies showed that IVIg has a beneficial effect on strength. There was a non-significant trend towards improvement in disability [7].

In daily practice, many patients with CIDP or MMN are on maintenance treatment with IVIg. There are no national guidelines. Cats et al. [8] found that 67 patients with MMN (76% of total group) were on maintenance treatment, on a median dose, converted to grams per week, of an increasing dose of 12 to 17 g/week. A questionnaire sent out by the patient organization VSN among patients with CIDP or MMN on IVIg maintenance treatment (answered by >100 patients), revealed that almost half of these patients were on a frequency of infusion once every 3-4 weeks; about 20% of patients received IVIg infusion every 1-2 weeks (personal communication). The large majority of patients prefer home-based treatment with IVIg.

3.5.2 Dermatomyositis / polymyositis

The CBO guideline (2005) on these disorders recommends prednisone as first line treatment, but it lists IVIg as alternative treatment in case of failure or progression of disease. Recommended dose is 400 mg/kg per day for 5 days (so 2 g/kg total). This is based on a small number of published studies with small numbers of patients (see CBO guideline dermatomyositis, polymyositis and sporadic 'inclusion body'-myositis, 2005).

3.5.3 Foetal and neonatal alloimmune thrombocytopenia (FNAIT)

A woman at risk for a pregnancy with FNAIT, which is usually only known because of a previous pregnancy with this complication, is treated for a 10-week period between week 28 and week 38 of pregnancy with 1 g/kg IVIg once weekly. Recently this dosage has been lowered to 0.5 g/kg once weekly, because of the results of an international multicenter trial (http://www.medscinet.com/noich/default.aspx).
Leiden University Medical Centre is the national referral centre for this disease. About 150 cases have been treated so far, and these pregnancies have shown only 20% incidence of thrombocytopenia in the children and no case of haemorrhaging.
Like in primary immunodeficiency and neuromuscular disease, the first dose of IVIg is given at the daycare unit of the hospital, thereafter the IVIg infusion is given at home with specialized care.

3.5.4 Other indications

For the other indications, as listed under section 1.5.5., there is only limited evidence on therapeutic efficacy, and no national guideline.

4. Safety

We collected the data on adverse events from the studies included in the systematic review. Details are given in section 9.6. of the Systematic Review. Overall, adverse events occur frequently in patients treated with IVIg (in 3 to 87% of patients), but the events are rather mild, including headache, fever, vomiting. In the approximately 1000 patients included in all these trials, suspected aseptic meningitis occurred two times. Once a deep venous thrombosis complicated by pulmonary embolism was reported.

A recent paper by Donofrio et al. reported on the safety and tolerability of IVIg in a large RCT, compared with placebo, which included 1096 infusions with IVIg [17]. They reported as main adverse events headache (4,0 per 100 infusions) and fever (2,4 per 100 infusions). Five drug-related serious adverse events (pulmonary embolism, fever, vomiting and headache) occurred in 3 patients; four of these events occurred after a first infusion.

As stated in a previous section, Octagam®, an IVIg preparation by Octapharma GmbH, was recalled from the European market in September 2010 on the advice of EMA, because of an unexpected increase in reports of thromboembolic reactions, including stroke, myocardial infarction and pulmonary embolism in patients receiving the medicine. This increase was thought to be related to problems with the medicine's manufacturing process (www.ema.europa.eu).

Because IVIg is purified from human donors there is a theoretical risk for transmission of infectious diseases. This risk appears to be very small with current vigilance and purification techniques.

5. Pharmacoeconomic considerations

5.1 Literature review for cost-effectiveness

See table 9.4.7. and 9.5.5. in the Systematic Review for details of the studies included in this pharmacoeconomic evaluation.

5.1.1 Kawasaki Disease

Sato (1999) performed also an economic evaluation alongside the clinical efficacy trial. The mean cost per treatment were lower in patients treated with IVIg 2 g/kg once as compared to IVIg 400 mg/kg for 5 days (difference $520). Because the higher effectiveness and lower costs, treatment with IVIg 2 g/kg once is dominant.

The search for economic evaluations yielded another economic evaluation. Klassen (1993) compared the costs and effectiveness (coronary artery dilation) of aspirin, low dose IVIg (400 mg/kg, 4 days), and high dose IVIg (2g/kg once) from a societal perspective. The time horizon was seven weeks. High dose IVIg was dominant, resulting in the lowest costs (estimated mean costs: $3,982 for high dose IVIg, $ 5,164 for low dose IVIg and $7,216 for aspirin) and highest effectiveness (% with coronary artery dilation 4% in high dose IVIg, 6% in low dose IVIg and 18% in aspirin). Sensitivity analysis showed that the results of IVIg versus aspirin were not sensitive to changes in parameters used. The results of high versus low dose IVIg were sensitive to the duration of hospitalization.

In conclusion, in economic evaluation treatment with high dose IVIg (2g/kg) once was cheaper and more effective (dominant) than treatment with a low dose IVIg (400 mg/kg) on 4 consecutive days.

5.1.2 Immune thrombocytopenic purpura (ITP)

5.1.2.1 Children with acute ITP

The search for economic evaluations yielded two studies of IVIg in children with acute ITP. In both studies, treatment with IVIg (0.8 g/kg single dose) was compared with anti-D treatment (75µg/kg, once), low dose prednisone (4 mg/kg, for 4 days), and high dose methylprednisolone (30 mg/kg, for 3 days).

O'Brien (2007) reported on short term results using a societal perspective. Anti-D resulted in 0.46 less utilities lost (0.46 QALD ~ 0.0004 QALYs) as compared to IVIg, and the average costs per patient were $457 less. Authors concluded that treatment with IVIg was dominated by anti-D . However, the differences in utilities between the four treatments were very small.

Blackhouse (2008) reported the results from a health care perspective, using a lifetime time horizon. The differences in costs and QALYs were small. Treated with IVIg resulted in 0.0043 QALYs gained and $ 236 extra costs as compared to prednisone, resulting in $56,000/QALY. In the sensitivity analysis, the dose IVIg, percentage of intracranial haemorrhage and weight of the patient (which is related to a child's age) had high impact on the results.

In conclusion, in terms of QALYs, treatment of acute ITP in children with IVIg, low dose prednisone, anti-D, or high dose methylprednisolone was equally effective. At short term, costs for low dose prednisone were lower than the other three treatment. Using a lifetime perspective, the differences in costs between the interventions are small.

5.1.2.2 Children with chronic ITP

For children with chronic ITP, one report of an economic evaluation was found (Hollenberg 1988). Hollenberg compared two strategies for the treatment of children with chronic ITP (at least 6 months): initially IVIg (2g/kg once + 1g/kg maintenance) followed by splenectomy if patients did not response or initially splenectomy followed by IVIg if patients did not respond. The time horizon was 10 years, and costs from a health care perspective were included. The mean costs per patient were higher in the strategy in which initially IVIg treatment was given then the strategy in which was

started with splenectomy ($ 21,000 and 17,000 respectively). The percentage of patients that were alive after 10 years was similar for both strategies (IVIg: 98.6%, splenectomy 97.9%). The incremental cost-effectiveness ratio is $ 540,000 per additional life saved. The results were strongly affected by variation in the following parameters: percentage of children curable on IVIg, Costs IVIg (dominance IVIg when low price / dose), and the age child (related to weight of the child and thus the dose of IVIg).

5.1.2.3 Adults with ITP

Xie (2000) reported on an economic evaluation in which IVIg (1g/kg, 2 days) was compared to oral prednisone (1mg/kg for a month) for adults with chronic ITP. A health care perspective and a lifetime horizon were used. The mean total costs were Canadian $ 18,000 for IVIg treatment and $ 10,000 for prednisone. The QALYs were 9.884 for IVIg and 9.877 for prednisone, resulting in an incremental ratio of $1,15million/QALY. The results were sensitive to changes in time horizon (between IVIg dominance or very high ICER). Probabilistic sensitivity showed that IVIg has a probability of 20% of being cost effective given a willingness to pay for a QALY Canadian $ 100,000.
In conclusion, considering a life time horizon, treatment of chronic ITP in adults with IVIg is associated with equal QALYs and higher costs as compared to treatment with low dose prednisone.

5.1.3 Guillain-Barré syndrome (GBS)

Our search for economic evaluations yielded two evaluations in which IVIg (0.4 g/kg for 5 days) was compared with plasma exchange (4-8 times). Both assumed similar effectiveness and performed a cost minimization analysis.

Nagpal (1999) reported on a decision analysis from health care perspective, using a time horizon of 48 weeks. They used a decision analytical model filled with data from literature. The mean costs per patients when treated with IVIg were $ 3,961 higher as compared to treatment by plasma exchange. In the sensitivity analysis, the results were sensitive to the cost of IVIg. At a price just below the cheapest available IVIg in the USA ($43,66/g), the costs of treatment of IVIg and plasma exchange would be equivalent.

Tsai (2007) performed a economic evaluation from a health care perspective, time horizon of 2-10 weeks. Costs were measured using data from the medical charts of 17 patients (7 patients received IVIg, 10 patients received plasma exchange). The results showed that plasma exchange was more expensive than treatment with IVIg (difference in mean cost per patient 156,533 New Taiwan $, which corresponds to 4,884 US$ (statistically significant)).

The results of these two studies seemed conflicting. A possible explanation is that Tsai included costs of complications and Nagpal did not. Three of ten patients (30%) treated with plasma exchange experienced complications, and one of the 7 patients (16%) treated with IVIg. Especially, in the patients treated with plasma exchange, the mean total costs were higher in patients who experienced complications as compared to patients without complication. Furthermore, in the study of Tsai the mean costs for drugs were lower than the costs for IVIg as used in the study of Nagpal.
In conclusion, treatment of patients with Guillain-Barré syndrome with IVIg seemed to cost less than treatment with plasma exchange.

5.1.4 Hypogammaglobulinemia / immunodeficiency

No economic evaluations were found in which IVIg was compared to an alternative intervention in patients with primary immunodeficiency.
In an economic evaluation, Weeks (1991) compared prophylactic treatment with IVIg with no IVIg in patients with CLL. This decision analytic study used data from the Cooperative Group trial (Cooperative Group CLL 1988). From a societal perspective and life time horizon, the marginal costs for IVIg were $14,000 and the marginal effects 0.0023 QALYs, resulting in a incremental cost-effectiveness ratio of $6 million per QALY. Sensitivity analyses revealed that the results were sensible to assumptions on survival and quality of life. Results were minimally altered by variations in costs.

Thus, in conclusion, considering a life time horizon, treatment with IVIg did not result in a difference in QALYs in patients with CLL. Therefore, the additional costs per QALY for IVIg as compared to no IVIg were high (unfavourable).

5.2 Translation to Dutch situation

There are no Dutch pharmacoeconomic evaluations for IVIg available. This, in combination with the absence of guidelines for most of the indications, makes it hard to directly translate the results to the Dutch situation.

5.3 In hospital versus at home

There are no good pharmacoeconomic evaluations comparing chronic IVIg treatment at home versus administration at the day-care unit of a hospital, in cost and/or in QALYs, which can be applied for the Dutch situation. The majority of patients have a great preference for treatment at home for diverse reasons: the extra time for travel to and from hospital, the fatigue of this travel (especially for patients with neuromuscular disease), the fear for infections when treated in a hospital-setting (for patients with an immunodeficiency), the comfort at home, the flexibility of time which enables patients to continue with school or work without too much interruption.
At present, there is a significant difference in the way IVIg treatment at home or in hospital is financed. Treatment at hospital is financed through the hospital pharmacy, at home through the patient's local pharmacy. One of the Dutch health insurance companies is questioning the current practice of home-based care for IVIg treatment, and has taken a stand that it will no longer finance at-home-treatment through the local pharmacy (and more companies seem set to follow this lead). A number of patients have already felt the consequences of this. Though most patients who were already on home-based treatment have been enabled to stay on it, a growing number of health insurance companies no longer automatically grant this option for new patients.
This issue is part of the larger issue which concerns all medication on the "Beleidsregel Dure Geneesmiddelen". The Ministry of Health, Welfare and Sport is planning to institute new guidelines on financing of expensive pharmaceuticals. This is likely to have huge consequences for the chronic treatment with IVIg in daily practice. A new solution is needed to make sure patients do not suffer the consequences.

6. Cost prognosis per indication and in general

6.1 "Apotheek inkoopprijs" (AIP)

The "apotheek inkoopprijs" (AIP) for diverse preparations of immunoglobulins is given in Figure 6-1. Gammagard and Kiovig are fabricated by Baxter Pharmaceuticals, Nanogam by Sanquin. The 'Gammagard' preparations come in powder form and need to be reconstituted.
The average AIP for immunoglobulins is €65 per gram IVIg.

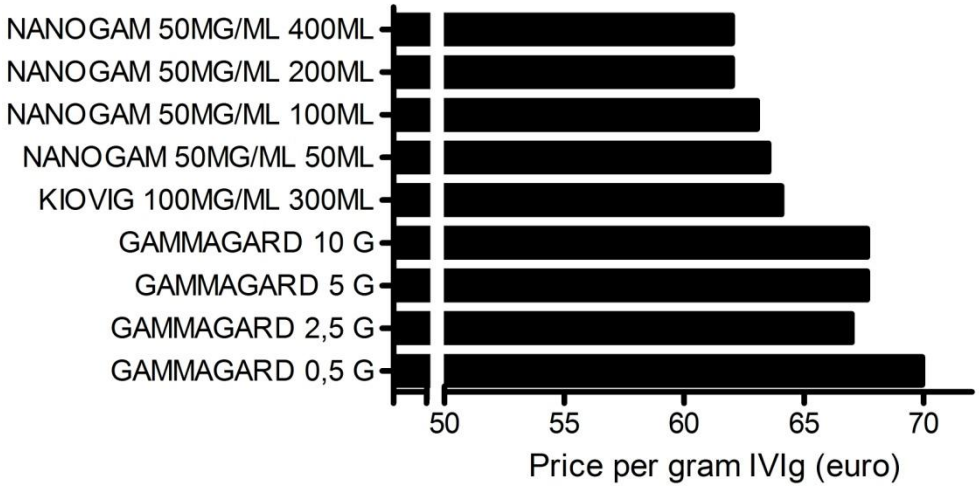

Figure 6-1. "Apotheek inkoopprijs" per gram for diverse preparations of immunoglobulins.

The numbers used in the following sections are estimates based on literature. Exact numbers per indication are missing.

6.2 Kawasaki Disease

6.2.1 Patient population and number of patients

In Western countries, the annual incidence of Kawasaki Disease is estimated at 8-18 children younger than 5 years per 100.000. It occurs primarily in children between the age of 6 months and 5 years.; 76% of patients are <6 years old, and boys outnumber girls by approximately 1.6:1. [4]. The Central Bureau of Statistics (CBS) in 2010 counted a total of 1.118.226 children in the age of 0-5 years in the Netherlands, of whom 572.068 were boys and 451.601 girls (a ratio of 1.3:1).
If for simplicity's sake we ignore the slight skewing towards boys (1.6:1 in Kawasaki Disease versus 1.3:1 in general population), an estimated incidence of 8-18/100,000 would mean an absolute number of 90-200 patients per year in the Netherlands.

6.2.2 Cost of therapy (per patient per year)

Treatment regimen as stated in section 3.1.2. is a single IVIg dose of 2 g/kg. Approximately 10% of patients need a second dose of 2 g/kg [4].
At age 6 months, the 50th percentile of weight for boys is 8 kg (95% interval 6.5-10 kg), at age 5 years this is 18 kg (95% interval 14-24 kg). For girls this is 7.5 kg (6-9.5 kg) and 18 kg (14-25 kg) respectively. If we take these 50th percentiles of weight, that would mean for each patient between 16 and 36 g total IVIg for a single treatment. This is doubled in 10% of the patients, who fail to defervesce with initial IVIg therapy.
Estimated cost per patient for a single course of IVIg is estimated at €1040-2340 euro.
Estimated cost per year in the Netherlands: 99-220 (this includes the 10% of patients who need the treatment twice) * €1040-2340: €103.000-514.000.

6.3 Immune thrombocytopenic purpura (ITP)

6.3.1 Patient population and number of patients

The incidence of ITP is estimated to be 50 per 1 million[5], so about 800 patients per year. There are no known trends of increase or decrease in incidence.
In adults, IVIg is not part of routine first line treatment but reserved for special situations [5]. In children with acute ITP IVIg is given sometimes as first line treatment, but only in case of severe bleeding (see section 3.2.2.).

6.3.2 Cost of therapy (per patient per year)

If patients with ITP are treated with IVIg, it is not done in a chronic regimen, but only as a rescue treatment. This will be either 1 g/kg/day for 2 days (adults) or 1 day (children). There is no adequate way of estimating how often this is needed in clinical practice.

6.4 Guillain-Barré syndrome

6.4.1 Patient population and number of patients

Incidence in the Netherlands is 1.3 per 100.000 per year, which means that about 200 persons per year get GBS (CBO guideline 2010). Mild cases of GBS may not need treatment with IVIg, but the percentage of mild patients is not known.

6.4.2 Cost of therapy (per patient per year)

Treatment regimen is 400 mg/kg/day for 5 days, so 2 g/kg per patient. In approximately 10% of patients a relapse occurs which warrants a second course of IVIg treatment.
The disease occurs in adults as well as children, but mostly in adults. If we take an average weight of 70 kg, this means 140 g per GBS patient for one course of IVIg treatment.
Cost per patient for a single treatment: 140 g * €65 = €9100

Cost per year in the Netherlands: 220 times (200 + 10% for patients who need treatment twice) cost per patient for single treatment : 220 * €9100 = €2 million.

6.5 Hypogammaglobulinemia

6.5.1 Patient population and number of patients

Only a rough estimate of the patient population can be given at present. Members of the Dutch Working Group on Immunodeficiencies (WID) are at present actively adding patient data to the European database for primary immunodeficiencies of the European Society for Immunodeficiencies (ESID). Submission is not complete at the moment; only about 60% of patients have been added so far (estimated). At present the ESID database contains data on 454 Dutch patients with a primary immunodeficiency; approximately 280 of these patients would potentially be candidates for long-term IVIg treatment. If this is about 60% of total patients, this would mean about 450 patients in the Netherlands are candidates for chronic IVIg therapy. When the ESID registry has been completed, this estimate may be improved.

6.5.2 Cost of therapy (per patient per year)

Treatment with IVIg in patients with primary hypogammaglobulinemia is generally lifelong. Dosage is individually adjusted to reduce the annual rate of infection; aim is a sufficient trough level of IgG (general recommendation: 5 g/L, recent literature [15, 16] suggests a higher trough level of 7 g/L might be beneficial (see section 3.4.2.). This is generally reached by a regimen of 300 mg/kg once every 28 days. Sometimes higher dose or higher frequency is necessary.

Estimated average dose per treatment per patient: 0,3 g * 70 kg = 21 g
Estimated average cost per year per patient: 21 g * 12 times yearly * €65 = €16.400
Estimated cost per year for 450 patients: 450 * €16.400 = €7,4 million

6.6 Other indications / off label use

6.6.1 Multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

6.6.1.1 Patient population and number of patients

Cats et al. [8] in their national study identified 97 patients with MMN in the Netherlands. Eighty-four of those patients had received at least one dose of IVIg of 2 g/kg. A total of 67 patients with MMN (76% of total group) were on maintenance IVIg treatment.
The prevalence of CIDP is less known. Estimated prevalence is 0,8 and 8,9 per 100,000 [6], which would indicate at least somewhere between 130 and 1400 patients.

6.6.1.2 Cost of therapy (per patient per year)

For MMN, Cats et al. [8] found that patients were on a median dose that increased from 12 g/week to 17 g/week because of less response over time. If we take an average of 15 g/week, this would mean 60 g/month.
Estimated cost per patient per year: 60 g * 12 * €65 = €46.800
At a rough estimate of 250 patients nationwide: 250 * €46.800 = €11,7 million

6.6.2 Foetal and neonatal alloimmune thrombocytopenia

Every year, in the Netherlands, an estimated 400 pregnancies are newly affected by FNAIT, with development of sever foetal thrombocytopenia (platelet count <50x10^9/l) in 125 cases. This leads to an adverse outcome in 20-25 pregnancies with 13-17 children born with intracranial haemorrhage each year, often resulting in life-long neurodevelopmental handicaps. Most of these cases are at present not treated because they are not recognized before birth of the child.
Therapeutic regimen: during 10 weeks of pregnancy (from 28 to 38 weeks from start of pregnancy) dosage of 500 mg/kg intravenously once a week. (Until recently this was 1000 mg/kg once a week). This would translate on average to about 35 gram i.v. per week, or 350 g i.v. per patient per pregnancy. Costs: 350 * 65 = €22.750 per pregnancy.
Estimated number of pregnancies treated per year at present: 50. Estimated total costs: 50 * €22.750 = €1,1 million.

6.6.3 Other off label use

This is hard to quantify, since IVIg will be used only sporadically for very diverse indications. This use is probably (?) confined to academic medical centres, and usually in cases of failure of regular treatment options.

6.7 Cost prognosis overall

In the most recent publication “Stichting Farmaceutische Kengetallen, april 2010” (SFK), the overall costs on IVIg in the “Beleidsregel dure geneesmiddelen” in 2008 through hospitals is given as €18.1 million. Extramural costs of IVIg through public pharmacies amounted to €9.8 million.
The numbers mentioned in the sections above are rough estimates, but they make clear that the bulk of the cost is for chronic treatment with IVIg in MMN / CIDP and in primary hypogammaglobulinemia.

7. Current studies with therapeutic immunoglobulins in The Netherlands

7.1 Current studies in Kawasaki Disease

There are no current studies in Kawasaki Disease in the Netherlands as far as we are aware.

7.2 Current studies in Immune thrombocytopenic purpura (ITP)

In ITP: the TIKI study, coordinated from the Wilhelmina Children's Hospital by dr. M.C.A. Bruin, aims to investigate to what extent early IVIg treatment in children with newly diagnosed acute ITP reduces the risk of development of chronic disease. This is a randomized controlled trial, non-blinded, which aims to include 300 patients. (Recruiting started January 2009, planned closing date January 2013). For details: Nederlands Trial Register, NTR1563.

7.3 Current studies in Guillain Barré syndrome (GBS)

One national trial is ongoing, to determine whether a second IVIg course in GBS patients with a poor prognosis improves functional outcome (SID-GBS trial, coordinated by Prof.dr. P.A van Doorn, ErasmusMC Rotterdam). This study aims to include 176 patients; planned start date was February 2010, planned closing date February 2013 – for details see het Nederlands Trial Register, NTR2224

7.4 Current studies in hypogammaglobulinemia / immunodeficiency

A national trial for the treatment of IgG subclass deficiency or anti-polysaccharide antibody response is open at this moment. This trial compares treatment with prophylactic antibiotics to intravenous immunoglobulin therapy in children and adults. This is a randomized controlled crossover trial, coordinated by JT van Dissel of Leiden UMC. This study started in November 2007 and aims to complete recruitment in Autumn 2011; the aim is to include 40 patients. For details, see ClinicalTrials.gov NCT00522821.

7.5 Current studies for other indications

7.5.1 Organ transplantation

Desensitization of highly pre-sensitized dialysis patients waiting for kidney transplantation by Rituximab, IVIg-L and rescue Plasmapheresis. Donor-specific antibodies form a significant barrier in transplantation of highly pre-sensitized dialysis patients. Increased waiting time is associated with increased morbidity and mortality among these patients. Thus, there is a need to further develop desensitizing therapies not only to make transplantation for this group of patients feasible, but also to reduce the occurrence of acute and chronic antibody-mediated graft damage caused by HLA or non-HLA specific antibodies. Acute and chronic antibody-mediated graft damage is increasingly associated with decreased graft function and survival. This study had a target of 17 patients and closed January 2010 according to the Trial Register. For details: Nederlands Trial Register, NTR1000

7.5.2 Parvovirus B19 mediated cardiomyopathy

A prospective randomized double-blind placebo-controlled trial to investigate the effect of high doses of IVIg on cardiac functional capacity and virus presence in a subgroup of patients with chronic symptomatic cardiomyopathy and a high parvovirus B19 load in the heart. This trial is coordinated by dr. S. Heymans, AZM, Maastricht; it aims to enroll 50 patients and started recruiting in November 2009. For details: Clinicaltrials.gov NCT00892112.

8. Missing data and suggestions

There exist only a limited number of good pharmacoeconomic evaluations of the use of IVIg, and none of these are Dutch studies. Such evaluations at least for the major indications could be of value. Missing data also made the cost prognosis in chapter 6 very rough estimates.

Data are missing on use of immunoglobulin in orphan diseases that do not fall under the registered indications. The impression of the experts is that these are usually diseases where IVIg is used as a (last-line) alternative upon failure of first- or second-line treatment, and it will always be exceptional or severe cases. Because of the rarity of these cases, it will not be possible to apply formal evidence-based medicine. This category could not be further substantiated at present. However, these cases probably only make up a small proportion of IVIg use.

Screening program for fetal and neonatal alloimmune thrombocytopenia (FNAIT): Dr Oepkes' group wants to set up a prospective study to test the hypothesis that a screenings program in all pregnant women would be efficacious, safe and cost effective in the Dutch population. This study would aim to examine whether antenatal administration of IVIg, weekly from week 32 to 38 of gestation, compared with no antenatal treatment would reduce adverse outcome of the pregnancy, in pregnant woman HPA-1a antibodies identified through a screening program. They are currently seeking funding for this study.

There are CBO guidelines for Guillain-Barré syndrome and Dermatomyositis/Polymyositis, that include recommendations on the use of IVIg, and there is a National Guideline on the management of ITP in adults. But for some of the major indications for IVIg there are no national guidelines on treatment in clinical practice. Suggestion: promote and facilitate the development of national guidelines on use of IVIg for at least the major categories, especially:

- Primary hypogammaglobulinemia
- Secondary hypogammaglobulinemia
- Kawasaki Disease
- ITP in children

This recommendation was also made recently by the 'Regieraad Kwaliteit van Zorg' (Rapport Dure geneesmiddelen in richtlijnen, October 2010, www.regieraad.nl).

Suggestion: concentrate patients on chronic IVIg therapy in a limited number of centres: for the two major indications for chronic use of IVIg, i.e. primary hypogammaglobulinemia and MMN/CIDP, centralization of care in the academic medical centres and a few specialized peripheral hospitals may be feasible. Both these indications have a good network of both professionals and patients, for hypogammaglobulinemia the Dutch Working Group on Immunodeficiency (WID) and the patient organization Stichting voor Afweerstoornissen (SAS), and for MMN/CIDP the Interuniversitair Steunpunt Neuromusculair Onderzoek (ISNO) and the patient organization Vereniging Spierziekten Nederland (VSN). Both these patient populations are confronted with the issue of at home administration of IVIg (see section 5.3.), and they are likely to make up the bulk of the cost of IVIg in the Netherlands. Centralization of care for these patient populations would improve quality of care and cost effectiveness.
Such centralization is not recommended for acute IVIg therapy in patients with e.g. Guillain-Barré syndrome or ITP. This should be available in both smaller and larger medical centres. For FNAIT, there is currently already centralization in one centre nationwide.

9. Conclusions

Therapeutic immunoglobulins have a range of indications in clinical practice, either through supplementation of endogenous IgG deficiency or through immunomodulatory effects. It is prescribed by various medical specialists, including internists, paediatricians, clinical immunologists, neurologists, haematologists and gynaecologists. This makes it complicated to get a good overview of its use in daily practice, and of patterns of expenditure.
Safety of IVIg is remarkably good. Adverse effects are usually limited and short-lived. Thus, IVIg is ideal for use at home with specialized care, in case of chronic treatment.
There are only few good pharmacoeconomic evaluations of IVIg use, none directly applicable to the Dutch situation.

10.Appendices

10.1 Biographies authors

10.1.1 Anna Simon

Anna Simon, MD PhD, is an internist and infectious disease specialist of the Department of General Internal Medicine of the Radboud University Nijmegen Medical Centre. In 2010 she was appointed as Associate Professor and Junior Principal Investigator in the field of autoinflammatory diseases and immunodeficiency. She is co-founder of the N4i Centre for Immunodeficiency and Autoinflammation (NCIA).

10.1.2 Margriet Moret-Hartman

Margriet Moret-Hartman, PhD, is an epidemiologist. She completed her PhD thesis on improving the usefulness of Health Technology Assessment for health policy and clinical practice. Currently she is appointed as assistant professor of health technology assessment (HTA) at the department of Epidemiology, Biostatistics and Health Technology Assessment, Radboud University Medical Centre, Nijmegen, The Netherlands.

10.1.3 Marcel van Deuren

Marcel van Deuren, MD PhD, is an internist and clinical immunologist of the Department of General Internal Medicine of the Radboud University Nijmegen Medical Centre. He is co-founder of the N4i Centre for Immunodeficiency and Autoinflammation (NCIA). He is a member of the Dutch National Working Group on Immunodeficiency (WID).

10.1.4 Eddy Adang

Eddy M.M. Adang, PhD, is Associate Professor of Health Economics and junior principal investigator at the Depatment of Epidemiology, Biostatistics and Health Technology Assessment, Radboud University Medical Centre, Nijmegen, The Netherlands

10.1.5 Jos WM van der Meer

Professor Jos WM van der Meer, MD PhD is head of the Department of General Internal Medicine of the Radboud University Nijmegen Medical Centre. He is an internist, infectious disease specialist and clinical immunologist. He is a member of the Dutch National Working Group on Immunodeficiency (WID).

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*A **systematic review** on effectiveness, safety and efficiency of intravenous immunoglobulin (IVIg)*

Appendix to "Therapeutic immunoglobulins in clinical practice", by Anna Simon, Margriet Moret-Hartman, Marcel van Deuren, Eddy Adang and Jos WM van der Meer

Content

1. Introduction

Intravenous immunoglobulin (IVIg), is a blood product administered intravenously. It contains IgG (immunoglobulin G) extracted from the plasma of blood donors. It is mainly used as treatment in immune deficiencies (replacement therapy) and inflammatory and autoimmune diseases (immunomodulation). Indications described in the Dutch Pharmacotherapeutic Formulary (farmacotherapeutisch kompas) include: primary immunodeficiency syndromes, secondary immunodeficiency syndromes (patients with Chronic Lymphatic Leukemia; children with AIDS; premature neonates with birth weight <1500g), immune thrombocytopenic purpura (ITP), especially acute ITP in children, Kawasaki Disease and Guillain-barré syndrome.

Patients with primary or secondary immunodeficiency syndromes have persistent / frequent infections which can lead to pulmonary damage and loss of pulmonary function. Kawasaki disease (Mucocutaneous lymph node syndrome) is an autoimmune disease that manifests as a systemic necrotizing medium-sized vessel vasculitis and is largely seen in children under 5 years of age. It can cause severe coronary artery aneurysms in untreated children. ITP: condition of having a low platelet count (thrombocytopenia) of no known cause. a very low platelet count can lead to visible symptoms, such as purpura (bruises) or more serious bleedings. Guillain Barre is an acute inflammatory demyelinating polyneuropathy; usually triggered by an acute infection. It can cause life-threatening complications

We performed a systematic review to assess the evidence on the effectiveness, safety and efficiency of IVIg as replacement therapy in patient with immune deficiencies and as treatment in patients with ITP, Kawasaki or Guillain Barre Syndrome.

2. Methods

Research questions

IVIg is used in several populations. We limited our review to populations that are mentioned in the Dutch Pharmacotherapeutic Formulary (Farmacotherapeutisch Kompas): patients with immunodeficiency (both primary and secondary immunodeficiency syndromes), patients with Kawasaki disease, patients with idiopathic thrombocytopenic purpura and patients with Guillain-Barré Syndrome. As in current practice HIV is no longer used as indication for IVIg, we excluded studies including HIV populations.

In this review, we searched for evidence on the effectiveness, efficiency and safety of IVIg in the above mentioned patient groups. For Kawasaki disease, the primary outcome measure is the number of patients with coronary abnormalities. For ITP the primary outcome measure is the number of patients with bleeding event. A secondary outcome measure is platelet counts (number of patients that reached predefined level). A platelet count (PC) lower than $20x10^9$/L is associated with a high risk of complications. We therefore extracted data concerning response rates using a PC> 20 or $30x10^9$/L where possible. For immunodeficiency, the primary outcome measure for effectiveness is the number of infections. For efficiency and safety no specific outcome measures were defined.

We selected studies in which IVIg was compared to no treatment or a placebo (in case of immunodeficiency syndromes), or an alternative active treatment (ITP: corticosteroids or Anti-D; Kawasaki: aspirin). Studies in which different preparations of IVIg were compared or different ways of administration of immunoglobulin (for example IVIg versus subcutaneous administration) were not included in this review.

This resulted in the following research questions (PICO):
-Does treatment with IVIg decrease the rate of cardiovascular complications in patients with Kawasaki Disease as compared to alternative interventions (such as aspirin)?
-Does treatment with IVIg decrease the rate of bleedings in patients with idiopathic thrombocytopenic purpura as compared to alternative interventions (such as corticosteroids)?
-Does treatment with IVIg decrease the rate of infections in patients with immunodeficiency syndromes?
- Is treatment with IVIg safe?
- What are the costs and effects of treatment with IVIg as compared to alternative interventions?

Secondarily, we selected studies in which the effectiveness of different doses of IVIg were compared.

Search methods for identification of studies

We searched in Medline (OVID), EMBASE (OVID), and the Cochrane database of controlled clinical trials for relevant studies on the effectiveness of IVIg. For economic evaluations, we searched Medline (OVID), EMBASE (OVID) and the NHS Economic Evaluation Database (via Cochrane Library). Searches covered the period from 1946 until December 2010 (Medline) and from 1980 until December 2010 (Embase).

We also performed hand searching for relevant studies in references

Types of studies

We searched for randomized clinical trials (RCTs). However, it was expected that no RCTs might be available for some indications. Therefore, if no RCTs were found, we extended our search to non-randomized trials in which IVIg was compared to doing nothing, placebo, or another intervention.

Types of participants

For each of the populations a search strategy was developed. A detailed description is provided in appendix 9.3. We identified two relevant and recent Cochrane reviews. One reported on the effectiveness of IVIg in patients with Guillain-Barré Syndrome. The other reported on prophylactic use of IVIg in neonates. A revealed that no new trials were published after these Cochrane reviews. Therefore, in this systematic review, we will summarize these two Cochrane reviews.

Selection, data collection and analysis

Two persons with complementary background (research methodology and clinical medicine, respectively) independently selected potentially relevant studies, based on title and abstract. The same two persons independently read full text reports and extracted data. In the review of cost effectiveness, selection was conducted by a methodologist and an HTA expert.
Data extraction forms were used to collect relevant data.

Assessment of risk of bias randomization, blinding of patients, physicians, and study personnel, comparability of groups at baseline; and the completeness of follow up. For cost-effectiveness, quality criteria were: a full economic evaluation (measuring both costs and effectiveness, unless there clinical equivalence in which case a cost-minimization analysis was accepted), explicit time horizon, sensitivity analysis, and discounting (see table 9.3.4.).

Due to the high heterogeneity in included studies, no meta-analysis was performed. Therefore, results were synthesized qualitatively.

3. Results

Search and selection

Kawasaki

The literature search for clinical effectiveness of IVIg in Kawasaki Disease yielded 43 hits. Based on title and abstract 16 potentially relevant studies were selected. Three publications were not available in the Netherlands. After reading full text reports, 7 studies were excluded (2x other research question; 3x not a RCT; 1x other intervention was evaluated, 1 comparison between different preparates of IVIg). Manual search yielded 3 extra studies.

Four studies reported on the effectiveness of IVIg as compared to alternative interventions. In 6 studies, a comparison of different doses of IVIg was made (one study reported on 2 trials, 1x IVIg versus alternative treatment, 1x different doses of IVIg). In Figure 9.2.1 and table 9.3.1., a summary of the search and selection is presented.

ITP

The literature search for clinical effectiveness of IVIg in ITP yielded 59 hits. After reading title and abstract 23 potentially relevant references were selected. Of these 23 articles, 2 articles were not available in the Netherlands. Five studies were excluded after reading full text reports (4x not RCT; 1x insufficient information on methods or results to assess quality). A summary of the search and selection process is presented in Figure 9.2.2 and table 9.3.2.

In 14 of the 19 included studies the effectiveness of IVIg was compared to an alternative treatment (12 children with acute ITP, 3x children with chronic ITP, 4x adults with ITP). In 5 studies different doses of IVIg were compared. The results are reported separately for 1) children with acute ITP, 2) children with chronic ITP and 3) adults with ITP.

Guillain-Barré Syndrome

In 2010, a systematic review on IVIg or patients with Guillain-Barré Syndrome was published by the Cochrane collaboration (Hughes 2010). For this review, RCTs published until June 2009 had been searched. Since June 2009 no new RCTs have been published.

Immunodeficiency syndromes

For patients with primary immunodeficiency syndromes, no RCTs were found. We therefore expanded our search to include clinical trials. The expanded literature searches yielded 202 references. Based on title and abstract 34 potentially relevant studies were selected. After reading the full text reports, 26 studies were excluded (7x report on new IVIg preparations in which no comparison was made; 6x comparison between two or more preparates of IVIg; 2x double publication of same study, 2x IVIg compared to intramuscular or subcutaneous immunoglobulin, 4x (review / no original study / no RCT), 2x other research question; 1x other population, 1x insufficient info on period during with infections are measured in pretreatment period, 1x patients who crossed over were counted in both groups (doubled), 1x no relevant outcome measure)
Of the 8 included studies, 5 studies report on the effectiveness of IVIg as compared to no treatment or a placebo (2x in primary immunodeficiency syndromes; 3x in secondary immunodeficiency syndromes). Three studies report on a comparison of different doses of IVIg. A summary of search and selection process is presented in Figure 9.2.3. and table 9.3.3.

4. Kawasaki Disease

Clinical effectiveness

In three trials, treatment with ASA (aspirin) was compared with treatment with the combination of IVIg and aspirin (see table 9.4.1.). Furusho (1984) compared IVIg 400 mg/kg for 3 days plus aspirin with aspirin alone in 85 children with Kawasaki disease. In a next trial, Furusho compared a lower dose of IVIg alone (200 mg/kg, 5 days) with aspirin alone and the combination of IVIg and aspirin. Newburger (1986) compared IVIg 400 mg/kg during 4 days plus aspirin with aspirin alone in 168 children.

Furusho (1984) reported a lower percentage of patients with coronary arterial lesions after 30 days in patients treated with the combination of IVIg and aspirin treatment as compared to patients treated with aspirin alone (15% and 42% respectively, NNT 4). After 60 days, the percentage of patients with coronary arterial lesion was lower in both treatment groups, but the difference between the group remained (7.5% and 31% respectively, NNT 4).
In the study of Furusho (1991), the percentage of patients with coronary arterial lesions were slightly lower in patients treated with IVIg alone (7.8%) then in patients treated with the combination of IVIg and aspirin (10.2%, IVIg vs combination NNT=42) or with aspirin alone (19,1%, IVIg vs aspirin NNT=8.8), but differences were not statistically significant.

Newburger (1986) also found a lower percentage of patients with coronary abnormalities in patients treated with the combination of aspirin and IVIg as compared to treatment with aspirin alone (4% versus 18%, NNT 7).

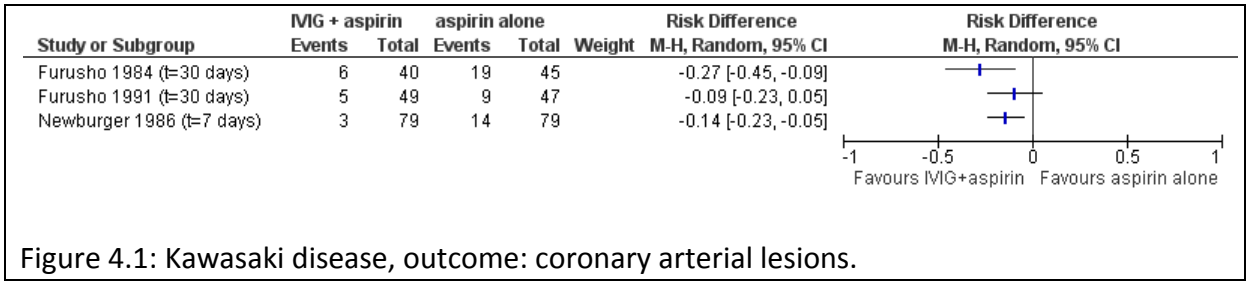

Figure 4.1: Kawasaki disease, outcome: coronary arterial lesions.

Hashino reported the results of a trial on IVIg versus methylprednisolone in 17 children. After 7 days, the percentage of patients with coronary artery abnormalities was slightly lower in patients treated with IVIg (63%) than in patients treated with methylprednisolone (78%, NNT 6.7, N.S.).

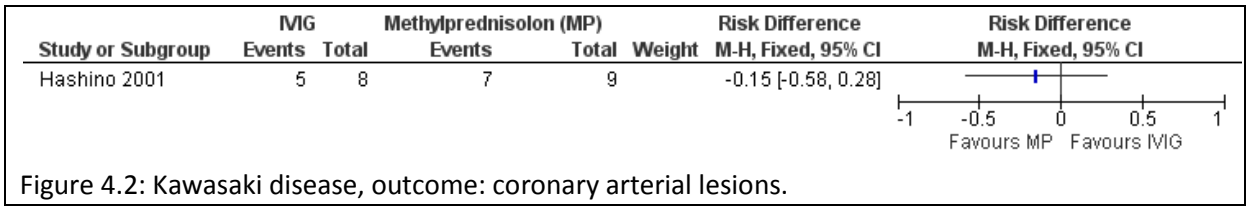

Figure 4.2: Kawasaki disease, outcome: coronary arterial lesions.

Dose response

In six trials, treatment of children with Kawasaki with different doses of IVIg were compared (see table 9.5.1.).
Furusho (1991) compared treatment with 100, 200 or 400 mg/kg/day, for 5 days. No clear dose response relation was found. Thirty days after onset of the disease, the number of patients with coronary abnormalities was slightly, but not statistically significant, lower in patients receiving 200 mg IVIg (6%) as compared to 100mg (14%) or 400 mg (11%).
In 4 trials a dose of 400 mg/kg on 4 or 5 consecutive days was compared with a dose of 1 or 2 g/kg once. In these trials, no clear dose-response relations was founds. Sato (1999)compared 2g/kg IVIg

once with 400 mg/kg IVIg for 5 days in 145 children. After 7 days, 1.4% of the children treated with IVIg 2g and 9.6% of the children treated with IVIg 400 mg had an aneurysm (statistically significant difference; NNT 12). Newburger (1991) compared a single dose of 2g/kg with 400 mg/kg IVIg for 4 days in 549 children. After two weeks, the number of children with aneurysm was statistically significant lower in patients treated with 2 g/kg IVIg as compared to children receiving 400 mg (4,5% versus 9%, NNT=22). After 7 weeks, however, the number of children with aneurysms was no longer significantly different between the two groups (2g: 4%, 400mg: 7%,NNT=30 N.S.) Barron (1990) and Liang (2004) found no differences in coronary abnormalities between IVIg 2 g/kg once or IVIg 400 mg/kg for 5 days.

Cost-effectiveness

Sato (1999) performed also an economic evaluation alongside the clinical trial (table 9.4.7.). The mean cost per treatment were lower in patients treated with IVIg 2 g/kg once as compared to IVIg 400 mg/kg for 5 days (difference $520). Because the higher effectiveness and lower costs, treatment with IVIg 2 g/kg once is dominant.

The search for economic evaluations yielded another economic evaluation. Klassen (1993) compared the costs and effectiveness (coronary artery dilation) of aspirin, low dose IVIg (400 mg/kg, 4 days), and high dose IVIg (2g/kg once) from a societal perspective (table 9.5.5.). The time horizon was seven weeks. High dose IVIg was dominant, resulting in the lowest costs (estimated mean costs: $3,982 for high dose IVIg, $ 5,164 for low dose IVIg and $7,216 for aspirin) and highest effectiveness (% with coronary artery dilation 4% in high dose IVIg, 6% in low dose IVIg and 18% in aspirin). Sensitivity analysis showed that the results of IVIg versus aspirin were not sensitive to changes in parameters used. The results of high versus low dose IVIg were sensitive to the duration of hospitalization.

Conclusions

1. In three RCTs with children with Kawasaki Disease, the proportion of children with coronary aneurysms was lower after a short term treatment with IVIg (4 or 5 days) and aspirin as compared to treatment with aspirin alone.
2. a high dose of IVIg (1 or 2 g/kg) once was more effective than a lower dose (400 mg/kg) on 4 or 5 consecutive days in 'preventing' coronary aneurysms
3. Treatment with high dose IVIg (2g/kg) once was cheaper and more effective (dominant) as treatment with a low dose IVIg (400 mg/kg) on 4 consecutive days

5. Immune Trombocytopenic Purpura (ITP)

Children with acute ITP

Clinical effectiveness

Ten RCTs on IVIg in acute ITP in children were included (Table 9.4.2.). In eight RCTs, treatment with IVIg was compared to treatment with corticosteroids; In three RCTs IVIg was (also) compared to treatment with anti-D.

IVIg vs corticosteroids

No trials that reported the number of bleedings as an outcome measure were found.

In three studies, short term response (PC>20 x 10^9/L within 2 or 3 days) was slightly better for patients treated with IVIg as compared to patients treated with high dose methylprednisolone (Erduran 2003, Rosthoj 1996, Ancona 2002). Ancona compared IVIg 1 g/kg (2 doses) with MP 30 mg/kg (3 doses). Erduran compared IVIg 1 g/kg for 2 days with high dose MP (3 days 30 mg/kg/day +

4 days 20 mg/kg/day). Rosthoj (1996) compared IVIg 1 g/kg for 2 days with high dose MP (30 mg/kg for 2 days). The numbers needed to treat (NNT) ranged between 3-8. However, after a few days, the differences between the two interventions diminished (Erduran 2003). In the trial of Erduran (2003) the time until response was statistically significant lower in patients treated with IVIg as compared to patients treated with methylprednisolone.

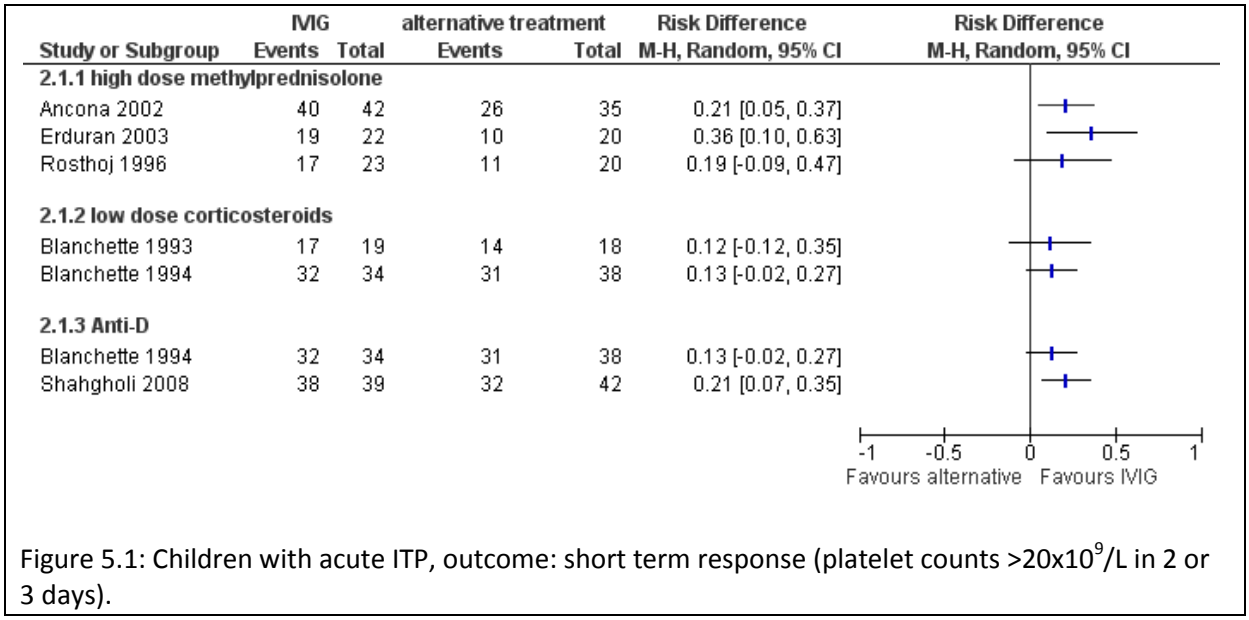

Figure 5.1: Children with acute ITP, outcome: short term response (platelet counts >20x10^9/L in 2 or 3 days).

Two trials reported the number of patients with complete response (PC>100 or 150 x 10^9/L) after 1-12 months of follow up (Albayrak 1994, Ozsoylu 1993). Albayrak reported slightly higher response for IVIg, not statistically significant (NNT 20). Özsoylu reported higher response for patients treated with MP (NN 6.7, N.S.).

In three RCTs, IVIg was compared to long term treatment with a low dose of corticosteroids. Blanchette (1993) compared IVIg (1g/kg, 2 days) with low dose prednisolone (initial dose 4 mg/kg/day; total 17 days treatment) or no treatment in 53 patients. Blanchette (1994) compared IVIg 1 g/kg for 2 days, IVIg 0.8 g/kg once, low dose prednisolone (initial dose 4 mg/kg; treatment 21 days) and Anti-D (25 µg/kg for 2 days). Imbach compared treatment with IVIg 0.4 g/kg on 5 days with oral corticosteroid (60 mg/m^2 for 21 days).

In the trial of Blanchette (1994), the number of days with PC< 20x10^9/L was lower in patients treated with IVIg 0.8 g/kg as compared to patients treated with prednisolone. In patients treated with IVIg 1.0 g/kg, the results were comparable to patients treated with prednisolone. Blanchette (1993) reported no difference in median number of days with an low platelet count (PC<20 x10^9/L) between patients treated with IVIg and patients treated with corticosteroids.
Imbach (1985) reported the number of patients with complete response (PC>100 x 10^9/L) after 12 months of follow up. A slightly higher response rate was found in patients treated with IVIg as compared to patients treated with corticosteroids, but this difference not statistically significant (NNT 17).

IVIg vs anti-D treatment

In the three RCTs, the percentage of patients with a short term response was higher when treated with IVIg as compared to anti-D (NNT between 3.3 and 12.5). Shahgholi (2008) compared IVIg 1 g/kg for 2 days with a single dose of Anti-D (75 µg/kg) in 81 children. Tarantino compared a single dose of IVIg 0.8 g/kg with a single dose of Anti-D 75 µg/kg or Anti-D 50 µg/kg. Blanchette (1994) compared

IVIg 1 g/kg for 2 days, IVIg 0.8 g/kg once, low dose prednisolone (initial dose 4 mg/kg; treatment 21 days) and Anti-D (25 µg/kg for 2 days).

In the trial of Shahgholi (2008), the rate of patients with short term response was significantly higher in patients receiving IVIg then in patients receiving anti-D (NNT 4.8). In the RCT of Blanchette (1994) response rate after 72 hour was 94% in patients receiving IVIg 1 g/kg, 97% in patients receiving IVIg 0.8 g/kg and 82% in patients receiving Anti-D. In the trial of Tarantino (2006) IVIg was better than Anti-D 50µg once (NNT ~ 3.3) and slightly better than Anti-D used in a dose of 75µg once (NNT ~13). After 7 days, the percentage responders was comparable for IVIg and Anti-D 50µg. The results were only graphically reported.

Dose response

In two RCTs, different doses of IVIg were compared (table 9.5.2.). Benesch (2003) compared IVIg 1g/kg/day for two days with 0.3 g/kg/day for two days in 34 children with acute ITP. The number of patients who responded (PC<20x10^9/L) 72 hour after the first infusion was slightly lower in patients receiving the low dose (76% versus 88%, NNT 8, N.S.).
Warrier (1997) reported the data of two small trials. In the first trial IVIg 400 mg/kg for 2 days was compared with IVIg 1 g/kg for 2 days in children between 5 and 12 years of age. In the second trial, a dose of 250 mg/kg for 2 days was compared with a dose of 500 mg/kg for 2 days in children younger than 5 years of age. All doses were equally effective. Within 10 days, all children treated with 250 mg/kg, 400 mg/kg or 1g/kg responded (PC>30x10^9/l). Of the patients receiving 500 mg 5 out of 6 children responded (83%).

Cost effectiveness

The search for economic evaluations yielded 2 studies of IVIg in children with acute ITP (table 9.4.7.). In both studies, treatment with IVIg (0.8 g/kg single dose) was compared with anti-D treatment (75µg/kg, once), low dose prednisone (4 mg/kg, for 4 days), and high dose methylprednisolone (30 mg/kg, for 3 days).

O'Brien (2007) reported on short term results using a societal perspective. Authors concluded that treatment with IVIg was dominated by anti-D (higher costs and more utilities lost). However, the differences in utilities between the four treatments were very small.

Blackhouse (2008) reported the results from a health care perspective, using a lifetime time horizon. The differences in costs and QALYs were small. Treated with IVIg resulted in 0.0043 QALYs gained and $ 236 extra costs as compared to prednison, resulting in $56,000/QALY. In the sensitivity analysis, the dose IVIg, percentage of intracranial hemorrhage and weight of the patient (which is related to a child's age) had high impact on the results.

Conclusions

1. No trials were found in which the number of bleeding events was reported as outcome measure.

2. In children with acute ITP, the short term response (PC>20 x 10^9/L within 2 or 3 days) might be better for patients treated with IVIg (1 g/kg for 2 days) as compared to patients treated with high dose methylprednisolone (30 mg/kg for 2-3 days), low dose corticosteroids or anti-D. However, after a few days, the differences between the interventions diminished.

3. In terms of QALYs, treatment with IVIg, low dose prednisone, anti-D, or high dose methylprednisolone was equally effective. At short term, costs for low dose prednisone were lower than the other three treatment. Using a lifetime perspective, the differences in costs between the interventions are small.

Children with chronic ITP

Clinical effectiveness

In three RCTs, the effectiveness of IVIg in children with chronic ITP was investigated (table 9.4.3.).

In one study (El Alfy, 2006b) the data of two RCTs on the effect of interventions on the number of severe bleedings were reported shortly. The number of severe bleedings ranged between 8.6 (IVIg 0.8 g/kg once) and 10.1 (oral methylprednisolone 4mg/kg 4 days) However, the information on methods and results was minimal. >

El Alfy (2006 a), compared IVIg (250 mg/kg ,2 days) with anti D (50 µg/kg every 3-4 weeks) in 34 children. Response was defined as a plate count above 50x109/L or doubling the baseline platelet count. The number of children with response seemed slightly better after 3 days in patients treated with IVIg as compared to children treated with anti-D (37% versus 33%, NNT8 N.S). After 28 days the number of patients with response was comparable in both treatment groups (IVIg: 38%, Anti-D 39%, NNT 72, N.S).

Hedlund (2003) compared IVIg (800 mg/kg once + retreatment if PC<30x10^9/L) and dexamethasone. After 3 days, the number of patients who partial responded (PC>30x10^9/L) seemed higher in patients treated with IVIg then patients treated with dexamethasone (87% versus 67%, NNT=5, N.S.). At long term (at least 3 months without therapy) the percentage of complete response (PC>150x10^9/L) was comparable for IVIg and dexamethasone (12,5% and 13% respectively, NNT 120).

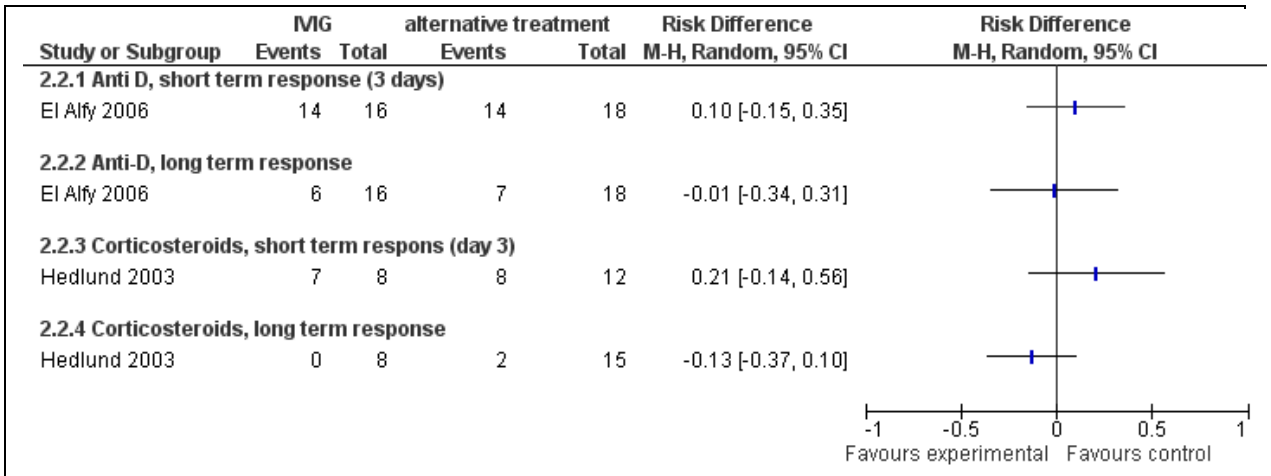

Figure 5.2. Children with chronic ITP, outcome measure platelet count > 20-30 x10^9/L

Cost-effectiveness

One report of an economic evaluation was found (Hollenberg 1988) (table 9.4.7.). Hollenberg compared two strategies for the treatment of children with chronic ITP (at least 6 months): initially IVIg (2g/kg once + 1g/kg maintenance) followed by splenectomy if patients did not response or initially splenectomy followed by IVIg if patients did no response. The time horizon was 10 years, and costs from a health care perspective were included. The mean costs per patient were higher in the strategy in which initially IVIg treatment was given then the strategy in which was started with splenectomy ($ 21,000 and 17,000 respectively). The percentage of patients that were alive after 10 years was almost comparable for both strategies (IVIg: 98.6%, splenectomy 97.9%). The incremental cost-effectiveness ratio is $ 540,000 per additional life saved. The results were strongly affected by variation in the following parameters: percentage of children curable on IVIg, Costs IVIg (dominance IVIg when low price / dose), and the age child (related to weight of the child and thus the dose of IVIg).

Conclusions

1. In children with chronic ITP, the number of patients who responded after treatment with IVIg (at long term) was comparable as treatment with anti-D or dexamethason.

Adults with ITP

Clinical effectiveness

Two trials were identified in IVIg was used for the treatment of adults with ITP (table 9.4.4.). In these trials, different comparators and levels of platelet counts for defining clinical response were used.

Godeau (2002) compared IVIg (0,7 g/kg, 3 days) with methylprednisolone in 122 patients. The short term response (PC>20x10^9/L at day 5) was slightly higher in patients treated with IVIg compared to patients treated with MP, but not statistically significant (89% versus 80%, NNT 11). In neither of both treatment groups, patients died or had severe life threatening hemorrhagic events.

Jacobs (1994) compared treatment with IVIg (400 mg/kg, 5 days) with oral prednisolone or a combination of IVIg and oral prednisolone in 43 adults with symptomatic ITP. After 2 years, the percentage of patients with complete response (PC>100x10^9/L) was 29% in patients treated with prednisolone alone, 23% in patients treated with IVIg and 7% in patients treated with the combination (IVIg versus prednisolone NNT=16, N.S.).

Dose response

In two RCTs, different doses of IVIg were compared (table 9.5.3.). In 1993, Godeau compared treatment with 1 g/kg IVIg for 2 days with 2 g/kg IVIg for 2 days. Reinfusions were given as long as platelet counts were below 50x10^9/l. The number of patients with response (PC>150x10^9/l) 90 days after last booster seemed higher in patients receiving 2g/kg than in patients receiving 1 g/kg (44% versus 11%, NNT 3, N.S.) The follow up period varied between patients and ranged from 5 to 75 months.

In 1999, Godeau compared treatment of 1 g/kg IVIg with 0.5 g/kg as initial treatment. In both groups patients received a reinfusion if they did respond to the first infusion. After 8 days, number of patients who responded (PC>80x10^9/l) was slightly lower in patients who received 1 g/kg initially. (78% versus 88%, NNT=10, N.S.)

Cost-effectiveness

Xie (2009) reported on an economic evaluation in which IVIg (1g/kg, 2 days) was compared to oral prednisone (1mg/kg for a month) for adults with chronic ITP (table 9.4.7.). A health care perspective and a lifetime horizon were used. The mean total costs were Canadian $ 18,000 for IVIg treatment and $ 10,000 for prednisone. The QALYs were 9.884 for IVIg and 9.877 for prednisone, resulting in an incremental ratio of $1,15million/QALY. The results were sensitive to changes in time horizon (between IVIg dominance or very high ICER). Probabilistic sensitivity showed that IVIg has a probability of 20% of being cost effective given a willingness to pay for a QALY Canadian $ 100,000.

Conclusion

1. Two RCT showed no difference in platelet counts at long term (1-2 year) between 3-5 days of IVIg treatment with either high-dose methylprednisolon, low dose oral prednisone, or anti – D.
2. Considering a life time horizon, treatment with IVIg is associated with equal QALYs and higher costs as compared to treatment with low dose prednisone.

6. Guillain-Barré Syndrome

Clinical Effectiveness

In the Cochrane review (Hughes 2010), randomized and quasi randomized trials published until June 2009 were search. The primary outcome was improvement in disability grade. Five trials were included in which IVIg treatment was compared to plasma exchange. Primary outcome was the disability grade after four weeks (GBS scale, scores ranges from 0-6, 0=healthy). The meta analysis included data from 273 patients treated wih IVIg and 263 patients treated with plasma exchange. The difference in change in a 7-grade disability scale after four weeks was not statistically significant between IVIg and plasma exchange (mean difference -0.02, 95%CI[-0.25;0.20]).

Cost-effectiveness

Our search for economic evaluations yielded two evaluations in which IVIg (0.4 g/kg for 5 days) was compared with plasma exchange (4-8 times) (table 9.4.7.). Both assumed similar effectiveness and performed a cost minimization analysis.

Nagpal (1999) reported on a decision analysis from health care perspective, using a time horizon of 48 weeks. They used a decision analytical model filled with data from literature. The mean costs per patients when treated with IVIg were $ 3,961 higher as compared to treatment by plasma exchange. In the sensitivity analysis, the results were sensitive to the cost of IVIg. At a price just below the cheapest available IVIg in the USA ($43,66/g), the costs of treatment of IVIg and plasma exchange would be equivalent.

Tsai (2007) performed a economic evaluation from a health care perspective, time horizon of 2-10 weeks. Costs were measured using data from the medical charts of 17 patients (7 patients received IVIg, 10 patients received plasma exchange). The results showed that plasma exchange was more expensive than treatment with IVIg (difference in mean cost per patient 156,533 New Taiwan $, which corresponds to 4,884 US$ (statistically significant)).

The results of these two studies seemed conflicting. Possible explanations are that Tsai included costs of complications and not by Nagpal. Three of ten patients (30%) treated with plasma exchange experienced complications, and one of the 7 patients (16%) treated with IVIg. Especially, in the patients treated with plasma exchange, the mean total costs were higher in patients who experienced complications as compared to patients without complication. Furthermore, in the study of Tsai the mean costs for drugs were lower as the costs for IVIg as used in the study of Nagpal.

Conclusions

1. In patients with Guillain-Barré syndrome, treatment with IVIg and plasma exchange were equally effective as measured with the change on a disability scale.
2. Treatment of patients with Guillain-Barré syndrome with IVIg seemed to costs less then treatment with plasma exchange.

7. Immunodeficiency / hypogammaglobulinemia

Primary immunodeficiency syndromes

Clinical effectiveness IVIg

Two before-after studies were found in which the frequency of infections during a period on IVIg treatment was compared to the period before starting IVIg (Table 9.4.5.).

Abdou (2009) investigated the effectiveness of IVIg (400 mg/kg each month) in 10 patients with immunoglobulin subclass deficiency. The number of infections during 12 months of treatment were compared to the number of infections during a 12-month period prior to start of IVIg. Gracia

(2004) reported on IVIg (200-300 mg/kg each 3 weeks) in 24 patients with CVID (newly diagnosed). The number of infections during a 2-year period of treatment were compared to 2-year prior to the start of IVIg.

Both studies reported a decrease in number of infections per year. Abdou reported a decrease in the mean number infection per year from 7.9 to 3.1 ($p<0.01$). In the study by Gracia, the rate of mild infections decreased from 4.9 infections per year to 2.2 infections per year ($p=0.01$). The annual rate of serious infections decreased from 0.48 to 0.047. Pulmonary functioning, measured with FEV1 % predicted, did not differ in the period on IVIg treatment, compared with the period before starting IVIg.

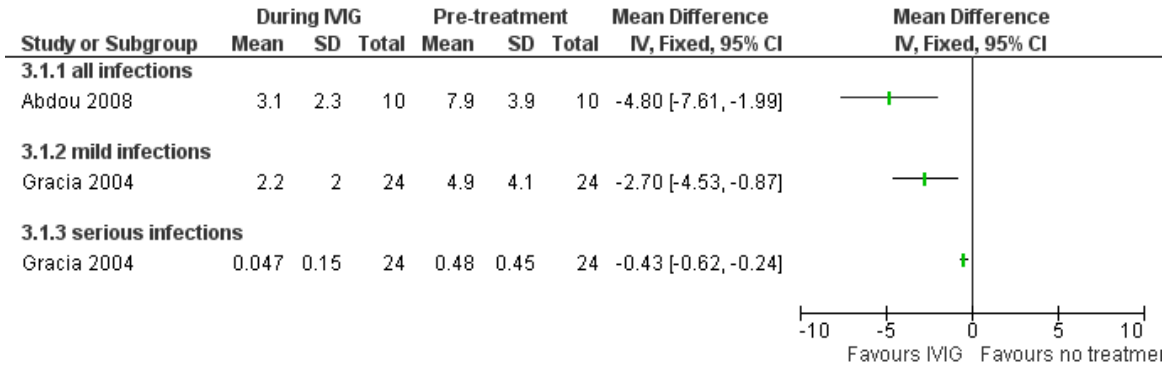

Figure 7.1: Primary immunodeficiency syndromes, outcome: Annual rate of infections.

Dose response

In three cross-over trials, different doses for IVIg were compared (Table 9.5.4.). Eijkhout (2001) compared standard IVIg dose (300 or 400 mg/kg) with a high dose of IVIg (600 or 800 mg/kg) in 43 children and adults with primary hypogammaglobulinemia. The mean number of immunodeficiency related infections was lower in patients treated with high dose IVIg as compared to patients treated with a standard dose (on average 2.5 and 3.5 infections per patient respectively, $p=0.004$). Roifman compared 200 mg/kg IVIg with 600 mg/kg in 12 patients with antibody deficiency and chronic pulmonary disease. Pruzanski compared 200 mg/kg, 400 mg/kg and 600 mg/kg in 21 adults with CVID. Pruzanski (1996) and Roifman (1987) found comparable outcomes in the number of infections per patient between patients treated with a high or a low dose of IVIg.

Cost-effectiveness

No economic evaluations were found in which IVIg was compared to an alternative intervention in patients with primary immunodeficiency syndromes.

Conclusions

1. In patients with primary immunodeficiency, treatment with IVIg may decreases the annual number of infections per patient with approximately 50 percent as compared to no treatment.
2. The mean number of immunodeficiency related infections seemed lower in patients treated with high dose IVIg as compared to patients treated with a standard dose.

Secondary immunodeficiency syndromes

Clinical effectiveness IVIg

Three RCTs reported on the effectiveness of IVIg in secondary immunodeficiency syndromes (Table 9.4.6.). Two trials reported on the use of IVIg in patients with chronic lymphocytic leukemia. In the third trial, IVIg was used in low weight neonates.

Two RCTs reported on IVIg versus placebo in patients with chronic lymphocytic leukemia (CLL) (Anonyous 1988, Boughton 1995). In the trial of Cooperative Group for the Study of Immunoglobulin in CLL (Cooperative Group CLL 1998), 81 patients with CLL and at risk for infections were treated with IVIg (400 mg/kg every 3 weeks) or a placebo for 1 year. In the study of Boughton (1995) 42 patients with CLL started with IVIg (18 g every 3 weeks) or a placebo.

In the study of the Cooperative Group, the number of bacterial infections per patient was lower in patient treated with IVIg as compared to patients receiving a placebo (0.56 and 1.05 infections per patient respectively, p=0.01). Bougthon reported a statistically significant lower risk of three or more serious infections in patients treated with IVIg as compared to placebo (21% and 56% respectively, NNT 2.9).

	IVIG			placebo			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
4.1.1 Bacterial infections							
CLL group 1988	23	-	41	42	-	40	Not estimable
4.1.2 Serious bacterial infections							
CLL group 1988	18	-	41	31	-	40	Not estimable

Fig 7.2. Secondary immunodeficiency syndromes; outcome Annual rate of infections

We identified one RCT with neonates with secondary immunodeficiency (Baker 1992) . Most trials, however, evaluated the prophylactic use of IVIg in neonates. In 2010, a systematic review on this subject by was published Cochrane collaboration (Ohlsson 2010). As the study of Baker was included in the Cochrane review, we only describe this review. In the Cochrane review, Sixteen RCTs in which IVIg was compared to either a placebo or no treatment, were included (update of earlier version, last search until December 2009). Outcome measures included the number of patients with sepsis, the number of patients with any serious infection, and mortality. When the results of these trials were combined in a meta-analysis, a reduction in the number of patients with a serious infections was found for IVIg (absolute risk difference = 0.04 (NNT=24)). There were no differences in mortality.

Cost-effectiveness

In an economic evaluation, Weeks (1991) compared prophylactic treatment with IVIg with no IVIg in patients with CLL (table 9.4.7.). This decision analytic study used data from the Cooperative Group trial (Cooperative Group CLL 1988). From a societal perspective and life time horizon, the marginal costs for IVIg were $14,000 and the marginal effects 0.0023 QALYs, resulting in a incremental cost-effectiveness ratio of $6 million per QALY. Sensitivity analyses revealed that the results were sensible to assumptions on survival and quality of life. Results were minimally altered by variations in costs.

Conclusions

1. In patients with CLL, treatment with IVIg decreased the annaul rate of infections per patient as compared to treatment with a placebo.
2. Considering a life time horizon, treatment with IVIg did not result in a difference in QALYs in patients with CLL. Therefore, the additional costs per QALY for IVIg as compared to no IVIg were high (unfavorable).
3. The prophylactic use of IVIg in preterm and/or low birth neonates reduces the proportion of patients with a serious infection as compared no treatment or a placebo.

8. Safety

In Table 9.6, the frequencies of adverse events for studies on the effectiveness of IVIg are summarized. Overall, the frequency of adverse events in patients treated with IVIg was highly variable and ranged from 3 to 87% of patients. Most adverse events were rather mild, including headache, fever, vomiting. In these trials, two times an indication of an aseptic meningitis was reported. Once a deep venous thrombosis complicated by pulmonary embolism was reported.

9. Appendices

9.1 References

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9.2 Flow charts searches and selection

Figure 9.2.1 Flow Diagram Kawasaki Disease

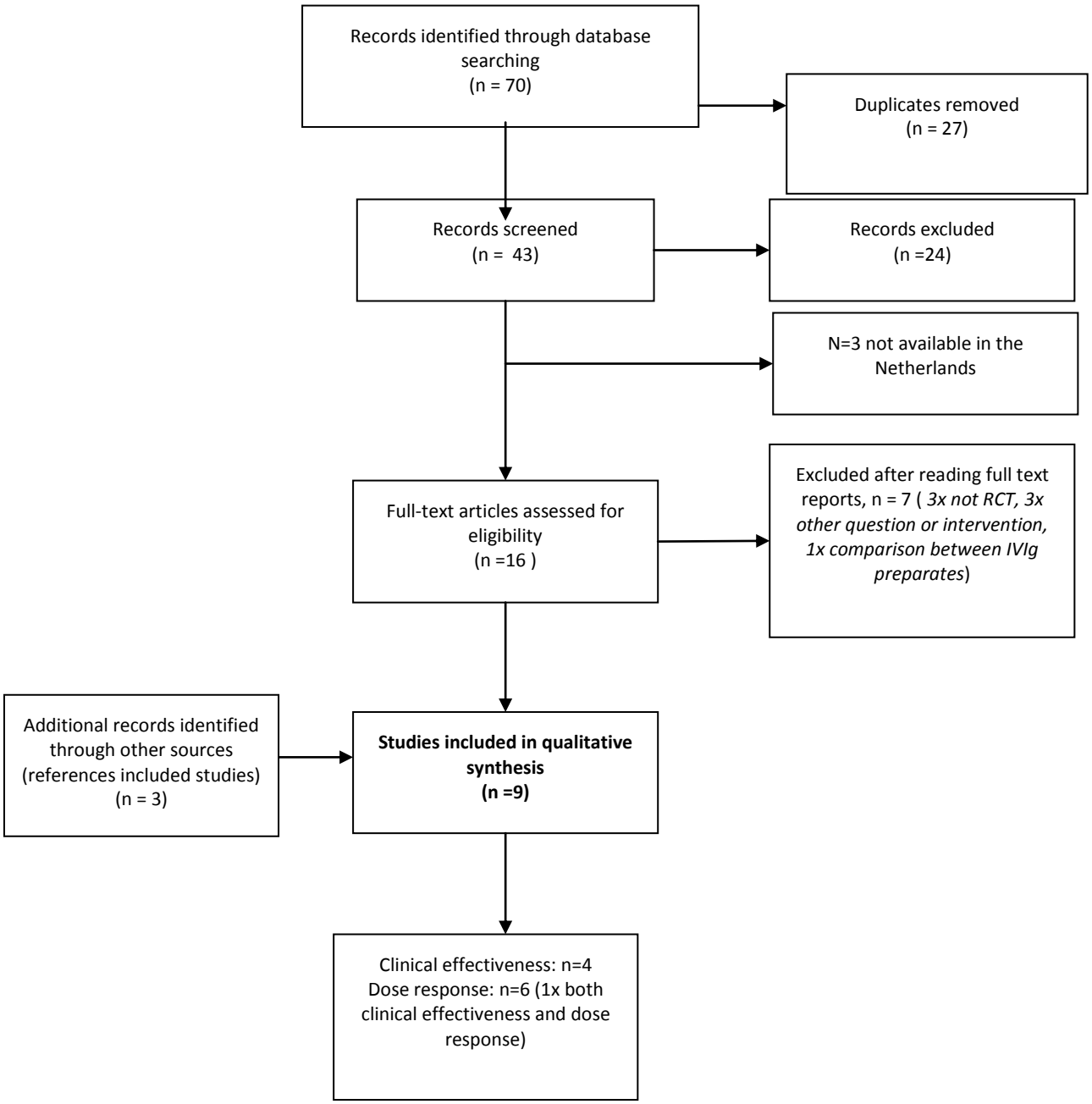


Figure 9.2.2 Flow Diagram ITP

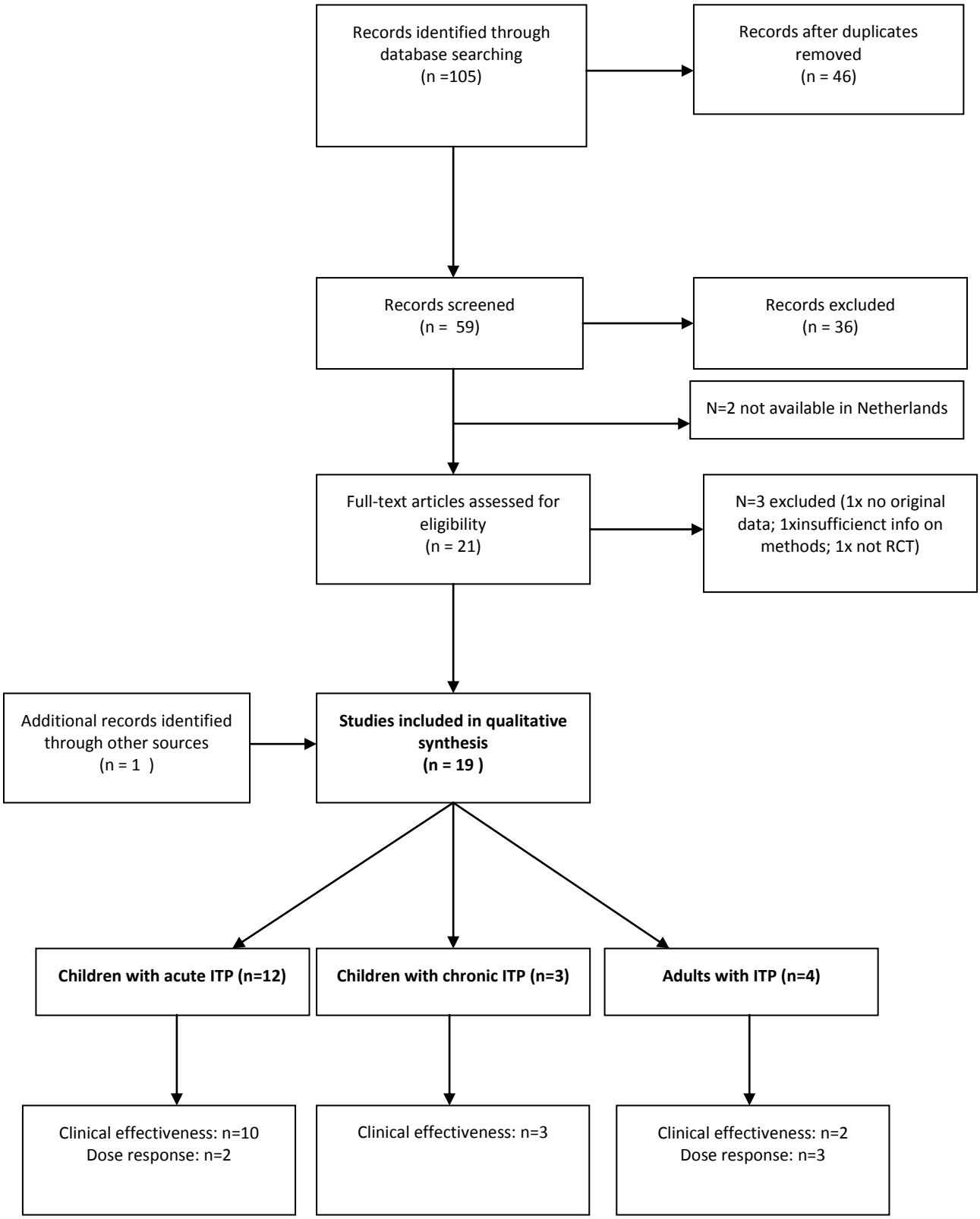


Figure 9.2.3 Flow Diagram Immunodeficiency syndromes

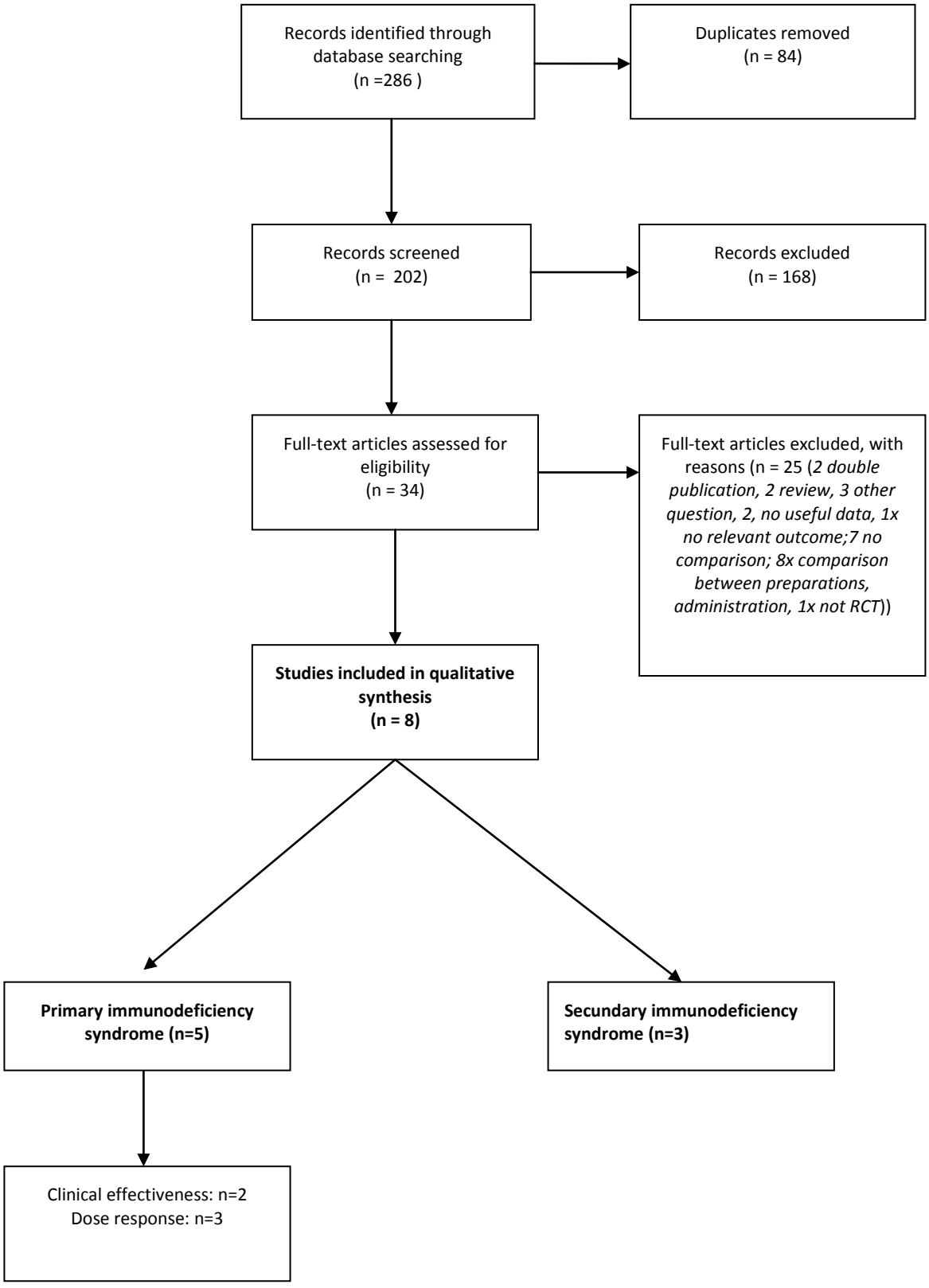
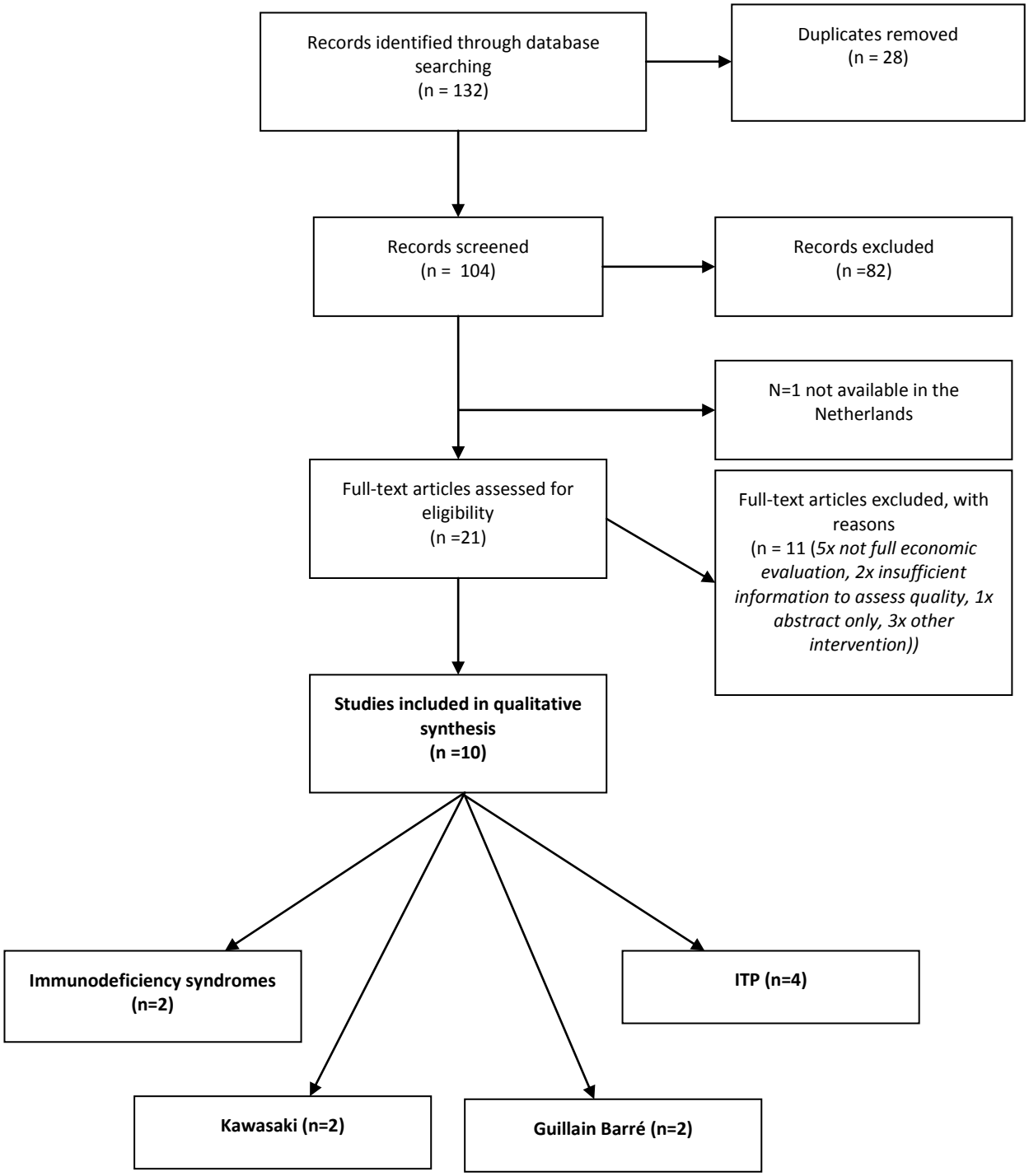


Figure 9.2.4 Flow Chart Economic Evaluations



9.3 Search strategies

9.3.1 Kawasaki disease

Source	Population	Intervention	limit	Number of hits
EMBASE	exp mucocutaneous lymph node syndrome/ kawasaki.mp. 1 or 2	exp immunoglobulin/iv [intravenous drug administration] exp immunoglobulin/ exp intravenous drug administration/ (intravenous adj2 immunoglobulin*).mp 2 and 3 (flebogamma* or gammagard or kiovig or nanogam or octagam).mp. 1 or 4 or 5 or 6	-	1608
			+ Dutch or English	1378
			+ RCT	27
Medline (ovid)	exp Mucocutaneous Lymph Node Syndrome/ kawasaki.mp. 1 or 2	Immunoglobulins, Intravenous/ Immunoglobulins/ Infusions, Intravenous/ 2 and 3 (flebogamma* or gammagard or kiovig or nanogam or octagam).mp. (intravenous adj2 immunoglobulin*).mp. 7. 1 or 4 or 5 or 6	-	695
			+ Dutch or English	608
			+ RCT	15
Cochrane (clinical trials)	MeSH descriptor Mucocutaneous Lymph Node Syndrome explode all trees (kawasaki):ti,ab,kw 1 or 2	MeSH descriptor Immunoglobulins, Intravenous explode all trees (intravenous immunoglobulins):ti,ab,kw (flebogamma* or gammagard or kiovig or nanogam or octagam):ti,ab,kw 1 OR 2 OR 3		37
			Clinical trials	28
All				70 hits of which 27 double -> **43 hits**

9.3.2 ITP

Source	Population	Intervention	limits	Number of hits
EMBASE	exp idiopathic thrombocytopenic purpura/ idiopathic thrombocytopenic purpura.mp. 1 or 2	exp immunoglobulin/iv [intravenous drug administration] exp immunoglobulin/ exp intravenous drug administration/ (intravenous adj2 immunoglobulin*).mp 2 and 3 (flebogamma* or gammagard or kiovig or nanogam or octagam).mp. 1 or 4 or 5 or 6	-	1828
			+ Dutch or English	1569
			+ RCT	39
Medline (ovid)	Purpura, Thrombocytopenic, Idiopathic/ idiopathic thrombocytopenic purpura.mp. 1 or 2	Immunoglobulins, Intravenous/ Immunoglobulins/ Infusions, Intravenous/ 2 and 3 (flebogamma* or gammagard or kiovig or nanogam or octagam).mp. (intravenous adj2 immunoglobulin*).mp. 7. 1 or 4 or 5 or 6	-	760
			+ Dutch or English	644
			+ RCT	33
Cochrane (clinical trials)	(idiopathic thrombocytopenic purpura):ti,ab,kw MeSH descriptor Purpura, Thrombocytopenic, Idiopathic explode 1 OR 2	MeSH descriptor Immunoglobulins, Intravenous explode all trees (intravenous immunoglobulins):ti,ab,kw (flebogamma* or gammagard or kiovig or nanogam or octagam):ti,ab,kw 1 OR 2 OR 3		39
			Clinical trials	33
All				105 hits of which 46 double -> **59**

9.3.3 Immunodeficiency syndromes

Source	Population	Intervention	limits	Number of hits
EMBASE (ovid)	exp humoral immune deficiency/ exp ataxia telangiectasia/ or exp common variable immunodeficiency/ or exp nijmegen breakage syndrome/ or exp severe combined immunodeficiency/ or exp wiskott aldrich syndrome/ exp acquired immune deficiency syndrome/ limit 3 to child <unspecified age> (common variable immunodeficiency or igg deficiency or immunodeficiency syndrome or immunologic deficiency syndrome).mp. 1 or 2 or 4 or 5	exp immunoglobulin/iv [intravenous drug administration] exp immunoglobulin/ exp intravenous drug administration/ (intravenous adj2 immunoglobulin*).mp 2 and 3 (flebogamma* or gammagard or kiovig or nanogam or octagam).mp. 1 or 4 or 5 or 6	-	1619
			+ Dutch or English	1420
			+ Clinical trial / RCT	191
			+ not "review" (publication type)	88
Medline (ovid)	exp agammaglobulinemia/ or exp ataxia telangiectasia/ or exp common variable immunodeficiency/ or exp digeorge syndrome/ or exp dysgammaglobulinemia/ or exp severe combined immunodeficiency/ or exp wiskott-aldrich syndrome/ HIV Infections/ limit 2 to "all child (0 to 18 years)" (common variable immunodeficiency or igg deficiency or agammaglobulinemia or immunodeficiency syndrome or immunologic deficiency syndrome*).mp. 1 or 3 or 4	Immunoglobulins, Intravenous/ Immunoglobulins/ Infusions, Intravenous/ 2 and 3 (flebogamma* or gammagard or kiovig or nanogam or octagam).mp. (intravenous adj2 immunoglobulin*).mp. 7. 1 or 4 or 5 or 6	-	1119
			+ Dutch or English	948
			+ Clinical trial / RCT	123
Cochrane (clinical trials)	MeSH descriptor Immunologic Deficiency Syndromes explode (common variable immunodeficiency or igg deficiency agammaglobulinemia or immunodeficiency syndrome or (immunologic deficiency syndrome*):ti,ab,kw (#1 OR #2)	MeSH descriptor Immunoglobulins, Intravenous explode all trees (intravenous immunoglobulins):ti,ab,kw (flebogamma* or gammagard or kiovig or nanogam or octagam):ti,ab,kw (#1 OR #2 OR #3)		85
			Clinical trials	75
All				286 hits, 84 double -> n=**202**

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer; ti,ab,kw = title, abstract, keywords

9.3.4 Economic evaluations

source	Population / intervention	Economic evaluations	limits	Number of hits
EMBASE	See above	exp "cost benefit analysis"/ or exp "cost effectiveness analysis"/ or exp "cost minimization analysis"/ or exp "cost utility analysis"/ (pharmacoeconomics or pharmacoeconomic evaluation or economic evaluation or cost effectiveness or cost utility or cost benefit).mp. 1 or 2	-	
			+ Dutch or English	N=71
Medline (ovid)	See above	exp Cost-Benefit Analysis/ (pharmacoeconomics or pharmacoeconomic evaluation or economic evaluation or cost effectiveness or cost utility or cost benefit).mp. 1 or 2	-	
			+ Dutch or English	N=25
Cochrane (NHS economic evaluations database)	See above	-		
			Economic evaluations	N=9
All				N=105 hits of which 23 double 82

(date 4 January 2011)

9.4 Summary tables clinical effectiveness and pharmacoeconomic evaluation, compared with alternative treatment

Table 9.4.1 Kawasaki disease

Reference /country	Population	No of patients	interventions	Follow up	Outcome measure	results
Furusho 1984 Japan	Kawasaki	85	**IVIg** 400 mg/kg/day, 5 days + **aspirin** (see below) **Aspirin** alone: 30-50 mg/kg/day during fever; 10-30 mg until reaction disappeared (Venilon)	Until 60 days after onset disease	# patients with coronary arterial lesion (ECG increase Ø with ≥150% or Ø ≥3 mm)	# patients with CAL, t=30 days ASA: 19/45=42% IVIg+ASA: 6/40 =15% ARR=0.27(95%CI[-0.08;0.44]); NNT=4 # patients with CAL, t=60 days ASA: 14/45=31% IVIg+ASA: 3/40 =7,5% ARR=0.24(95%CI[0.07;0.39]); NNT=4
Furusho 1991b*) Japan	kawasaki	151	IVIg 200 mg/kg/day, 5 days ASA IVIg + ASA (~Furusho 1984)	Until 30 days after onset disease	coronary arterial lesion (no definition)	# patients with CAL at day 30 IVIg : 4/51=7.8% ASA: 9/47=19.1% IVIg+ASA: 5/49=10.2% IVIg vs IVIg+ASA, ARR=0.24, NNT=4
Hashino 2001 Japan	Kawasaki, failed respons on 2x IVIg;	17	IVIg 1g/kg single dose Methylprednisolon pulse therapy iv 20mg/kg	7 days	Coronary artery abnormalities (ECG); (no definition)	# patients CAL IVIg: 5/8=63% MP:7/9=78% ARR=0.15(95%CI[-0.25;0.51]); NNT=6.7
Newburger 1986 USA	Kawasaki	168	IVIg 400 mg/kg/d 4 days + aspirin (see below) Aspirin alone 100 mg/kg/d every 6 hours 14 days, then 3-5 mg/kg/d	7 weeks	Coronary abnormalities (ECG) Ø ≥3 mm Ø ≥150% Ø adjacent vessel	#CA at t=2 weeks IVIg+ASA: 6/75=0.08 ASA: 18/78=0.23 # CA at t=7 weeks IVIg+ASA: 3/79=0.04 ASA: 14/79=0.18 ARR=0.14 (95%CI[0.04;0.24]); NNT=7

*) In Furusho 1991 the results from 3 trials are reported, including results Furusho 1984. Remaining two trials separately reported in this Table.
**) Ø = diameter coronary artery

Table 9.4.2 : Children with acute ITP

Reference	Population	Interventions	No. of patients	Follow up	Outcome measure	Results
Albayrak 1994, Turkey	Children acute ITP PC <25x10^9/L	IVIg 0.5g/kg for 5 days (sandoglulin) Oral MP 30 mg/kg for 7 days Oral MP 50 mg/kg for 7 days	57	30 days	# patients with Success (PC>100x10^9/L at t=2, 4, 6, 8, 14, 30 days)	Complete response (t= ?) IVIg: 15/19=79% MP30: 14/19 =74% MP50: 14/19 =74% $ARR_{IVIg\ vs\ MP30}$ =0.05 (95%CI[-0.21;0.32]) ; NNT=20
Ancona 2002	Children acute ITP PC <20x10^9/L	IVIg 1g/kg x 2 doses MP 30 mg/kg x 3 doses	77	4 weeks	# patients with PC >20x10^9/L	t=24 hour IVIg: 23/42=55% MP: 13/35=37% ARR=-0.18(95%CI[-0.37;0.05]) t=72 hour IVIg: 40/42=95% MP: 26/35=74% ARR=-0.18(95%CI[-0.38;-0.05] ; NNT=5.5
Blanchette 1993, Canada	Children acute ITP PC <20x10^9/L	IVIg 1 g/kg/day, for 2 days Prednisolone (4 mg/kg/d day 1-7; 2 mg/kg/d day 8-12; 1 mg/kg/d day 13-17) No treatment	53		% patients with PC >20x10^9/L 72 hour after randomization	IVIg: 17/19=93% Predn.: 14/18=79% No treatment: 9/17=58% $ARR_{IVIg\ vs\ no\ treatment}$ =-0.33 95%CI[-0.58;0.04]); NNT=3 $ARR_{IVIg\ vs\ prednisone}$=-0.12 (96%CI[-0.36;0.13]); NNT=8
Blanchette 1994, Canada Switzerland, USA	Children acute ITP PC <20x10^9/L	IVIg 1 g/kg/d for 2 days IVIg 0,8 g/kg once Prednisolone (4 mg/kg/d day 1-7; 2 mg/kg/d day 8-14; 1 mg/kg/d day 15-21) Anti D 25 µg/kg/d for 2 days	146		% patients with PC >20x10^9/L 72 hour after start treatment	IVIg 1g: 32/34=94% IVIg 0.8 g: 34/35=97% Anti D: 31/38=82% Predn: 31/38=97%
Erduran 2003, Turkey	Children acute ITP PC <20x10^9/L	IVIg 1 g/kg/d for 2 days (octagam) MP 30 mg/kg/d for 3 days; 20 mg/kg/d for 4 days	42	180 days	% patients with PC >20x10^9/L after 2 days	IVIg: 19/22= 86% MP: 10/20= 50% ARR=0.36 (95%CI[-0.08;0.58]; NNT=3 No differences in response at t=4,7, or 14 days

Table 9.4.2 : Children with acute ITP						
Reference	Population	Interventions	No. of patients	Follow up	Outcome measure	Results
					Time until PC >20x10^9/L	IVIg: mean 2.9 days MP: mean 4.1 days P<0.05
Imbach 1985 (lancet), Germany	Children acute ITP PC <30x10^9/L	IVIg 0.4 g/kg on 5 days; if non response in 14 days: other treatment Oral corticosteroids 60 mg/m2 daily for 21 days; if non response in 14 days: other treatment	94	360 days	% patients with response (PC >100x10^9/L % patients with PC >30x10^9/L	IVIg: 39/47=83% Corticosteroids: 36/47=77% ARR=0.06(95%CI[-0.10;0.23]); NNT=17 Only graphically reported After 20 days ca 60% in corticosteroids, 77% in IVIg treated patients
Özsoylu 1993, Turkey	Children acute ITP PC <50x10^9/L	MP 30 mg/kg/d for 3 days + 20 mg/kg/d for 4 days IVIg 0.4 g/kg/d on 5 days	20	6 months	# patients Complete remission (PC >150x10^9/L) at day 3, 7; week 2,3,4;month 3,6 # patients with PC >50x10^9/L in 3 days	T=3 days MP: 6/10=60% IVIg: 6/10=60% T=6 months MP: 9/10=90% IVIg: 6/8=75% ARR=-0.15(95%CI[-0.50;0.20]); NNT=-6.7 MP: 8/10=80% IVIg: 8/10=80%
Rosthoj 1996, Denmark	Children with acute ITP PC <20x10^9/L	IVIg 1 g/kg for 2 days MP (pulse) 30 mg/kg for 2 days	43	6 months	# patients with PC >20x10^9/L in 2 days Recurrence during follow up (PC<20x10^9/L)	IVIg:17/23=74% MP: 11/20=55% ARR=0.19(95%CI[-0.09;0.47]); NNT=5 IVIg:6/23=26% MP:8/20=40% ARR=0.14(95%CI[-0.14;0.42]); NNT=7
Shahgholi 2008, Iran	Children with acute ITP	Anti-D single dose 75 µg/kg IVIg (vigam-s) 1 g/kg for 2 days	81	14 days	Response 72 hour after initial treatment	IVIg 38/39=98% Anti-D 32/42 =76%

Table 9.4.2 : Children with acute ITP						
Reference	Population	Interventions	No. of patients	Follow up	Outcome measure	Results
	PC <20x10^9/L				(PC>20x10^9/L)	ARR=0.21 (95%CI[0.07;0.35]); NNT=4.8
Tarantino 2006, USA, Hong Kong	Children with acute ITP PC <20x10^9/L	Anti-D 50 µg/kg single dose Anti-D 75 µg/kg single dose IVIg 0.8 g/kg single dose All: retreatment if no response > 72h after initial treatment	105	7 days	% patients with response (PC>20x10^9/L)	Only graphically reported T=24 hour IVIg: ca. 78% Anti-D50: ca. 48%; ARR ~0.3; NNT ~ 3 Anti-D75:ca. 70%; ARR ~0.08; NNT ~13 T=7 days IVIg: ca. 90% Anti-D50: ca. 88% Anti-D75:ca. 97%

ARR = Absolute risk reduction
NNT= number needed to treat
MP= methylprednisolone
PC= platelet count

Table 9.4.3 Children with chronic ITP						
Reference	Population	Interventions	No. of patients	Follow up	Outcome measure	Results
El Alfy 2006a, Egypt	Children with chronic ITP PC <30x10^9/L	Anti-D iv bolus 50 µg/kg, repeated every 3-4 weeks IVIg (Vigam-S) 250 mg/kg for 2 days	34	28 days?	Response (PC>50x10^9/L or doubling baseline PC) at t=3,7,14,28 days % patients with PC >20x10^9/L after 3 days	T=3 days Anti-D:6/18=33.3% IVIg:6/16=37.5% ARR=0.04 (95%CI[-0.28;0.36]) ; NNT=25 T=28 days Anti-D:7/18=39% IVIg:6/16=38% ARR=0.014(95%CI[-0.31;0.34]) ; NNT=72 Anti-D: 14/18=78% IVIg:14/16=87% ARR=0.097(95%CI[-0.15;0.35]); NNT=10
El Alfy 2006b, Egypt	Children chronic ITP PC <10x10^9/L	Protocol 1 IVIg 0.8 g/kg once High doseMP 10 mg/kg/d for 3 days Protocol 2 IVIg 0.25 g/kg 2 days Anti-D 50 µg/kg Oral MP 4 mg/kg 4 days	 8 8 7 8 7	30 months	Number of severe bleeding/patient	IVIg 0.8g: 8.6±1.1 high dose MP:9.9±0.9 IVIg 0.25g:9.4±1.2 antiD:8.9±1.3 oral MP:10.1±0.9
Hedlund 2003 Sweden	Children with chronic ITP (PC <30x10^9/L or bleeding symptoms + PC <50x10^9/L)	IVIg 800 mg/kg first day + retreatment if PC<30x10^9/L on day3 Dexamethasone 0.6 mg/kg/d 4 days, every 28 days for 6 cycles	23	12 months	% patients with short term response (PC >30x10^9/L on day 3) % patients with long term response at least 3 months without therapy (partial; PC >30x10^9/L complete: PC>150x10$^{9/}$L)	IVIg: 7/8=87.5% Dexam: 8/12=67% ARR=0.21(95%CI[-0.14;0.56]) ; NNT=4.8 Partial response IVIg: 0/8=0% Dexa: 2/15=13% Complete response IVIg: 1/8=12.5% Dexa: 2/15=13% ARR 0.008 (95%CI[-0.35;0.27]); NNT=120

Table 9.4.4 Adults with ITP

Reference	Country	Population	Interventions	No. of patients	Follow up	Outcome measure	Results
Godeau 2002	France	Adults severe ITP;Platelet cnt <20x10^9/L	IVIg 0,7 g/kg/d day 1-3 MP 15 mg/kg/d day 103	122	12 months	Response at day 5 (PC>20x10^9/L)	IVIg: 50/56=89% MP:48/60=80% ARR=0.09 (95%CI[-0.05;0.22]); NNT=11
						severe haemorrhagic events	No patients died or had severe life threatening haemorrhagic events
Jacobs 1994	South Africa	Adults with symptomatic ITP	IVIg 400 mg/kg/d day 1-5 Oral prednisolone 1 mg/kg/d Combination of both treatments All: splenectomy if treatment failed (PC < 50x10^9/L or high doses or corticosteroids needed)	43	Min. 2 years	Complete response (PC>100x10^9/L)	IVIg: 3/13=23% Predn:5/17=29% combi: 1/13=7% ARR $_{\text{IVIg vs predn}}$ =-0.06(95%CI[-0.34;0.25]) NNT=16

Table 9.4.5 Primary immunodeficiency syndromes							
Reference/ country	Design	Population	No. of patients	Interventions	Duration	Outcome	Results
Abdou 2009 USA	Before-after comparison	Immunoglobulin G subclass deficiency and / or antibody deficiency; illness duration on average 7.2 years	10	IVIg (Gamunex 10%) 400 mg/kg, monthly	12 months pre-treatment; 12 months during treatment; 3 months post treatment	# infections /patient / year (Prestudy: medical records/ patient report; During treatment?)	Prestudy: mean=7.9 (sd=3.9) During treatment: mean=3.1 (sd=2.3) P<0.01 Post treatment: n=3, mean = 0.3 /patient /3 months
Gracia 2004 Spain	Before-after comparison	CVID, adults newly diagnosed; 9 of 24 patients also chronic pulmonary disease	24	IVIg (flebogamma 5%) 200-300 mg/kg weekly for 3 weeks + each 3 weeks thereafter; after 3 months dose increased if IgG<600 mg/dl or persisting infections	2 yrs before diagnosis + 2 yrs during IVIg treatment	Rate mild infections (=infections / patients-years) Bronchitis, otitis, sinusitis, fevers (questionnaires)	Before IVIg: mean =4.9 (sd 4.1) During IVIg: mean =2.2 (sd 2.0) P=0.01
						Rate serious infections (=infections / patients-years) Pneumonia, sepsis, meningitis, pulmonary abcess	Before IVIg : mean =0.48 (sd 0.45) During IVIg: mean 0.047 (sd 0.15) P=0.001
						Pulmonary functioning FEV1 % predicted	Before IVIg: 75 ±23 During IVIg: 78±20 N.S.

Table 9.4.6 Secondary immunodeficiency syndromes						
Reference/ country	Population	No. of patients	Interventions	duration	Outcome	results
Cooperative group CLL 1988 Europe + North America	chronic lymphocytic leukemia, at risk for infections (IgG <50% of lower limit of normal or history of serious infections since inset disease)	81	IVIg 400 mg/kg every 3 weeks Placebo	1 year	# bacterial Infections (Results of culture; If no etiologic agent: based on clinical grounds)	# infections /patient IVIg: 23/41 = 0.56 / patient Placebo: 42/40 = 1.05 / patient P=0.01
					# serious bacterial infections *(Requiring treatment)*	IVIg: 18/41 =0.44 /patient Placebo: 31/40=0.78/patient
					# patients with infections	IVIg: 28/41 =68% Placebo: 29/40=72% ARR=0.042 (95%CI[-0.15;0.23]) NNT=23
Baker 1992 USA	low birth weight neonates (500-1750 g; premature; 3-7 days old)	588	IVIg (gammagard) 500 mg/kg on day 1, after 1 week, then every 14 days until n=5 infusions / discharge Placebo (frequency ~IVIg)	56 days	# patients with at least one proven infections (1 or more clinical finding neonatal sepsis; a culture + bacterial or fungal pathogen / isolated pathogen)	IVIg: 70 / 287=24% Placebo: 104 / 297=35% RR (corrected)= 0.6 (95%CI 0.4-0.8)
Boughton 1995 UK	chronic lymphocytic leukemia and secondary hypogammaglobulinaemia; history of 2 or more infections preceding 12 months; serum IgG <5.5g/L	42	IVIg (sandoglobulin) 18 g every 3 weeks (if > 3 infections = treatment failure, then 24 g IVIg) Placebo (if > 3 infections = treatment failure, then 18 g IVIg)	12 months	Serious infections (Life threatening infections which require hospital admission for iv antibiotics)	# patients with ≥ 3 infections IVIg : 7/24 = 29% Placebo : 11/18 = 61% # patients with ≥ 3 serious infections IVIg : 5/24 = 21% Placebo : 10/18 = 56% ARR=0.35(95%CI[0.05;0.58]) ; NNT=2.9

Table 9.4.7 Economic evaluations for IVIg versus alternative treatment								
Reference/ country	Design/ Type EE	Population	Interventions	Perspective / time horizon	Cost categories	Results	Sensitivity analysis	Discounting
Kawasaki								
Klassen 1993 Canada	Decision-analytic model CEA	Children with kawasaki	Aspirin IVIg low dose (400mg/kg/day 4 days) IVIg high dose (2g/kg once)	societal / Until 7 weeks after diagnosis	Hospitalization, clinical visits, laboratory costs, IVIg, time off work Charges+ internal cost model Canadian $ (1992)	Costs ($) per 100 patients Aspirin: $721,600 IVIg LD: $ 516,400 IVIg HD: $ 389,200 Effectiveness, coronary artery dilation (# CAD per 100 patients) Aspirin: 18 IVIg LD: 6 IVIg HD: 4 IVIg HD dominant	+	
ITP								
Blackhouse 2008, Canada	Markov model CUA	Children with acute ITP (PC<20x10^9/L)	Observation IVIg single dose 0.8g/kg Anti-D single dose 75 µg/kg Prednisone 4 mg/kg, 4 days IV methylprednisolone 30 mg/kg, 3 days	Health care/ lifetime	Hospital related costs, physician fees, hospital administered drugs, drugs covered by provincial formularies 2009 Canadian $	Total costs ($) Prednisone:1,844 Methylprednisolone: 1,969 Anti-D: 1,940 IVIg: 2,080 Observation: 2,820 QALYs Predn: 17.6915 MPredn: 17.6919 antiD: 17.6933 IVIg: 17.6958 Observ: 17.6856 ICER anti-D vs predn. $53,333/QALY ICER IVIg vs predn $56,000/QALY	+	
Hollenberg 1988, USA	Markov model	Child with ITP at least 6	Initially IVIg 2g/kg once+1g/kg	Health care/ 10 years	Diagnostic test, prescriptions, ancillary	Costs IVIg: 20,964	+	

Table 9.4.7 Economic evaluations for IVIg versus alternative treatment								
Reference/ country	Design/ Type EE	Population	Interventions	Perspective / time horizon	Cost categories	Results	Sensitivity analysis	Discounting
	CEA	months	maintenance; when not cured splenectomy Initially splenectomy, when not cured VIG		products (blood / IVIg), hospitalizations Standard unit costs; 2003 US$	Splenectomy: 16,913 % alive after 10 years IVIg: 98.63% Splenectomy: 97.89% = $540,130 per additional life saved		
O'Brien 2007, USA	Decision-analytical model CUA	Children with acute ITP and platelet count <20x10^9/L	Prednisone 4mg/kg, 4 days IVIg 0.8 g/kg, once Anti-D 75µg/kg, once MDMP IV, 30 mg/kg, 3 days	Societal/ short term	Drugs, hospitalization, intracranial hemorrhage, infusion, lost parental wages both costs and prices; 2005 US$	Total cost / child ($) Prednisone: 786 IVIg: 2492 Anti-D: 2035 MDMP IV:1346 Utility lost (QALD) Prednisone: -0.33 IVIg: -0.308 Anti-D: -0.166 MDMP:-0.496 IVIg dominated by anti-D MDMP dominated by prednisone Anti-D vs prednisone: $7616/QALD	+	
Xie 2009, Canada	Markov model CUA	Adults with chronic ITP (PC<20x10^9/L)	IVIg 1g/kg/day for 2 days Oral prednisone 1 mg/kg/day for a month	Health care /lifetime	Drugs, splenectomy 2007 canadian $	Mean total costs ($) IVIg: 18,027 Prednisone: 9,947 QALYs IVIg:9.884 Prednisone:9.877 Incremental $/QALY	+	

Table 9.4.7 Economic evaluations for IVIg versus alternative treatment								
Reference/ country	Design/ Type EE	Population	Interventions	Perspective / time horizon	Cost categories	Results	Sensitivity analysis	Discounting
						$1,15 million / QALY		
Guillain Barre								
Nagpal 1999, Canada	Decision analysis; CMA	Guillain Barre	IVIg 0.4 g/kg, 5 days Plasma exchange 3,5 L/exchange; 5 times	Health care/ 48 weeks	Professional costs, overhead, capital costs 1997 US $ Cost prices and charges	Total costs per patient ($) IVIg: 10,165 PE: 6,204 Δ = $3,961	+	
Tsai 2007, Taiwan	Retrospective; review medical records (n=17); CMA	Guillain Barre	IVIg 0.4 g/kg, 5 days Plasma exchange 40-50 ml/kg, 4-8 times	Health care/ until patients recovered to walk =2-10 weeks	Hospitalization, drug costs, procedures costs, costs infections, complications New Taiwan 2005 $	Mean total costs $ (SEM) PE: 517,357 (114,813) IVIg: 360,824 (137,228) Δ= 156,533 New Taiwan $ (≈ 4,884 US$)	-	
Immunodeficiency syndromes								
Weeks 1991, USA	Decision analytic model CUA	Chronic lymphocytic leukemia at high risk for infection	IVIg 400 mg/kg every 3 weeks for 1 yr No IVIg	Societal/ life time	Treatment (incl. IVIg, preparation, administering), , adverse reactions, infections Cost prices 1989 US$	Marginal costs ($) IVIg Versus no IVIg = $13,985 Additional QALYs IVIg versus no IVIg = 0.0023 Ratio: $6 million per QALY	+	+

9.5 Summary tables clinical effectiveness and pharmacoeconomic evaluation, different doses

Table 9.5.1 Kawasaki disease

Reference	population	No of patients	interventions	Follow up	Outcome measure	results
Barron 1990 USA, Canada	Kawasaki disease Age: 9-11 months	44	**IVIg** 1 g/kg, single dose **IVIg** 400 mg/kg/day, 4 days (gammagard) Both arms: + aspirin	1 year	#dilated coronary artery (ECG; Ø ≥4 mm) # aneurysms (ECG: local increase Ø with ≥150%)**)	# aneurysms (t=day 15-21) IVIg 1 g/kg: 2/22=0.09 IVIg 400mg/kg: 1/22=0.045 ARR=0.045 (95%CI[-0.10;0.19]) NNT=22 # aneurysms (t= 1 year): IVIg 1 g/kg: 0/22=0 IVIg 400mg/kg: 1/22=0.045 ARR=0.045 (95%CI[-0.07;0.16]) NNT=22 No dilated coronary arteries without aneurysms
Furusho 1991*) Japan	Kawasaki	145	IVIg 100mg/kg/day, 5days IVIg 200 mg/kg/day, 5 days IVIg 400 mg/kg/day, 5 days All treated with ASA (~Furusho 1984)	Until 30 days after onset disease	Coronary abnormalities; no definition	# patients with CAL at day 30 IVIg 100mg: 6/40=0.14 IVIg 200mg: 3/51=0.06 IVIg 400mg: 6/53=0.11 ARR $_{200 \text{ vs } 100 \text{ mg}}$ 0.09 (95%CI[-0.04;0.22]) NNT=11
Liang 2004 Taiwan	Kawasaki	120	Gamimune 400 mg/kg/day 5 days Gamimune 2g/kg once Intraglobin F 400 mg/kg/day 5 days Intraglobin F 2g/kg once	long term follow up, but not defined	Coronary abnormalities (CA) ECG Ø ≥3 mm (age<5 yrs) Ø ≥4 mm (age≥5 yrs) Ø ≥150% Ø adjacent vessel	CA at long term follow up Gamimune 400 mg: 4/33=0.12 Gamimune 2g: 6/47=0.13 Intraglobin F 400 mg: 0/10=0 Intraglobin F 2g: 0/10=0
Newburger 1991, USA	Kawasaki	549	IVIg 400 mg/kg/day, 4 days+aspirin IVIg 2g/kg once + aspirin		Coronary abnormalities Ø ≥3 mm (age<5 yrs) Ø ≥4 mm (age≥5 yrs) Ø ≥150% Ø adjacent vessel	# aneurysms (t=2 weeks) IVIg 400: 24/263=0.09 IVIg 2G: 12/260=0.046 ARR=0.045(95%CI[0.002;0.009]); NNT=22

Table 9.5.1 Kawasaki disease						
Reference	population	No of patients	interventions	Follow up	Outcome measure	results
						# aneurysms (t=7 weeks) IVIg 400: 19/263=0.07 IVIg 2G: 10/257=0.04 ARR=0.038 (95%CI[-0.005;0.007]); NNT=30
Sakata 2007 Japan	Kawasaki; Age: 2-101 months	109	IVIg 2g/kg once; if resistance 2g/kg repeated IVIg 1g/kg once; if resistance 1g/kg repeated; if still resistance 2g/kg	1 month within onset disease	Coronary artery Aneurysm Ø ≥4 mm (age≥5 yrs) Ø ≥150% Ø coronary orifice	IVIg 2g: 1/54=0.02 IVIg 1g: 4/55=0.07 ARR=0.05(95%CI[-0.02;0.13]); NNT=18
Sato 1999 Japan	Kawasaki; harara score ≥ 4 (scheme for selecting patients for IVIg treatment)	145	IVIg 2 g/kg once IVIg 400 mg/kg/day, 5 days	7 days	Coronary artery Aneurysm Ø ≥3 mm (age<5 yrs) Ø ≥4 mm (age≥5 yrs) Ø ≥150% Ø adjacent vessel	# patients with CAA IVIg 2g: 1/72=0.014 IVIg 400 mg: 7/73=0.096 ARR=0.08(95%CI[0.009;0.15]); NNT=12

Table 9.5.2 Children with ITP

Reference	Population	Interventions	No. of patients	Follow up	Outcome measure	Results	Remarks
Benesch 2003	Children acute ITP PC <20x10^9/L	IVIg 1 g/kg/day, for 2 days IVIg 0.3 g/kg/day, for 2 days	34	360 days	# patients with response (PC >20x10^9/L) 72 hour after 1st IVIg	IVIg 1 g: 15/17=88.2% IVIg 0.3g: 13/17= 76.5% ARR=0.12(95%CI[-0.14;0.37]) NNT=8.3	
Warrier 1997, USA	Children with ITP, both acute and chronic PC <30x10^9/L or PC<50x10^9/L and bleeding	Child 5-12 yrs: IVIg 400 mg/kg/d, 2 days IVIg 1 g/kg/d, 2 days Child <5 yrs: 250 mg/kg/d, 2 days 500 mg/kg/d, 2 days If no response, booster within 10 days	24	3 months	% patients with response (PC>30x10^9/L) within 10 days Duration response to initial infusion	250 mg: 6/6=100% 400 mg: 6/6=100% 500 mg: 5/6=83% 1 g: 6/6=100% Low dose (250,400 or 500mg): median 85 days (range 2-95) High dose: median 86 days (range 13-92)	Pooled data from 2 RCTs

Table 9.5.3 Adults with ITP

Reference	population	interventions	No. of patients	Follow up	Outcome measure	results
Godeau 1993 France	Adults chronic ITP PC <50x10^9/L	IVIg 1 g/kg, for 2 days + reinfusions if PC <50x10^9/L IVIg 2g/kg for 2 days + reinfusions if PC <50x10^9/L	18	5-75 months	% patients with response (PC>150x10^9/L) after 1st IVIg infusion	IVIg 1g: 7/9=0.78 IVIg 2g: 6/9=0.67 ARR=0.11 (95%CI[-0.30;0.50]) NNT=9
					% patients with response (PC>150x10^9/L) 90 days after last IVIg booster	IVIg 1g: 1/9=0.11 IVIg 2g: 4/9=0.44 ARR=0.33 (95%CI[-0.05;0.72]) NNT=3
Godeau 1999 France	Adults ITP PC<50x10^9/L	IVIg 0.5g/kg initial + reinfusion non responders day 4+5 (total 1.5 g/kg) IVIg 1 g/kg initial + reinfusion non responders day 4+5 (total 1 g/kg)	37	8 days	% patients with response (PC>80x10^9/L) at day 4	IVIg 0,5g:4/19=0.21 IVIg 1g: 12/18=0.67 ARR=0.46(95%CI[0.17;0.74]) NNT=2
					% patients with response (PC>80x10^9/L) at day 8	IVIg 0,5 g:15/17=0.88 IVIg 1g:14/18=0.78 ARR=0.10 (95%CI[-0.14;0.35]) NNT=10

Table **9.5.4 Primary immunodeficiency syndromes** Reference/ country	design	Population	No. of patients	Interventions	**D**uration	Outcome	Results	
Eijkhout 2001 NL	Cross over	Adults + children with primary hypogammaglobulinemia IgG Ca 6.4 g/L	43	standard (300 (adults) or 400 mg/kg (children)) high dose (600 (adults) or 800 mg/kg(children))	2x9 months + 3 months wash out	# immunodef related infections (judgement physician) /patient	Standard: mean 3.5 high dose: mean 2.5 Δ 1.1 (95%CI 0.4-1.8)	
						# patients with infections	standard: 37/41=90% high dose: 36/43=84% ARR = 0.06 (95%CI[-0.09;0.21] NNT=16.7	
Pruzanski 1996 Canada	Cross over	Adults with CVID	21	200 mg/kg, 400 mg/kg, 600 mg/kg) Iveegam, monthly infusions	Treatment 6 months each dose; follow up 18-65 months	# infections / month	Mean # infections / month 200 mg/kg: 2.43 400 mg/kg: 2.23 600 mg/kg): 2.58	Blinded No wash out
Roifman 1987 Canada	Cross over	antibody deficiency (CVID, XLA) + chronic pulmonary disease	12	0.6 g /kg 0.2 g/kg	2x 6 months	# episodes of acute infections	# mild infections / patient 0.6 g /kg: 19/12=1.6 0.2 g/kg: 24/12=2.0	no wash-out
						Lung indices	"FEV1 values were significantly higher during high dose phase than during low-dose phase"	

Table 9.5.5 Economic evaluations for comparison of different doses							
Reference/ country	Design/ Type EE	Population	Interventions	Perspective /Time horizon	Cost categories	Results	Sensitivity analysis
Högy 2005 Germany	Cost-minimization	Primary immunodeficiencies	IVIg 0.4 g/kg monthly dose SCIG 0.4 g/kg monthly dose (weekly infusion)	Health insurance/ 1 year	Medications, infusion pump use, infusion materials, treatment by physician and diagnostic procedures in outpatient / private practice, sick leave for children's caregivers Charges Euro's 2003	Adults: IVIg: € 31,027 SCIG: € 14,893 Δ=16,133 Children: IVIg: €17,329 SCIG: € 8,659 Δ=8,670	+
Sato 1999 Japan	Cost analysis alongside RCT	Kawasaki	IVIg 2g/kg once IVIg 400 mg/kg/d, 5 days	Health care/ ? 7 days	Hospitalization, IVIg, aspirin, lab. examinations, diagnostic procedures Charges US$	IVIg 2g: $5048 ± 992 IVIg 400 mg: $5568 ± 1336 Coronary artery complications IVIg 2 g: 1/72=1.4% IVIg 400 mg: 7/73 = 9.6%	-

9.6 Summary adverse events IVIg

Table 9.6.1. Adverse events Kawasaki disease

Reference	Population	Number of adverse events (IVIg)	Number of patients on IVIg / infusions
Furusho 1984	kawasaki	1x chills and fever	N=40 patients
Furusho 1991	Kawasaki	"no severe side effects"	
Newburger 1986	kawasaki	No serious side effects; Mild congestive heart failure 3x; 1x sepsis; 1x rash + fever with lymphadenopathy and splenomegaly	N=84 patients

Table 9.6.2. Adverse events ITP

Reference	Population	Number of adverse events (IVIg)	Number of patients on IVIg / infusions
Albayrak 1994	Children with acute ITP	1x mild fever, vomiting, neck stiffness 2x headache	N=19 patients
Ancona 2002	Children with acute ITP	-	
Blanchette 1993	Children with acute ITP	75% nausea, vomiting, headache, fever	N=19 patients
Blanchette 1994	Children with acute ITP	17% fever, nausea, vomiting, headache	N=69 patients
Erduran 2003	Children with acute ITP	5x fever, headache and vomiting 1x macular eruption No hemolysis or anaphylaxis	N= 22 patients
Imbach 1985	Children with acute ITP	Headache, fever, vomiting, vertigo; 14x	N=474 infusions
Rosthoj 1996	Children with acute ITP	Headache, fever, vomiting, 14x; 1x prolonged fever, headache, spinal fluid pleocytosis	N=23 patients
Shahgholi 2008	Children with acute ITP	Mild to moderate; transient fever, vomiting, headache	N=39 patients
Tarantino 2006	Children with acute ITP	Headache,chills, fever	
El Alfy2006	Children with chronic ITP	Mild to severe toxicities; 1x aseptic meningitis	N=15 patients
Hedlund 2003	Children with chronic ITP	70% headache	N=8 patients
Godeau 2002	Adults with ITP	14x, mainly headache and fever; in 1 patients episode of convulsions 1x deep venous thrombosis complicated by pulmonary embolism	N=56 patients

Table 9.6.3. Adverse events Immunodeficiency syndromes

Reference	Population	Number of adverse events (IVIg)	Number of patients on IVIg / infusions
Furusho 1984	kawasaki	1x chills and fever	N=40 patients
Furusho 1991	Kawasaki	"no severe side effects"	
Newburger 1986	kawasaki	No serious side effects; Mild congestive heart failure 3x; 1x sepsis; 1x rash + fever with lymphadenopathy and splenomegaly	N=84 patients

9.7 Levels of evidence

Table 9.7.1. Kawasaki Disease; levels of evidence					
Reference	**Randomization**	**Blinding patient**	**Blinding analyst**	**Groups comparable at baseline**	**Completeness follow up**
Furusho 1984	+	-	-	+	+
Furusho 1991	+	-	-	±	+
Hashino 2001	+	-	-	?	+
Newburger 1986	+	-	+	+	+

Table 9.7.2. Idiopathic Thrombocytopenic Purpura; levels of evidence					
Reference	**Randomization**	**Blinding patient**	**Blinding analyst**	**Groups comparable at baseline**	**Completeness follow up**
Albayrak 1994	+	-	-	?	+
Ancona 2002	+	-	-	+	?
Blanchette 1993	+	-	-	±	+
Blanchette 1994	+	-	-	±	+
Erduran 2003	+	-	-	+	+
Imbach 1985	+	-	-	+	-
Ozsoylu 1993	+	-	-	+	+
Rosthoj 1996	+	-	-	±	+
Shahgholi 2008	+	-	-	+	+
Tarantino 2006	+	-	-	+	?
El Alfy 2006	+	?	?	?	?
Hedlund 2003	+	-	-	±	±
Godeau 2002	+	-	-	+	+
Jacobs 1994	+	-	-	?	+

Table 9.7.3. Immunodeficiency syndromes; levels of evidence					
Reference	**Randomization**	**Blinding patient**	**Blinding analyst**	**Groups comparable at baseline**	**Completeness follow up**
Abdou 2009	-	-	-	Not applicable	+
Gracia 2004	-	-	-	Not applicable	+
Cooperative group CLL 1988	+	+	+	+	+
Baker 1992	+	+	+	+	+
Boughton 1995	+	+	?	+	?