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Evidence for the Use of Intravenous Immunoglobulins—A Review of the Literature

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Abstract Intravenous immunoglobulins (IVIg) were first introduced in the middle of the twentieth century for the treatment of primary immunodeficiencies. In 1981, Paul Imbach noticed an improvement of immune-mediated thrombocytopenia, in patients receiving IVIg for immunodeficiencies. This opened a new era for the treatment of autoimmune conditions with IVIg. Since then, IVIg has become an important treatment option in a wide spectrum of diseases, including autoimmune and acute inflammatory conditions, most of them off-label (not included in the US Food and Drug Administration recommendation). A panel of immunologists and internists with experience in IVIg therapy reviewed the medical literature for published data concerning treatment with IVIg. The quality of evidence was assessed, and a summary of the available relevant literature in each disease was given. To our knowledge, this is the first all-inclusive comprehensive review, developed to assist the clinician when considering the use of IVIg in autoimmune diseases, immune deficiencies, and other conditions.

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Abbreviations

y/o	year old
IVIg	intravenous immunoglobulins
RCT	randomized controlled trial
IFN	interferon
CS	corticosteroids
BMT	bone marrow transplantation
HCV	hepatitis C virus
PD	prednisone
CP	cyclophosphamide
CNS	central nervous system
MPGN	membranous-proliferative glomerulonephritis
MP	methylprednisolone
PP	plasmapheresis
LMWH	low-molecular-weight heparin
LDA	low-dose aspirin
NYHA	New York Heart Association
EF	ejection fraction
CHF	congestive heart failure
DCM	dilated cardiomyopathy

PPCM	peripartum cardiomyopathy
CIP	chronic idiopathic pericarditis
NLE	neonatal lupus erythematosus
MMP	mucous membrane pemphigoid
EDSS	expanded disability status scale
VLCFA	very-long-chain fatty acids
GTOE	glycerol trioleate/erucic supplementation
INCAT	inflammatory neuropathy cause and treatment disability score
MCV	motor conduction velocities
CMAP	compound muscle action potential
MRC scale	medical research council
RRMS	relapsing–remitting multiple sclerosis
Ref	reference
MTX	methotrexate
MMF	mycophenolate mofetil
CAA	coronary artery aneurysm
CRP	C-reactive protein

Introduction

Intravenous immunoglobulins (IVIg) are gamma globulins purified from the pooled plasma of thousands of donors, typically containing more than 95% of unmodified immunoglobulin G (IgG) and only trace amounts of IgA or IgM. Immune globulin products from human plasma were first used in 1952 to treat immune deficiencies. About 30 years later, Paul Imbach observed that patients with immune thrombocytopenia and agammaglobulinemia receiving immunoglobulins as immune replacement therapy recovered from their thrombocytopenia [1]. This was the first observation to suggest treatment of autoimmune diseases with IVIg. Later on, the ability to administer large quantities of immunoglobulin intravenously was gained owing to technological advances, among them the improvement in plasma fractionation. As a result, IVIg slowly became an important treatment option in a number of diseases beyond primary immune deficiencies, including autoimmune and acute inflammatory conditions, most of them off-label indications. These indications have crossed over into almost every medical specialty. The US Food and Drug Administration (FDA) has approved the use of IVIg for the following six conditions: primary immunodeficiencies, immune thrombocytopenic purpura (ITP), Kawasaki disease, hematopoietic stem cell transplantation, chronic B cell lymphocytic leukemia, and pediatric HIV. Many off-label indications have emerged; some of these new indications for IVIg are based on solid clinical evidence; others are based on relatively few data or anecdotal reports (case series, case reports). This lack of firm evidence is due to the difficulty in performing appropriate clinical trials in diseases with low prevalence. There is a need for an evidence-based guidance for the use of IVIg to help improve patient care consistency.

Another issue is the efficacy of different preparations of IVIg. The FDA has recommended the use of particular preparations of IVIg for each labeled indication in accordance to the specific preparation used to demonstrate a beneficial effect. Of course, there is selection bias since generally only a few preparations have been tested for a given disease. This is in recognition of the difficulty to reproduce the properties of an IVIg preparation, which may vary from one manufacturer to the other due to differences in the donor population, number of donors, period of donation, production methods, virus/bacteria inactivation methods, etc. IVIg properties may also vary from batch to batch made by the same manufacturer, complicating homogeneity even more.

Possible mechanisms of action of IVIg in autoimmune and inflammatory diseases are: intact Fc-dependent blockage of IgG (as in ITP), inhibition of membrane attack complexes (C5b-C9) and activated components C3b and C4b (as in Kawasaki's disease), and anti-idiotypes against autoantibodies (as in acquired hemophilia due to autoantibodies against factor VIII). IVIg also contains various cytokines and natural antibodies that may act against pathogens, altered molecules, cells, autoreactive B cell clones, and tumors.

Methods

A panel of immunologists and internists with experience in IVIg therapy reviewed the medical literature indexed in PubMed using specific terms for each specific disease/condition AND ("IVIg" OR "IgIV" OR "Intravenous Immunoglobuli*" OR "gamma globuli*"). There was no limitation on language, year of publication, or publication status. We used all clinical data ranging from multicentered randomized controlled trials (RCT) and meta-analysis to case reports. From each article, we extracted details of the study design, number of patients, type of intervention including the dose and IVIg preparation used (if mentioned), and response to treatment. The relevant data were summarized in a hierarchical manner according to the study design and number of participants. When evidence was based on higher level of evidence studies, such as RCTs, lower levels of evidence studies (such as case control studies) were disregarded. Specific diseases were classified in tables according to the specialty they belong to and are followed by a short summary of recommendations, including the level of evidence and the strength of recommendation, as assessed by known guidelines (Table 1) [2]. To our knowledge, this is the first comprehensive review which summarizes all up-to-date published data regarding the

Table 1 Recommendation guidelines [2]

Level of evidence
A: more than one randomized controlled trial (RCT)/meta-analysis
B: a single RCT or well-designed nonrandomized trial like prospective observational registries (case–controls, cohorts).
C: expert consensus: this includes case reports and retrospective series; here, the expert decides based on his experience
Strength of recommendation
Class I: conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective
Class II: conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of performing the procedure/therapy
Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb: usefulness/efficacy is less well established by evidence/opinion
Class III: conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful

usage of IVIg in autoimmune diseases, immune deficiencies, and other indications.

Results

The tables below summarize the clinical data gathered from studies dealing with IVIg treatment for different conditions. Each table is followed by our evidence-based recommendations for the usage of IVIg.

The following conditions refer to (Table 2).

SLE—systemic flare-up

Level of evidence B Systemic lupus erythematosus (SLE) is a multisystemic disease with various manifestations. There is some evidence that IVIg, given in patients without an increased risk for thromboembolic events or renal failure, is a safe and beneficial adjunct therapy for SLE patients with systemic flare-ups who are resistant to or refuse conventional treatment (*strength of recommendation IIa*).

Lupus myocarditis

Level of evidence C Lupus myocarditis is an uncommon but severe complication of SLE. There is no consensus on the specific treatment of SLE myocarditis. Most reports describe treatment with high-dose corticosteroids (CS), followed by either cyclophosphamide or azathioprine, in addition to conventional treatment for heart failure. There is little evidence that IVIg is effective when immunosuppressive therapy fails (*strength of recommendation IIa*).

SLE and thrombocytopenia

Level of evidence B As with the treatment of ITP, IVIg seems to be useful in managing the bleeding complications of patients with lupus-associated thrombocytopenia (*strength of recommendation I*).

Subacute cutaneous lupus erythematosus

Level of evidence C Standard therapy for subacute cutaneous lupus erythematosus (SCLE) includes CS (topical, intralesional, systemic), antimalarials, and other immunosuppressive agents**.** IVIg may be considered in refractory cases, but more study should be done (*strength of recommendation IIa*).

Level of evidence C Kikuchi, also called histiocytic necrotizing lymphadenitis, is a rare benign disease. There is little evidence that treatment with IVIg is superior to other anti-inflammatory treatments (*strength of recommendation IIa*).

Adult still disease

Level of recommendation C Giving the fact that adult still disease responds to CS and biological and anti-tumor necrosis factor (TNF) treatment, there is low-level evidence that IVIg has an additional benefit for treatment of this disease (*strength of recommendation IIa*).

Systemic vasculitis (including GA and MPA)

Level of recommendation B Immunosuppression with CSs and cytotoxic agents should be used in systemic vasculitis before considering IVIg. There is however some evidence that IVIg might be useful and therefore in refractory cases it may be worth to try (*strength of recommendation IIa*).

Churg–Strauss syndrome

Level of evidence B CSS is a rare disease. The initial management of CSS consists of high doses of CS. For patients with severe disease or those who are unresponsive to CS, treatment with IVIg was warranted (*strength of recommendation IIa*).

Hepatitis C virus with autoimmune features

Level of evidence B Infection with hepatitis C virus (HCV) may be associated with a variety of autoimmune phenomena causing a therapeutic dilemma for treatment with interferon alpha (IFN alpha), which stimulates autoimmune symptoms, or with CS, which may lead to an increase of viral load. Treatment with IVIg may act synergistically with

Table 2 The use of intravenous immunoglobulins in rheumatologic diseases

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
Systemic lupus erythematosus (SLE) systemic flare-up	[37]	Controlled trial	IVIg 0.4 g/kg for 5 days, between 1 and 8 monthly courses (mean 5; ISIVEN-Instituto Sierovaccinogeno, Italiano ISI SpA.)	20 patients with active SLE	Beneficial clinical response in 17 out of 20 pts ($p<0.0001$); especially in arthritis, fever, thrombocytopenia, and CNS lupus
	[38]	Uncontrolled multicenter trial	IVIg 0.4 g/kg for 5 days	13 females with acute exacerbation of SLE	After IVIg treatment, the modified European Consensus Lupus Activity Measurement (mECLAM) declined in 12 out of 13 pts by ≥3 points ($p=0.0002$)
	[39]	Uncontrolled trial	30 g of sulfonated IVIg preparation on days 1–4 and 21–24	12 patients with mild-to-moderate active SLE	Within 6 weeks, the mean Systemic Lupus Activity Measure (SLAM) score declined from 7.3 to 5.25 ($p<0.01$); in a minority, this effect lasted 5–12 months
	[20]	Retrospective trial	Review of medical records of patients with SLE that were treated with low-dose IVIg (0.5 g/kg) for several courses	62 patients	Clinical improvement in most disease manifestations including pericarditis; not including thrombocytopenia and alopecia
Lupus myocarditis	[40]	Case series	IVIg 0.4 g/kg per day for 5 days, in addition to CP or MMF (given to 2 patients)	3 patients with lupus myocarditis and severe deterioration in contractile functions; high-dose CS had little effect	Marked clinical improvement; decreased need for CS
	[41]	Case report	IVIg 0.4 g/kg per day for 5 days	1 patient with lupus myocarditis refractory to CS	Marked improvement of severe cardiac dysfunction after one course of IVIg
SLE and thrombocytopenia	[42]	Retrospective trial	IVIg 2 g/kg for 2 to 5 days	31 patients with severe thrombocytopenia associated with SLE refractory to PD treatment	A transient response was observed in 20 patients (65%); no sustained response was observed
Subacute cutaneous lupus erythematosus (SCLE)	[43]	Case series	IVIg with starting doses of 1 g/kg for 2 days, followed by 0.4 g/kg monthly, until disease resolution or for 6 months	12 patients with resistant SCLE	5 patients had complete or near-complete clearing of their skin disease; two had partial improvement and 3 had limited responses
	[44]	Case series	IVIg 0.3 g/kg per day for 5 days each month for 12 months	7 patients with skin disease (5 had systemic LE; two had SCLE)	IVIg was unable to control cutaneous disease efficiently
	[45]	Case series	IVIg	3 patients with SCLE resistant to topical and systemic therapy	Good response
	[46]	Case report	IVIg 2 g/kg monthly	30-year-old woman with SCLE	Good response
Various manifestations of SLE	[47]	Various case reports	Different IVIg preparations and doses	26 patients with specific lupus manifestations refractory to standard Tx.: autoimmune hemolytic anemia (2), acquired factor VIII inhibitors (2), acquired von Willebrand disease (2), pure red cell aplasia(3), pancytopenia (1), myelofibrosis (1), pneumonitis (2), pleural effusion (1), pericarditis (2), myocarditis (2), CNS	Improvement of SLE-related condition

Table 2 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
				lupus (6), peripheral neuropathy (1), polyradiculoneuropathy (1)	
For lupus nephritis, see kidney section					
For Kawasaki disease, see cardiology section					
Kikuchi Disease	[48]	Case report	IVIg 0.4 g/kg per day for 3 days	A 35-year-old patient with Kikuchi, refractory to steroids and thalidomide	Adefinite improvement in her facial swelling occurred within 4 days, followed by gradual but complete resolution of lymphadenopathy over the subsequent 8 weeks, despite stopping steroid medication
	[49]	Case report	IVIg 1 g/kg per day for 2 days, plus PD (2 mg/kg per day)	2 children who had Kikuchi complicated with hemophagocytic syndrome	One responded dramatically; second case responded partially to IVIg and fully after PD was added
Still's disease	[50]	Uncontrolled trial	Patients received monthly IVIg	7 patients unresponsive or poorly responsive to nonsteroidal anti-inflammatory drugs	5 patients responded after 4–6 treatments; 2 failed to respond
	[51]	Uncontrolled trial	Between 1 and 8 IVIg monthly infusions with a dose of 1 g/kg per day for 2 days	7 patients suffering from adult Still's disease	All patients improved but relapsed after 3–24 months
	[52]	Case report	2 courses of IVIg 1 g/kg for 2 days	23-year-old patient with flare-up of disease while taking salicylates at gestational week 22	Significant clinical and laboratory improvement
Granulomatous arteritis (GA, Wegener's granulomatosis)	[53]	Multicentered RCT	14 patients received IVIg 2 g/kg in 5 days (sandoglobulin Novartis) vs. 14 placebo	34 patients with ANCA-associated vasculitis (GA or MPA), refractory to CS or CP	Reduction in Birmingham Vasculitis Activity Score of 50% in 14/17 and 6/17 of the IVIg and placebo groups, respectively
	[54]	Uncontrolled trial	Patients received IVIg (Sandoglobulin)	14 patients with GA who responded poorly to standard therapy	All patients were in full and partial remission after 8 weeks; clinical benefit was maintained a year later
	[55]	Uncontrolled trial	Single or multiple courses of IVIg, 30 g/day, over 5 days	15 patients with GA who responded poorly to standard therapy	40% of patients benefited from IVIg treatment but without complete remission
	[56]	Uncontrolled trial	Monthly IVIg, 0.4 g/kg for 5 days, 1–6 cycles (Isiven Instituto Sierovaccinogeno, Italiano ISI SpA.)	10 patients with GA, CSS, or undifferentiated vasculitis which were refractory to standard treatment	IVIg treatment was found beneficial in 6 out of the 10 patients
	[57]	Uncontrolled trial	IVIg 0.5 g/kg per day for 4 days; Sandoglobulin (Sandoz, Basel, Switzerland)	3 patients with GA not treated with immunosuppressants before	One patient had full remission; one had transitional response; one had no response
Microscopic polyangitis (MPA)	[58]	Uncontrolled trial	IVIg 0.4 g/kg per day for 5 days, before or along with CS or CP (kenketsu velilon-I, Teijin Co., Ltd., Tokyo or kenketsu Glovenon-I, Nihon pharmaceutical Co., Ltd., Tokyo, Japan)	30 patients with MPA plus rapidly progressive glomerulonephritis	At 6 months, renal and general survival were 92% and 93%, respectively, compared to 70% and 74% with conventional therapy in other studies
	[57]	Uncontrolled trial	IVIg 0.5 g/kg per day for 4 days (Sandoglobulin, Sandoz, Basel, Switzerland)	3 patients with MPA not treated with immunosuppressants before	One patient had full remission; one had transitional response; one had no response

Table 2 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
	[54]	Uncontrolled trial	Patients received IVIg (Sandoglobulin)	11 patients with MPA who responded poorly to standard therapy	8 weeks after IVIg, all patients were in full and partial remission, clinical benefit was maintained 12 months later in most patients
Churg–Strauss syndrome (CSS)	[59]	Controlled trial	All patients received PS and CP in severe cases; 9 received monthly PP, followed by IVIg 1 g/kg for 2 days (Ig vena N IVH; Sclavo, Siena, Italy)	18 patients with CSS	After 12 months, all patients in the IVIg group and 4 (44%) in the control group were in remission; a significant favorable outcome was kept after 3 years ($p<0.01$)
	[60]	Case series	Daily IVIg 0.4 g/kg for 5 days	5 patients with cardiac CSS who showed poor response to PS ± CP	Neuropathy improved; EF of patients improved from 35.2% to 61% ($p<0.02$)
	[56]	Case report	5–6 courses of monthly IVIg, each course 0.4 g/kg for 5 days (Isiven Instituto Sierovaccinogeno, Italiano ISI SpA.)	2 patients with CSS, nonresponsive to standard treatment	First patient had no improvement; second patient had clinical and laboratory improvement and was steroid-spared
Autoimmune hepatitis (AIH)	[61]	Case report	IVIg was initiated because of adverse affects of long-term steroid therapy	A patient with chronic AIH	Immediate clinical, serological, and histological improvement
Autoimmune features in hepatitis C virus (HCV) infection	[62]	RCT	IVIg 0.4 g/kg for 5 days, and then IFN alpha 3 times a week, compared to treatment with IFN alpha alone	42 patients with HCV and autoimmune phenomena	A higher percentage of patients who received IFN alpha plus IVIg showed complete virological and histological responses
Henoch–Schönlein purpura (HSP)	[63]	Cohort study	IVIg 1 g/kg for 2 days, every month for 3 months (Biotransfusion, Roissy, France)	11 adult patients with severe IgA nephropathy (9 idiopathic, 2 with HSP)	Substantial improvement in glomerular filtration rate and kidney functions; 2 patients with HSP had resolution of other systemic symptoms
	[64]	Case report	IVIg (Tegelines) 1 g/kg per day for 2 days	A 10-year-old boy with HSP and severe abdominal manifestations refractory to treatment with CS	Digestive symptoms disappeared within 3 days
	[65]	Case report	Patient was treated with IVIg	A 26-year-old woman with HSP with nephrotic syndrome refractory to CS	Dramatic resolution
	[66]	Case report	IVIg (polyglobulin N containing maltose) 0.4 g/kg, for 2 days	46-year-old man with HSP and MPGN	Developed hemolysis and rapid deterioration renal function
	[67]	Case report	IVIg 1 g/kg for 2 days	56-year-old man with HSP and severe digestive manifestations	The patient's purpura and abdominal syndrome improved dramatically
Mixed connective tissue disease (MCTD)	[68]	Case report	IVIg 0.4 g/kg for 5 days	A woman with MCTD and fasciitis	Quick improvement of her symptoms and decreased CRP
	[69]	Case report	Patient was treated with IVIg	A 69-year-old man with MCTD and nonresponsive skin eruptions	Successful control of disease
Systemic sclerosis (SSc)	[70]	Controlled trial	IVIg 0.4 g/kg daily for 5 days, monthly for 3–6 cycles	15 patients with SSc	Treatment resulted in significant improvement in quality of life ($p=0.03$) and a decrease in Rodnan skin score ($p<0.001$)
	[71]	Case series	IVIg 0.4 g/kg daily for 5 days	5 patients with diffuse SSc	Marked long-term improvement in skin thickness from 2 weeks of treatment ($p<0.01$)
	[72]	Controlled trial	Monthly IVIg 0.4 g/kg for 4 days, for 6 months	7 female patients with SSc (5 limited, 2 diffuse), with	Significant improvement in joint swelling and pain ($p<0.03$), as

Table 2 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
				a severe refractory joint involvement	well as skin score ($p<0.003$), after 6 months of therapy
	[73]	Case report	3–6 cycles of IVIg 0.4 g/kg for 5 days; ISIVEN (Instituto Sierovaccinogeno, Italiano ISI SpA, Italy)	3 patients with rapid deteriorating SSc refractory to treatment	All patients had a significant decrease in their skin score
For scleromyxedema, see dermatology section					
For Evan's syndrome, see hematology section					
Juvenile rheumatoid arthritis (JRA)	[74]	Multicentered RCT	Bimonthly IVIg 1.5–2.0 g/kg for the first 2 months, then monthly for up to 6 months (Iveegam, Immuno AG, Vienna) after 3 and a half months was switched to placebo	25 patients with resistant JRA	19 (76%) had moderate to large improvement; the group which switched to placebo showed rapid loss of this effect
	[75]	RCT	Patients were additionally treated with high-dose IVIg or MP	20 patients with JRA treated with MTX and CS	Clinical effects were rapid in both groups
	[76]	Retrospective cohort	IVIg monthly for 3–54 months	27 patients with systemic JRA	20 patients responded after 6 months, especially systemic features and CS dependence
	[77]	Controlled trial	High-dose IVIg	16 children with severe juvenile chronic arthritis	Mild–moderate systemic, articular and laboratory improvement in most patients
Rheumatoid arthritis (RA)	[78]	RCT	IVIg 5 g/kg every 3 weeks for 6 courses vs albumin	20 patients with refractory RA	No significant differences between treatment groups were noted during the 18-week trial
	[79]	Controlled trial	Patients were treated with IVIg	11 patients with refractory RA	In 6 patients, clinical results were impressive; lasting responses could be achieved in 3 patients only
	[80]	Case report	IVIg 1 g per day for 2 days, monthly for 3 months	4 patients with severe refractory RA who have failed at least 4 second-line drugs	None of the patients improved or worsened
	[81]	Case report	IVIg 0.4 g/kg for 5 days	A 50-year-old woman with acute systemic RA refractory to treatment with CS, CP, or PP	Clinical improvement 3 days after IVIg treatment
Sjögren's disease	[82]	Case series	3 monthly courses of IVIg 0.4 g/kg body for 5 days	5 Sjögren patients complicated with ataxic sensory neuropathy, refractory to CS or PP	4 patients showed remarkable improvement, 2 of whom responded after the first course
	[83]	Case report	IVIg 0.4 g/kg for 5 days	A patient with long-standing Sjögren's that developed a painful sensory neuropathy	Remarkable clinical improvement and reduction of pain
	[84]	Case report	IVIg 0.4 g/kg for 5 days every 3 weeks	A patient with Sjögren syndrome complicated with ataxic sensory neuropathy	Remarkable improvement that subsided after switching to CS but regained after reintroduction to IVIg despite withdrawal of CS
For antiphospholipid syndrome, see gyneco-obstetric section					
Polymyositis (PM) and dermatomyositis (DM)	[85]	RCT	Received PD 25 mg plus IVIg 2 g/kg or placebo every month for 3 months	15 patients with treatment-resistant DM	Significant improvement of muscle strength ($p<0.018$) and neuromuscular symptoms ($p<0.035$), with IVIg treatment compared to placebo
	[86]	Controlled trial	IVIg or standard therapy	16 patients with PM or DM	Clinical and functional remission in a higher percentage (81%) that

Table 2 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
					was maintained after a mean 5-year follow-up period, as compared to control group ($p<0.001$)
	[87]	Controlled trial	IVIg 0.4 g/kg per day for 5 days in addition to CS (Benesis Corporation, Osaka, Japan).	15 patients with Dm (7) or PM (8), who were refractory to traditional CS therapy	Significant improvement in muscle strength, daily activity scores with no severe adverse reactions
Inclusion Body myositis (IBM)	[88]	RCT	Randomized to receive IVIg or placebo monthly for 3 months	36 patients with IBM, treated with high dose PD	No clinical significant difference
	[89]	RCT	IVIg 2 g/kg Vs placebo	22 patients with sporadic inclusion body myositis	No significant changes between groups according to modified Medical Research Council (MRC) score; mild improvement with IVIg according to Neuromuscular Symptom Score (NSS)
	[90]	RCT	IVIg 2 g/kg vs placebo monthly for 3 months	19 patients with IBM	No significant changes between the groups according to MRC score; significant improvement in swallowing with IVIg ($p<0.05$)
Behcet's disease (BD)	[91]	Case series	0.4 g/kg daily of IVIg (Omr-*IgG*-am, a 5% solution of human normal immunoglobulin G; Omrix Biopharmaceuticals Ltd, Nes-Ziona, Israel) 5 times in the first week, an additional 3 applications in the first month, once every 20 days for the next 3 months, then every 6 weeks for 1 year	6 eyes of 4 patients with ocular BD refractory to CS and cyclosporin A	All 6 eyes of all 4 patients showed good response to IVIg therapy
	[92]	Case report	IVIg was started with 5 daily doses of 0.4 g/kg followed by reinforcement doses of 0.4 g/kg at 2-week intervals	A 28-year-old man with BD suffering from severe leg, mouth, and scrotal ulcers and phlebitis resistant to immunosuppressants	After 4 days, the ulcers started to heal; 2 months later, the patient became totally pain free and walked without limping

IFN alpha, achieving a better response to IFN treatment in patients with chronic HCV associated with autoimmunity (*strength of recommendation IIa*).

Henoch–Schönlein purpura/IgA nephropathy

Level of evidence B There is some evidence that IVIg treatment may be effective for systemic and kidney disease, rather without sucrose/mannose in the preparation (*strength of recommendation IIa*).

Mixed connective tissue disease

Level of evidence C Mixed connective tissue disease (MCTD) is an autoimmune condition which combines features of polymyositis, systemic lupus erythematosus, scleroderma, and dermatomyositis and is thus considered an overlap syndrome. There is scarce evidence that treatment with IVIg helps to improve skin manifestations in MCTD (*strength of recommendation IIa*).

Systemic sclerosis

Level of evidence B Systemic sclerosis is characterized by hardening and scarring of the skin and inner organs. There is some evidence that treatment with IVIg helps to improve skin and systemic symptoms (*strength of recommendation I*).

Juvenile rheumatoid arthritis

Level of evidence A There is evidence that IVIg is useful for the treatment of patients with severe chronic JRA;

its treatment may help also reduce the need for CS and other immunosuppressive therapy (*strength of recommendation I*).

Rheumatoid arthritis

Level of evidence B There is hardly any convincing evidence that IVIg benefits patients with RA (*strength of recommendation IIb*).

Sjögren's disease

Level of evidence C There is some evidence that patients with ataxic sensory neuropathy refractory to immunosuppressive therapy will benefit from IVIg (*strength of recommendation IIa*).

Myopathies (PM, DM, and IBM)

Level of evidence B In patients with DM and PM that are resistant or partially responsive to conventional therapies, IVIg was effective (*strength of recommendation I*).

Level of evidence A In IBM, IVIg showed marginal improvements in muscle strength which were nonsignificant and thus were not recommended (*strength of recommendation III*).

Behcet's disease

Level of evidence C Behcet's disease is a multisystemic disorder presenting with recurrent oral and genital ulcers as well as ocular and central nervous system involvement. The severe cases may respond to systemic CSs, interferon, or anti-TNF therapy. There is some evidence to support IVIg treatment for refractory eye and skin involvement (*strength of recommendation I*).

The following conditions refer to (Table 3).

Acquired hemophilia

Level of evidence B There is weak evidence that IVIg is useful in the treatment of acquired hemophilia. IVIg may be tried in the case in which CS and cytotoxic agents fail or when facing an emergency situation as an additional therapy IVIg (*strength of recommendation IIa*).

Acquired hypogammaglobulinemia

Level of evidence A There is strong evidence that IVIg is of benefit in reducing the number and severity of infections in patients with acquired hypogammaglobulinemia in the context of hematological malignancy (*strength of recommendation I*). While this is true, both cost and the potential of adverse effects, most prominently acute renal failure and thromboembolic phenomena [3–5], prevent a clear-cut recommendation for the use of IVIg in acquired hypogammaglobulinemia. With this in mind, IVIg may be recommended at the replacement dose of 400 mg/kg each 3 to 4 weeks in cases in which severe or recurrent infections have occurred.

Pure red cell aplasia

Level of evidence C Pure red cell aplasia may be immune-mediated due to a background neoplasia, most frequently hematologic, or due to an immune disease or as an immune response triggered by drugs. It may also occur secondary to parvovirus B19 infection which may also lead to aplastic anemia. Treatment of the causative disease is the most important issue. Weak evidence supports the use of IVIg in pure red cell aplasia. IVIg may however be used in the case in which first-line therapy (i.e., CS and immunosuppressive drugs) fails to achieve a remission (*strength of recommendation IIa*). IVIg is first-line therapy in immunosuppressed hosts in which infection with parvovirus B19 results in pure red cell aplasia.

Acquired von Willebrand syndrome

Level of evidence B and C According to Federici and colleagues [6], 48% of the cases of acquired von Willebrand syndrome are associated with lymphoproliferative diseases, 15% with myeloproliferative disorders, and 21% with cardiovascular diseases. In another paper, Federici and colleagues [7] claim that 33% of the reported cases are associated with a monoclonal gammopathy of uncertain significance. Then, the detection and specific treatment of the underlying disease is as important as the immediate therapy of the coagulation disorder. In accordance to the scant existing evidence of IVIg therapy in this disorder, IVIg should be used in cases of standard therapy (desmopressin and factor VIII/von Willebrand factor concentrate) failure and in urgent situations as an addition to such therapy (*strength of recommendation IIb*). IVIg may also be used in the preparation for surgery.

Aplastic anemia

Level of evidence C While idiopathic aplastic anemia can be transient as in the case of parvovirus-B19-induced bone marrow depression, idiopathic aplastic anemia should first be treated with immunosuppressive drugs like CS or cyclosporine or with antithymocyte or antilymphocyte immunoglobulins as well as supportive blood components transfusions. Stem cell

Table 3 The use of intravenous immunoglobulins in hematological diseases

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
Acquired hemophilia	[93]	Prospective multicenter study	Induction with IVIg (5% Gamimune-N, Miles Inc, Berkeley, CA, USA) 2 g/kg over 2 or 5 days, maintenance with 0.4 g/kg by clinician decision	19 patients with acquired factor VIII inhibitors	8 of 16 assessable patients (50%) had inhibitors reduced in more than 25%; in one third of these responses, concomitant CS treatment may have influenced results
	[94]	Review of published case reports	Different IVIg preparations, dose ranging from 1.6 to 2.8 g/kg over 2–7 days	26 patients with acquired factor VIII inhibitors	16 of 26 patients (62%) had inhibitors reduced in more than 25%; 7 of 26 patients (27%) had clinical benefit
	[94]	Case series	IVIg (Sandoglobulin) 2 g/kg over 5 days	4 patients with acquired factor VIII inhibitors	2 of 4 patients (50%) had inhibitors reduced in more than 25%, but with no clinical benefit; in 2 of 4 patients, the inhibitor reductions were no assessable due to concomitant CS or CP treatment, with clinical benefit in doubt
	[95]	Review of published case reports	Different IVIg preparations and doses; IVIg therapy alone	35 patients with acquired factor VIII inhibitors	30% had inhibitors reduced in more than 25% and clinical benefit
	[96]	Case series	Prednisolone 1 mg/kg per day with IVIg 2 g/kg over 2–5 days	7 patients with acquired factor VIII inhibitors	5 of 7 patients (71%) had inhibitors reduced in more than 25%
Acquired hypogammaglobulinemia	[97]	RCT crossover study	6 months IVIg (0.3 g/kg per month, Ig-Vena N, Sclavo, Siena, Italy) or placebo, then switch for 12 months and switch again for 6 months	42 CLL patients with hypogammaglobulinemia	IVIg treatment yielded more infection free patients at 6 months than placebo (20 vs. 9, $p<0.01$) as well as at 12 months (13 vs. 6, $p<0.02$)
	[98]	RCT crossover study	12 months IVIg 0.4 g/kg (Gammagard, Hyland Therapeutic Division, Baxter Healthcare, Glenoak, CA, USA) every 3 weeks or placebo, then switch for 12 months	12 B cell CLL or NHL patients with hypogammaglobulinemia	During IVIg treatment, there were more infection-free patients than during placebo administration (6 vs. 1, $p=0.001$); in addition, 10 of 12 had lower rates of severe bacterial infection while on IVIg ($p=0.001$)
	[99]	RCT	18 g IVIg or albumin each 3 weeks for 12 months	42 CLL patients with hypogammaglobulinemia	Fewer infections in IVIg-treated (29% vs. 61%, $p=0.04$) Fewer severe infections in IVIg-treated (21% vs. 56%, $p=0.02$)
	[100]	RCT	IVIg 0.4 g/kg (Gammagard, Baxter Healthcare) or albumin every month for 12 months	82 patients with multiple myeloma	19 serious infection in IVIg-treated compared with 38 in placebo-treated patients ($p=0.019$) No septicemia/pneumonia on IVIg treatment compared with 10 cases in placebo-treated ($p=0.002$)
	[101]	RCT	IVIg (Endobulin, Immuno) 0.4 g/kg or no treatment each month, for 6 months	60 children with acute lymphoblastic leukemia	Less infections in IVIg-treated patients
	[102]	RCT	Cefataxim and amikacin with or without IVIg	33 children with acute lymphoblastic leukemia and neutropenic fever	Shorter fever duration in IVIg group (5.2 vs. 7.9 days, $p<0.05$) Similar neutropenia and hospitalization duration

	[103]	RCT	IVIg (Gammagard Baxter Healthcare Corporation Hyland Division) 0.4 g/kg or placebo every 3 weeks for 12 months	84 CLL patients with hypogammaglobulinemia or a history of infection	Overall fewer bacterial infections in the IVIg group (23 vs. 42, p=0.01) Even more marked difference in those who completed 1 year (14 vs. 36, p=0.001)
	[104]	RCT crossover study	6 months IVIg 0.3 g/kg per month (Ig-Vena N, Sclavo, Siena, Italy) or no therapy, then switch for 12 months and switch again for 6 months	25 multiple myeloma patients with hypogammaglobulinemia	During IVIg treatment, ten serious infections occurred; during no therapy, phase 30 serious infections occurred, $p<$ 0.002
	[105]	Two trials: RCT and RCT crossover study	12 months IVIg 0.4 g/kg every 3 weeks (Gammagard Baxter Healthcare Corporation Hyland Division) or placebo, then switch for 12 months (only in the case of the RCT crossover trial)	RCT trial: 81 patients with B cell CLL or low-grade NHL patients with hypogammaglobulinemia	RCT trial: less bacterial infections in the IVIg group (23 vs 42, p=0.01)
				RCT crossover study: 12 patients with B cell CLL or low-grade NHL patients with hypogammaglobulinemia	RCT crossover trial: larger number of patients free of severe infections in the IVIg group (6 vs 1, p=0.001)
Pure red cell aplasia	[106]	Case series	IVIg 2 g/kg over 5 days	3 pure red cell aplasia patients	Good response in all patients
	[107]	Case series	IVIg 2 g/kg (2 patients received Sandoglobulin, Sandoz, Switzerland, 2 patients received Veinoglobulin, Institut Merieux, France) over 5 days	4 patients with red cell aplasia, one idiopathic, another with well-differentiated lymphoma and 2 with B cell CLL	Good response in all patients
	[108]	Case report	IVIg	42-year-old male with parvovirus-B19-induced red cell aplasia after stem cell transplantation	Good response
	[109]	Case report	IVIg 2 g/kg over 5 days	38 year-old male with parvovirus-B19-induced red cell aplasia after liver transplantation	Good response
	[110]	Case report	IVIg (Panglobulin, ZLB Bioplasma, AG, Bern, Switzerland) 2 g/kg over 2 days	14-year-old male with parvovirus-B19-induced red cell aplasia after renal transplantation	Good response but development of osmotic sucrose-related renal failure
	[111]	Case report	IVIg 1 g/kg single dose	26-year-old female with parvovirus-B19-induced red cell aplasia after CHOP chemotherapy, rituximab, and radiotherapy	Good response
	[112]	Case report	IVIg	Relapsing pure red cell aplasia in a patient with B-cell chronic lymphocytic leukemia, refractory to PD and CP	Good response
	[113]	Case report	IVIg 4 g/kg over 10 days	Patient with parvovirus-B19-induced red cell aplasia after renal transplantation	Good response
	[114]	Case report	IVIg	41-year-old male patient with acquired immunodeficiency syndrome and parvovirus-B19-induced red cell aplasia	Good response

Table 3 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
	[115]	Case series	IVIg 1 to 2 g/kg over 1 to 2 days + maintenance dose 0.4 g/kg each month	8 patients with acquired immunodeficiency syndrome and parvovirus-B19-induced red cell aplasia	Good response in 8 of 8 patients, 6 of 8 needed also maintenance IVIg
	[116]	Case report	0.3 g/kg IVIg (Venilon, Teijin, Osaka) over 6 days	28-year-old female patient with common variable immunodeficiency and parvovirus-B19-induced red cell aplasia	Good response
	[117]	Case report	1 g/kg IVIg	34-year-old male with acquired immunodeficiency syndrome and parvovirus-B19-induced red cell aplasia	Good response
	[118]	Case report	2 g/kg IVIg (Intragam, CSL) over 5 days	Male patient with acquired immunodeficiency syndrome and parvovirus-B19-induced red cell aplasia	Good response
	[119]	Case report	2 g/kg IVIg then variable maintenance doses	26-year-old male patient with acquired immunodeficiency syndrome and parvovirus-B19-induced red cell aplasia	Good response
	[120]	Case report	IVIg	Female patient with chronic idiopathic pure red cell aplasia	Good response including 2 uneventful pregnancies during treatment
	[121]	Case report	2 g/kg IVIg over 5 days	22-year-old female patient with systemic erythematosus lupus and pure red cell aplasia, after failure of CS therapy	Good and immediate response
	[122]	Case report	4 g/kg IVIg (Sandoglobulin) over 10 days, subsequent additional shorter courses and plasmapheresis to due to immune-complex disease	24-year-old female patient with parvovirus-B19-induced red cell aplasia after liver transplantation	Late response; it is questionable that the late response is due to IVIg due to the late timing
	[123]	Case report	2 g/kg IVIg (Sandoglobulin, Sandoz, East Hanover, NJ, USA) over 5 days, subsequent maintenance courses	4-year-old patient pure red cell aplasia	Good and long-term response, weaned of blood transfusions
	[124]	Case report	2 g/kg IVIg over 5 days, subsequent maintenance courses	65-year-old Waldenström's macroglobulinemia patient with parvovirus-B19-induced pure red cell aplasia	Good and long-term response, weaned of blood transfusions
Acquired von Willebrand syndrome	[7]	Prospective noncontrolled study with sequential treatments	Desmopressin and factor VIII/von Willebrand factor concentrate where compared to IVIg 2 g/kg over 2 days (Sandoglobulin, Novartis or Ig-Vena Sclavo)	10 MGUS patients with acquired von Willebrand syndrome: 8 had IgG-kappa or lambda, 2 had IgM-kappa	Transient increase in plasma von Willebrand factor with desmopressin and factor VIII/von Willebrand factor concentrate; IVIg infusion in IgG-MGUS resulted in a more sustained increase starting on day 4 and returning to preinfusion levels on day 21

	[95]	Case series	IVIg	9 acquired von Willebrand syndrome patients	Good response in 30%
	[125]	Case report	IVIg 0.9 g/kg over 3 days	43-year-old patient with multiple myeloma and gastrointestinal bleeding due to acquired von Willebrand syndrome not responsive to vasopressin	Rapid hematological correction after 4 days, bleeding control
	[126]	Case report	IVIg	2 SLE patients with von Willebrand syndrome	Good response in one of the 2 patients
Aplastic anemia	[1]	Case report	IVIg	2 patients with idiopathic aplastic anemia	No response
	[127]	Case report	IVIg	Aplastic anemia patient unresponsive to antithymocyte globulin and CS	Good response
	[128]	Case report	IVIg	Aplastic anemia due to parvovirus B19 infection in a heart transplant recipient	Good response
	[129]	Case report	IVIg (ISIVEN, Instituto Sierovaccinogeno, Italiano ISI SpA) 2 g/kg over 5 days	66-year-old woman with idiopathic aplastic anemia, unresponsive to CS	Good response
Autoimmune hemolytic anemia	[130]	Multicenter noncontrolled study + review of reported cases	IVIg (generally Sandoglobulin, Basel, Switzerland, but also Gamimmune N, Cutter Biological, Emeryville, CA, USA; Venilon, Teijin Institute, Tokyo; Sanglopor, Sankyo Institute, Tokyo) 2.5–7 g/kg over 5–7 days	73 patients with autoimmune hemolytic anemia: 36 from multicenter study, 37 from review of published cases	29 patients (39.7%) responded to IVIg: hepatomegaly and low pretreatment hemoglobin were correlated with good response
Autoimmune neutropenia	[131]	Case series	IVIg 0.4–1 g/kg for 5–3 days	20 infants with neutropenia	50% responded after IVIg as compared to 100% with G-CSF and 57% with CS
	[132]	Case series	IVIg 3 g/kg over 3 days	6 infants with neutropenia	Fast but transient rise in neutrophils in all
Evans' Syndrome	[133]	Case series	IVIg single or multiple courses + CS	40 patients (children and young adults)	Remission in 9/40, transient response in 26/40 (overall improvement in 87%)
	[134]	Case series	IVIg plus CS for either acute hemolysis or thrombocytopenia	5 pediatric patients	Transient effect that needed immunosuppressant therapy for maintenance
	[135]	Case report	IVIg 0.4 g/kg for 5 days	3 patients with ES refractory to conventional therapy, including CS and splenectomy in all of the patients, vincristine in 2, and CP in one	2 patients failed to respond, but the third had a clinical remission after IVIg therapy
	[136]	Case report	IVIg 0.4 g/kg for 5 days	A patient with steroid resistant ES associated with dermatomyositis	IVIg was transiently effective, but a sustain remission was achieved with CP
Fetal/neonatal alloimmune thrombocytopenia	[137]	Nonrandomized study	IVIg, 1 g/kg weekly, or CS given to pregnant women	37 pregnant women with previous pregnancy with alloimmune thrombocytopenia: 27 received IVIg, 10 received CS	There was an increase in platelets and no intracranial bleeding in 26% of patients/fetus treated with IVIg as compared with 10% of those treated with CS; in addition, there was no increase in platelets and no intracranial bleeding in 41% of patients/fetus treated with IVIg as compared with 20% of those treated with CS

Table 3 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
Stem cell/bone marrow transplantation: infections and graft-versus-host disease	[138]	RCT	16 weekly doses since 1 week before transplantation of either IVIg (Sandoglobulin, Novartis Pharma, Rueil-Malmaison) 0.05, 0.25, and 0.5 g/kg or placebo	200 patients with allogeneic stem cell transplantation	No protection against infections; GVHD and mortality were similar
	[139]	Randomized trial	64 patients received 0.4 g/kg per week of IVIg (Sandoglobulin, Sandoz, Switzerland); 64 patients received 0.1 g/kg per week of CMV-IgG	128 patients with allogeneic bone marrow transplantation	No significant difference in the occurrence or severity of acute or chronic GVHD, infections, or survival
	[140]	RCT	123 patients received 0.5 g/kg per month of IVIg; 127 patients did not receive IVIg, from the fourth to the 12th month after transplantation	250 patients with allogeneic bone marrow transplantation	No significant difference in the occurrence of chronic GVHD, infections, or survival
	[141]	Randomized trial	All received CMV-negative blood products, 25 received IVIg (1 g/kg per week) starting before pretransplant conditioning and then for 17 additional weeks	48 patients after allogeneic BMT, CMV seronegative, which received CMV seropositive or seronegative BMT	No difference in the number of bacterial/fungal infections, fewer non-CMV viral infections in the IVIg group (9 vs 15, $p=0.03$), less grade ≥II of GVHD in the IVIg group, $p=0.04$
	[142]	Multicenter RCT	IVIg (Venoglobulin S 5%, Alpha Therapeutic Corporation, LA, CA, USA), 0.1, 0.25, or 0.5 g/kg, started 2 days before transplant, continued weekly for 90 days and then monthly until 1 year after transplant	618 allogeneic bone marrow transplant recipients	Acute GVHD occurred in 39% (80/206) in the 0.1-g/kg group, 42% (88/208) in the 0.25-g/kg group, 35% (72/204) in the 0.5 g/kg group No difference in incidence of chronic GVHD, infection, interstitial pneumonia, type of infection, relapse of hematological malignancy or survival
	[143]	Randomized trial	IVIg (Sandoglobulin, Sandoz Pharmaceuticals, East Hanover, NJ, USA) 0.5 g/kg per week administered since the beginning of the cytotoxic therapy or nothing	170 autologous bone marrow transplant patients	IVIg did not reduce infection of infection-related death
	[144]	RCT	IVIg (Gamimune N, Cutter Biological, Berkeley, CA, USA) 0.5 g/kg per week to day 90, then 0.5 g/kg per month to day 360 after transplantation or nothing	382 patients after bone marrow transplantation	Lower risk of gram-negative septicemia ($p=0.0039$) in IVIg and of local infection ($p=0.029$) No difference in survival; there was a risk reduction in the incidence of acute GVHD ($p=0.0051$) Decrease in deaths due to transplant-related causes after transplantation of HLA-identical marrow ($p=0.023$)
Hemolytic disease of the newborn	[145]	Meta-analysis of 3 not-blinded RCT	IVIg and phototherapy or phototherapy alone	189 patients	Less use of exchange transfusion in the IVIg group: when given for prophylaxis RR=0.21 ($p<0.001$), when given as treatment RR=0.36 ($p<0.006$)

	[146]	Meta-analysis of 3 RCTs	IVIg and phototherapy or phototherapy alone	189 patients	Overall less use of exchange transfusion in the IVIg group: RR=0.28 ($p<0.00001$)
Hemolytic transfusion reaction	[147]	Case series	IVIg (Endobulin HT, Immuno AG, Vienna, Austria) 0.4 g/kg (single infusion) was administered within 24 h of transfusion	5 patients are known to develop non-ABO post-transfusional hemolytic reactions	No transfusion reaction and sustained increase in hematocrit
	[148]	Case report	IVIg (Sandoglobulin) 75 gr. over 3 days + CS	Rh-negative patient with anti-Jk, anti-K, and anti-Kp	Increase in hemoglobin, no evidence for hemolysis
Hemolytic transfusion reaction in sickle cell disease	[149]	Case reports	IVIg 2 g/kg over 5 days + high-dose MP	2 patients with sickle cell disease who developed a hemolytic reaction after compatible blood transfusion	Increase in hemoglobin and reticulocytes
	[150]	Case reports	IVIg 2 g/kg over 5 days + high-dose MP	2 patients with sickle cell disease who developed a hemolytic reaction after compatible blood transfusion	Increase in hemoglobin and reticulocytes
	[151]	Case report	IVIg (Sandoglobulin, 1 g/kg per day for 1 to 2 days) + CS	Patient with sickle cell disease who developed a hemolytic reaction after compatible blood transfusion	Increase in hemoglobin and reticulocytes
Hemolytic uremic syndrome	[152]	Case control study	IVIg 0.4–2.4 g/kg (Gamimune N, Cutter Etobicoke, Ontario, Canada) over 1–6 days (0.4 g/kg per day)	18 children with postdiarrhea hemolytic uremic syndrome, 9 received IVIg	No benefit of IVIg treatment
	[153]	Case control study	IVIg 2 g/kg (Sandoglobulin) over 5 days in 8 patients, FFP in 12 patients, no treatment in 23 patients	43 children with hemolytic uremic syndrome; 8 received IVIg	Improvement in platelet count against FFP ($p<0.05$) and against no treatment ($p<0.01$)
Thrombotic thrombocytopenic purpura	[154]	Case series	IVIg 0.4 g/kg per day, from 1 to 20 infusions; these patients were also treated with CS, also PP in 15 patients	17 patients with thrombotic thrombocytopenic purpura	10/17 (58.8%) patients had remission, 8/17 (47%) complete remission
	[155]	Case control study	IVIg 2 g/kg over 5 days in 29 patients only; all the patients received PP and CS	44 patients with thrombotic thrombocytopenic purpura	No benefit of IVIg treatment
Heparin-induced thrombocytopenia	[156]	Case series	IVIg (Sandoglobulin in 2 cases, Octagam in one case) 2 g/kg over 2 days	3 patients with heparin-induced thrombocytopenia	Increase in platelet count
	[157]	Case report	IVIg	51-year-old woman with heparin-induced thrombocytopenia and pulmonary embolism	Increase in platelet count starting 20 h after first IVIg infusion
HIV-associated thrombocytopenia	[158]	RCT crossover study	Weekly IVIg (Polygam) courses of 2 g/kg over 2 days or normal saline, for 4 weeks, then crossover	12 HIV patients with HIV-related thrombocytopenia	IVIg consistently and reproducibly raised platelet count after infusion; no patient with placebo did so ($p<0.00003$)
Acute immune thrombocytopenic purpura	[159]	RCT not blinded	IVIg 2.1 g/kg over 3 days (Gammagard SD, Baxter Bioscience, Glendale, CA) or high-dose MP 15 mg/kg per day for 3 days	Acute immune thrombocytopenic purpura adult patients, 56 randomized to IVIg, 60 to MP	Faster response and higher platelet counts in the IVIg group ($p=0.006$)
	[160]	RCT nonblinded	IVIg 2 g/kg over 5 days (7 patients), PD 1 mg/kg per day (13 patients) or both IVIg and PD (12 patients)	32 acute immune thrombocytopenic purpura adult patients	No difference in response rates or in requirements for splenectomy or in bleeding

Table 3 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
	[161]	RCT nonblinded	IVIg 2 g/kg over 2 days (19 patients) or PD with starting dose of 4 mg/kg per day and then tapering until discontinuation by day 21 (18 patients) or no therapy (16 patients)	53 children with acute immune thrombocytopenic purpura and less than 20,000 platelets per microliter	Both IVIg- and PD-treated children reached platelet counts over 50,000 per microliter faster than children not treated ($p<0.001$) Median time to reach more than 50,000 platelets per microliter was lower in IVIg group (2 days) than in PD group (4 days), $p<0.001$
	[162]	Partially randomized trial; patient's family chose no treatment or treatment (IVIg or CS upon randomization)	IVIg 1.6 g/kg over 2 days (12 patients) or MP with starting dose of 30 mg/kg per day for 3 days and then 20 mg/kg per day for 4 days (12 patients) or no therapy (26 patients)	50 children with acute immune thrombocytopenic purpura and less than 20,000 platelets per microliter	Both IVIg- and MP-treated children reached platelet counts over 20,000 per microliter and 50,000 per microliter faster than children not treated, $p<0.01$
Immune thrombocytopenic purpura in HIV	[163]	Controlled clinical trial	IVIg 2 g/kg of IVIg over 2 days, followed by IVIg 1 g/kg on day 15	14 patients with HIV-related thrombocytopenia (median platelet count 17,000/mm^3)	All achieved resolution of their bleeding by day 8, but this was temporary
	[164]	Controlled clinical trial	IVIg 0.04 g/kg per week during 5 weeks	13 thrombocytopenic AIDS patients	All patients responded in the first week but only 4 were responders after 3 months
Chronic immune thrombocytopenic purpura	[165]	Prospective noncontrolled trial	IVIg 2 g/kg over 2 or 5 days (BT681m, Biotest Pharma GmbH, Dreieich, Germany) in accordance to randomization, followed for 28 days	24 chronic immune thrombocytopenic purpura adult patients	91.7% of patients underwent a fast raise (in 2–5 days) of platelet count over 50,000 per microliter; at the end of the 28 days of follow-up, half of the patients had still platelet count over 50,000 per microliter
	[166]	Prospective noncontrolled trial	Induction with IVIg 1 or 2 g/kg (Biotransfusion, Roissy, France) over 2 days and 6 more maintenance infusions of IVIg 1 g/kg starting when platelets fell below 50,000 per microliter and then every 2 to 3 weeks unless platelets are over 150,000 per microliter or response is exhausted	20 chronic immune thrombocytopenic purpura adult patients	Initial response in all 18 evaluable subjects, 13 complete (>150,000 per microliter), 5 partial (>50,000 per microliter); no difference between both induction doses; maintenance: at 90-day failure in 61% (11 of 18), partial response (>50,000 per microliter in 2 of 18, 11%) and complete response (>150,000 per microliter in 5 of 18, 28%)
Posttransfusional purpura	[167]	Case series	IVIg	17 patients with severe thrombocytopenia after blood transfusion	In 16 patients, normal platelet counts were reached within days; 5 patients relapsed and again had a good response to new IVIg administration
	[168]	Case series	IVIg 0.4 g/kg per day, for 2–10 days	5 patients with severe thrombocytopenia after blood transfusion	Immediate raise in platelet count and cessation of bleeding in 4 of 5 patients (80%)
	[169]	Case series	IVIg, variable doses ranging from 1 to 2 g/kg per day	3 patients with thrombocytopenia after blood transfusion	Good response in 2 of 3 patients

Hemophagocytic syndrome	[170]	Case series	IVIg	6 renal transplant patients with hemophagocytic syndrome	Good response in all the cases
	[171]	Case series	IVIg	7 children with hemophagocytic syndrome treated with IVIg only	3 of 7 (43%) survived
	[172]	Case series	IVIg 2 g/kg over 2 days in one case, over 5 days in the other	2 cases of EBV-associated hemophagocytic syndrome treated with IVIg only	2 of 2 (100%) survived
	[173]	Case series	IVIg	8 children with infection-associated hemophagocytic syndrome treated with IVIg	0 of 8 (0%) survived
	[174]	Case series	IVIg 1 g/kg per day for 1 or 2 days	3 children with infection-associated hemophagocytic syndrome treated with IVIg	3 of 3 (100%) survived
	[175]	Case report	IVIg	A healthy patient with CMV-related hemophagocytosis	Symptoms and laboratory abnormalities improved dramatically after the onset of the treatment
POEMS syndrome	[176]	Case report	2 courses of IVIg 0.4 g/kg per day for 5 days, separated by 3 weeks, adjunctive to radiotherapy	49-year-old patient with rapidly progressive polyneuropathy associated with osteosclerotic myeloma	After 2 courses of IVIg improvement of respiratory and sexual function and gate, disappearance of numbness; doing well after 1 year
	[177]	Case report	IVIg 0.4 g/kg per day for 4 (case 1) or 5 days (case 2) adjunctive to prednisolone 30–50 mg/day	A 55-year-old man (case 1) and a 43-year-old woman (case 2) with late-stage POEMS	No change in motor and sensory impairment; case 1 continued to deteriorate and died after 6 months due to sepsis and DIC
	[178]	Case report	IVIg (one course)	A patient with POEM and Castleman's disease	No effect
Diffuse B cell posttransplant lymphoproliferative disorder	[179]	Case report	IVIg 0.5 g/kg every 15 days for 4 months (case 1) and for 12 and 7 months, respectively (case 2) adjunctive with IFN alpha (2×10^6 IU SC 3 times a week)	2 patients with diffuse B cell posttransplant lymphoproliferative disorder	Complete disappearance of all lesions after 3 months of the therapy in case 1 and after 7 months in case 2, remission for 47 months and 33 months, respectively

POEMS syndrome polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes

transplantation is always the alternative in the case of failure of the aforementioned treatments. Due to the low level of evidence of IVIg for the treatment of idiopathic aplastic anemia, we cannot recommend its liberal use but it may be tried in the case of treatment failure, before stem cell transplantation is performed (*strength of recommendation IIb*).

Autoimmune hemolytic anemia

Level of evidence B Immunosuppression with CS and then cytotoxic agents should be used in autoimmune hemolytic anemia before considering IVIg. There is however some evidence that IVIg might be useful and therefore in refractory cases before considering splenectomy it may be worth a try (*strength of recommendation IIb*).

Autoimmune neutropenia

Level of evidence C Although immune neutropenia may also be an adverse effect resulting from IVIg treatment as have been published elsewhere [8], IVIg has been used to treat immune neutropenia. The evidence is weak and responses are not as good as those with CS and granulocyte colony-stimulating factor (*strength of recommendation IIb*).

Evans' syndrome

Level of evidence C Evans' syndrome is usually a therapy-resistant condition that has been treated combining CS, IVIg, and immunosuppressive therapy. Although convincing evidence is lacking for the use of IVIg in view of the severity and the refractory nature of several cases of Evans' syndrome, IVIg may be considered among the treatment options generally together with CS with or without immunosuppressive therapy (*strength of recommendation IIb*).

Fetal/neonatal alloimmune thrombocytopenia

Level of evidence B The only study comparing IVIg against other treatment (CS), although nonrandomized, suggests that IVIg raises the platelet number and prevents intracranial bleeding in a significant percentage of treated patients. The level of evidence is low, but the alternatives for prenatal treatment of fetuses at risk are not better and the risks involved are huge (*strength of recommendation IIb*).

Stem cell/bone marrow transplantation

Level of evidence A Strong evidence denies any benefit from the use of IVIg around stem cell/bone marrow transplantation, both from the infectious or from the graft-versus-host disease point of views (*strength of recommendation III*).

Hemolytic disease of the newborn

Level of evidence A There is clear evidence for the use of IVIg when facing newborn hemolysis as it reduces the need of plasmapheresis (PP) therapy (*strength of recommendation I*).

Hemolytic transfusion reaction

Level of evidence C There is no reliable evidence to recommend the use of IVIg to prevent or to treat hemolytic transfusion reactions (*strength of evidence IIb*).

Hemolytic transfusion reaction in sickle cell disease

Level of evidence C Apart from two papers reporting two cases and another case, there is no evidence to recommend the use of IVIg either to prevent or to treat hemolytic transfusion reactions in sickle cell patients, specially taking into consideration the additional risk of thrombosis due to a change in the rheologic properties of the blood after IVIg infusion (*strength of recommendation IIb*).

Hemolytic uremic syndrome

Level of evidence B There is conflicting evidence that IVIg benefits patients with hemolytic uremic syndrome (*strength of recommendation IIb*).

Thrombotic thrombocytopenic purpura

Level of evidence B There is no evidence that IVIg benefits patients with thrombotic thrombocytopenic purpura (*strength of recommendation III*).

Heparin-induced thrombocytopenia

Level of evidence C There is low-level evidence that IVIg is useful for this disease. On the other hand, thromboembolic phenomena, which are part of the heparin-induced thrombocytopenia clinical picture, might be enhanced by the rheologic blood changes after IVIg infusion. Therefore, IVIg should not be generally recommended for this disease (*strength of recommendation IIb*).

HIV-associated thrombocytopenia

Level of evidence B Evidence comes only from one crossover randomized placebo-controlled trial which supports the use of IVIg in HIV-associated thrombocytopenia, especially when platelet count is very low or the risk of bleeding is high (*strength of recommendation IIa*).

Acute immune thrombocytopenic purpura

Level of evidence A Since Imbach's observation [1], acute ITP has been the prototype of IVIg-responsive immune disease. There is consistent evidence that IVIg is beneficial in children with ITP (*strength of recommendation I*). Notwithstanding this, CS therapy is still the first-line treatment for ITP, and single-dose anti-D immunoglobulin [9, 10] is a [8] good alternative for Rh-positive patients. IVIg should be considered when there is bleeding or when the bleeding risk is high or upon failure of other treatments. In adult acute ITP patients, there is no placebo-controlled RCT, but when compared with CS IVIg induces a faster response. Again, CS is the first-line treatment for adults but IVIg may be given in severe or refractory cases. There is weak evidence that IVIg can improve mother and fetal prognosis in pregnancy. IVIg may be used when a fast correction in platelet number is needed.

Immune thrombocytopenic purpura in HIV

Level of evidence B By the merits of its own research, IVIg may be considered to treat ITP in the context of HIV. Although no hard evidence exists due to the fact that this particular group of patients has not been investigated as well as has non-HIV-related ITP, it will be hard to argue that the recommendation of the latter may not be extended to HIV-related ITP (*strength of recommendation I*).

Chronic immune thrombocytopenic purpura

In chronic ITP, IVIg has so far not demonstrated a plausible benefit. Only prospective noncontrolled trials are available and we found only one evaluating maintenance IVIg for chronic ITP, in which the overwhelming majority of patients had a recrudescence of thrombocytopenia in spite of a good initial response to IVIg (level of evidence and strength of recommendation B-IIb). A small number of patients benefited and therefore IVIg might be tried in drug refractory cases of chronic ITP in which there is a contraindication for splenectomy.

Posttransfusional purpura

Level of evidence C Series of patients treated with fast response to IVIg suggest a benefit of IVIg treatment in posttransfusional purpura, although with low-level of evidence. In the context of a patient with severe risk to bleeding or actual bleeding, IVIg can be used if the diagnosis of posttransfusional purpura is made (strength of recommendation IIb).

Hemophagocytic syndrome

Level of evidence C Hemophagocytic syndrome is a severe reaction leading to high mortality. Inconsistent and low-level evidence do not warrant a clear-cut recommendation of IVIg for this syndrome. However, due to the lack of effective and standardized treatment in an otherwise highly lethal disease, IVIg may be used along with other therapies like monoclonal antibodies, CS, cytotoxic drugs, and support measures (*strength of recommendation IIb*).

POEMS

Level of evidence C There are only anecdotal reports, both showing benefit and lack of benefit. There is no evidence that IVIg has a beneficial effect on polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (*strength of recommendation IIb*).

Diffuse B cell posttransplant lymphoproliferative disorder

Level of evidence C There is no convincing evidence that IVIg has any beneficial effect in this disease (*strength of recommendation IIb*).

The following conditions refer to (Table 4).

Cytomegalovirus

Level of evidence B IVIg is not used for the treatment of CMV infection but may be helpful in treatment of hemophagocytic syndrome related to CMV and other viruses (see hematology section); there is some evidence for its effectiveness in preventing seroconversion in transplant patients who are immunosuppressed (*strength of recommendation IIa*).

Human immunodeficiency virus

Level of evidence B IVIg can reduce infections in children with perinatal HIV but has not been proven to reduce mortality (*strength of recommendation IIa*).

Malaria

Level of evidence B No evidence for the effectiveness of IVIg in the treatment in malaria exists (*strength recommendation III*).

Postpolio syndrome

Level of evidence A Postpolio syndrome (PPS) typically affects survivors of poliovirus infection, 15–20 years after the original infection, with fatigue, muscular weakness, and pain. There are two RCTs demonstrating some inconsistent evidence for the effectiveness of IVIg treatment on quality of life, pain, and muscle strength in patients with PPS (*strength of recommendation IIa*).

Table 4 The use of intravenous immunoglobulins in infectious diseases

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients.	Results/response
Cytomegalovirus (CMV)	[180]	Controlled trial	IVIg 0.25 g/kg weekly for 8 weeks, starting on the operative day	40 renal transplanted patients with negative serology for CMV	Effective prophylaxis, associated with excellent 1-year allograft survival
Human immunodeficiency virus (HIV) child infection	[181]	RCT	IVIg 0.4 g/kg or placebo (0.1% albumin) every 28 days	372 symptomatic children infected with HIV	Significant reduction in serious infections (p=0.01) and hospitalizations (p=0.03), in the IVIg group only for those entering treatment with CD4+ lymphocyte ≥200; no effect on mortality
	[182]	Controlled trial	IVIg (Gamimune-N, Miles Pharmaceutical Co.), 0.2 g/kg monthly for 1 year	135 symptomatic and asymptomatic children with perinatal HIV	Significant reduction in the frequency of bacterial infections in the symptomatic group
HIV-associated thrombocytopenia—see hematology section					
Malaria	[183]	RCT	All were treated with IV quinine dihydrochloride; in addition, patients were randomized to receive either IVIg, 0.4 g/kg over 3 h, or placebo	31 children with *Plasmodium falciparum* parasitemia and coma	Of 16 patients receiving immunoglobulin, 5 (31%) died, and 5 survivors had neurological sequelae; of 15 patients receiving placebo, one (7%) died and 2 had sequelae (trial was stopped)
	[184]	Controlled trial	IVIg was prepared from 180 donors after infection screening; 6 patients were treated with a 0.1-g/kg dose given over 3 days, one with a single 0.02-g/kg dose, and one with a single 0.02-g/kg dose	8 Thai patients with *P. falciparum* parasitemia	Clearance of parasites and symptoms was as fast as or faster than with drugs
Postpolio syndrome (PPS)	[185]	Multicentered RCT	90 g of IVIg during 3 days, repeated after 3 months	142 patients: 73 with IVIg and 69 placebos	Mild improvement in median muscle strength (p=0.03), vitality (p=0.04), no change and quality of life (p=0.3)
	[186]	RCT	Patients were randomized to IVIg, 2 g/kg, or placebo	20 patients with PPS	No effect was seen with IVIg treatment on muscle strength and fatigue; however, IVIg patients reported significantly less pain 3 months after treatment
	[187]	Open clinical trial	90 g of IVIg (30 g daily for 3 days)	14 patients with PPS	Significant improvement in the quality of life, no change in muscle strength and physical performance
Sepsis	[188]	Meta analysis of RCT's from PubMed	Different preparations of relatively low doses of IVIg for severe sepsis, mostly surgical patients with gram-negative infections	14 RCTs published between 1988 and 2006 were included	Significant but heterogenic reduction in mortality associated with use of IVIg (p<0.0005); this result was not confirmed when only high-quality studies were analyzed
West Nile Virus (WNV)	[189]	Case report	0.4 g/kg IVIg preparation from donors that contained a high titer of anti-WNV antibodies (1:1,600)	42-year-old male lung-transplant recipient with severe WNV encephalitis	Complete disappearance of signs and symptoms within 48 h
	[190]	Case report	IVIg 0.4 g/kg for 5 days (Omr-IgG-am, Omrix Biopharmaceutical Ltd., Tel Hashomer, Israel)	70-year-old with chronic lymphatic leukemia and coma due to WNV	Level of consciousness returned to normal over 5 days
Prophylaxis for infections (in intensive care units (ICU))	[191]	RCT	Patients received standard IVIg, 0.4 g/kg, hyperimmune globulin (HG), 0.4 g/kg, or placebo, weekly, for a maximum of 4 doses	329 postsurgical patients admitted to the surgical ICU	Significantly lower infections and hospital days in the IVIg group vs. placebo or HG (p=0.003); no lesser mortality/shock

Table 4 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients.	Results/response
	[192]	RCT	Patients received IVIg (36 g) versus 0.03% albumin	150 trauma patients in ICU ventilated for >24 h	Decreased overall incidence of infection (p=0.02) and antibiotic need in IVIg group
	[193]	RCT	Ten patients received IVIg and ten albumin	20 patients with extensive thermal injury	No statistically significant difference was found between mortality rates of the groups
	[194]	RCT	18 received IVIg, 0.4 g/kg, and 14 placebo within 48 h of admission	33 children (mean age, 6.67 years) with severe head injuries	No effect on the incidence of secondary infections
	[195]	RCT	Within 12 h of ICU admission, 1 g/kg of IVIg or human albumin divided over 4 days	39 trauma patients in an ICU	No difference in overall infection rates, but fewer pneumonias (p=0.003) and non-catheter-related infections (p=0.04); no difference in ICU length of stay or antibiotic use
	[196]	RCT	Patients were randomly assigned to either 20 g IVIg or saline	40 postoperative open-heart surgery patients with cutaneous anergy preoperatively	Infection incidence 5% in IVIg versus 43% placebo (p=0.007)
Prophylaxis for infections (in immune-compromised patients)	[143]	RCT	82 received IVIg weekly, 0.5 g/kg, from the initiation of cytotoxic therapy to the resolution of neutropenia and 88 were untreated controls	170 neutropenic patients undergoing BMT or severe myelosuppressive therapy	The use of IVIg did not prevent infection; fewer deaths occurred among controls due to a higher incidence of fatal hepatic veno-occlusive disease in patients receiving IVIg
	[197]	RCT	Monthly IVIg 0.4 g/kg or placebo for 1 year	82 patients with stable multiple myeloma	Less infection sepsis in the IVIg group (p=0.002)
Necrotizing fasciitis (NF)	[198]	Controlled trial	16 were treated with ≥1 mg/kg of IVIg; all were treated with antibiotics and debridement	20 patients with NF	No difference in case fatality
	[199]	Controlled trial	Patients were treated with effective antimicrobials, high-dose IVIg; surgery was either not performed or only limited exploration was carried out	7 patients with severe NF	All patients survived
	[200]	Controlled trial	Patients that had hypotension and multiorgan failure were treated with a single dose of IVIg 50 g in addition to antibiotics	11 patients with toxic shock syndrome with or without NF	Ten patients were fully recovered
	[201]	Case report	Patient declined on antibiotic therapy and was treated with IVIg, 0.4 g/kg (Omr-IgG-am 5% IV, Omrix, Israel)	A renal transplant lupus patient with NF	A marked improvement in patient's condition on the next day
Recurrent otitis media (OM)	[202]	RCT	IVIg or placebo	22 otitis-prone children, 1–4 years old	No significant difference in the frequency of OM attacks or other respiratory tract IVIg group
	[203]	Controlled trial	IVIg	9 children with recurrent sinopulmonary infections which failed to improve after antibiotic Tx	Significant decrease in the episodes of sinusitis and OM
Varicella (transmission prevention)	[204]	Controlled trial	IVIg prophylaxis (single-dose 0.5 g/kg) administered soon after birth or postnatal contact, either alone or with IV acyclovir	24 newborns whose mother had a varicella rash within 14 days before and after delivery	Treatment with IVIg + acyclovir effectively prevented perinatal varicella
	[205]	Controlled trial	IVIg 0.04 to 0.045 g/kg per day for 5 to 9 days was given soon after birth, along with acyclovir	5 infants whose mothers had varicella	Some had a mild–moderate transient rash but none had constitutional symptoms

Table 4 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients.	Results/response
Varicella (pulmonary disease)	[206]	Case report	IVIg and IV acyclovir	2 cases of varicella infection complicated by severe pulmonary involvement previously healthy adults	Gradual clinical improvement after administration
	[207]	Case report	IVIg, 2.5 g every 12 h, with IV acyclovir and ABx	A healthy adult with severe respiratory failure due to varicella pneumonia	Gradual clinical improvement after administration
	[208]	Case report	IVIg and IV acyclovir	32-year-old patient with varicella and ARDS	Quick improvement
	[209]	Case report	Patient was mechanically ventilated and treated with IVIg and acyclovir	26-year-old with ARDS secondary to varicella pneumonia	Quick improvement
Varicella (complicated with ITP)	[210]	Case report	IVIg	ITP in a 3-year-old girl with an active varicella infection	Drastically improved bleeding and active varicella infection
	[211]	Case report	IVIg, 0.4 g/kg per day for 3 days, and acyclovir	40-year-old with bleeding due to varicella-related ITP	The platelet counts increased to 254,000 per microliter over the next 5 days, and the skin rashes associated with varicella subsided within a week

Sepsis

Level of evidence A Sepsis is a life-threatening condition, resulting mainly from the patient's immune response to a severe infection. Significant but heterogenic reduction in mortality with IVIg treatment in septic patients was demonstrated in a meta-analysis of 14 RCTs. These results were not confirmed when only high-quality studies were analyzed (*strength of recommendation IIa*).

West Nile

Level of evidence C Infection with West Nile virus can cause fatal encephalitis in immunosuppressed and elderly patients, in which case effective treatment is lacking. The effectiveness of IVIg in these situations is supported by a few case reports and may be considered (*strength of recommendation IIa*)

Infection prophylaxis—in intensive care units

Level of evidence A Treatment with IVIg has not proven to reduce infectious-related mortality in postsurgical patients, but there is inconsistent evidence that IVIg reduces ICU-related infections and hospital stay in these patients (*strength of recommendation IIa*).

Infection prophylaxis—in immune-compromised patients

Level of evidence A There is conflicting evidence regarding the usefulness of IVIg treatment for these patients. It should be taken into consideration that patients treated with IVIg after bone marrow transplantation (BMT) may have a higher incidence of fatal hepatic veno-occlusive disease (*strength of recommendation IIa*).

Necrotizing fasciitis

Level of evidence B Necrotizing fasciitis is caused by deep-skin infection with bacteria, mainly group A streptococcus. The mainstay of nuclear factor treatment is prompt surgical exploration and antibiotic therapy. IVIg might have additional benefit to antibiotic therapy for treatment of patients who refuse surgery or are not surgical candidates. (*strength of recommendation IIa*).

Recurrent otitis media

Level of evidence B There is weak evidence that IVIg is useful in the treatment of recurrent otitis media (*strength of recommendation IIb*).

Varicella

Level of evidence B Some evidence that IVIg is effective in preventing perinatal transmission of varicella. IVIg may also be used for treatment adults with severe respiratory failure due to varicella pneumonia (*level of recommendation IIa*).

The following conditions refer to (Table 5).

Perinatal hemochromatosis

Level of evidence B Although the best level of evidence is not strong, the improvement shown for treated pregnancies is beyond the natural possibility of a subsequent spared pregnancy which has been estimated to be approximately 40% ([11] #110). In view of this data and the difficulty for large RCTs, IVIg may be considered to prevent recurrent perinatal hemochromatosis (*strength of recommendation IIa*).

Recurrent pregnancy loss excluding antiphospholipid syndrome

Level of evidence A There is evidence that IVIg improves the outcome of pregnancy in secondary recurrent miscarriage (in women that had a previous pregnancy that reached at least the second trimester (*strength of recommendation IIb*)). This has so far not been shown for primary recurrent miscarriage (*strength of recommendation III*).

Recurrent pregnancy loss due to antiphospholipid syndrome

Level of evidence A The evidence is against the use of IVIg in pregnancy of women affected by antiphospholipid syndrome (*strength of recommendation III*).

Prevention of infection after premature rupture of membranes

Level of evidence B Evidence from a small RCT indicates that IVIg may reduce the rate of fetal infection after premature rupture of membranes (*strength of recommendation IIa*).

Failure of in vitro fertilization

Level of evidence A The evidence is scarce but the only meta-analysis based on data from three RCTs found a benefit in the number of live births in women treated with IVIg. After in vitro fertilization (IVF) failure, IVIg along with IVF techniques may be weighted (*strength of recommendation IIb*).

The following conditions refer to (Table 6).

Congestive heart failure

Level of evidence B A randomized double-blind study has demonstrated significant increase of ejection fraction (EF) and improved quality of life following IVIg administration, regardless of the congestive heart failure (CHF) cause. CHF is a proinflammatory state due to an increase of cytokines such as TNF-α and interleukin (IL)-1. Some of the cytokines have been shown to induce myocardial dysfunction due to negative inotropic effect [12]. Another possible mechanism in CHF pathogenesis is mediated by anti-β1 adrenergic receptor (*strength of recommendation IIa*).

Dilated cardiomyopathy

Level of evidence B Dilated cardiomyopathy (DCM) is caused by various triggers or may be idiopathic. Immune abnormalities and autoantibodies may play a role in the pathogenesis. Nevertheless, no significant effect was noted following IVIg administration in recent-onset DCM compared to placebo [13]. A trial on 17 patients with idiopathic DCM showed significant improvement of EF and quality of life compared with placebo [14]. Therefore, IVIg treatment in DCM remains controversial, and it is possible that IVIg treatment is beneficial in specific subpopulation and when treatment is initiated at a certain time window (*strength of recommendation IIb*).

Peripartum cardiomyopathy

Level of evidence C Peripartum cardiomyopathy (PPCM) is a rare disorder. It is believed that autoimmune mechanisms play a role in the pathogenesis. In a small nonrandomized retrospective trial, there was a significant improvement of EF following IVIg administration compared with conventional treatment. Although there is partial evidence of IVIg effectiveness in PPCM, its use should be considered due to the generally poor prognosis of PPCM patients who show no clinical improvement (*strength of recommendation IIa*).

Myocarditis

Level of evidence B Treatment with CS or cytotoxic agents was found ineffective [15, 16]. In an RCT trial of 62 patients with new-onset DCM of which some had myocarditis [13], there was no significant difference in EF improvement between IVIg and placebo group. Nevertheless, in a prospective nonrandomized trial, there was a significant improvement of fractional shortening compared to control. We conclude that further research is warranted regarding IVIg use in myocarditis due to inconclusive results (*strength of recommendation IIb*).

Table 5 The use of intravenous immunoglobulins in gyneco-obstetric diseases

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
Perinatal hemochromatosis	[212]	Case–control study; previous patients' pregnancies used as their own controls	IVIg 1 g/kg weekly since week 18	15 patients (16 pregnancies) with previous pregnancies resulting in perinatal hemochromatosis	Good outcome (survived with or without medical therapy) in 15 gestations treated with IVIg; in historical controls of the same mothers, 2 pregnancies had good outcome and 13 had poor outcome (fetal or neonatal death, or liver failure necessitating liver transplantation), $p=0.0009$
Recurrent pregnancy loss excluding antiphospholipid syndrome	[213]	Meta-analysis	IVIg	442 women with recurrent spontaneous miscarriages (at least 3) from eight RCTs; secondary recurrent miscarriages are defined as those in women that had at least a previous successful birth	No significant difference ($p=0.21$) between women with primary recurrent miscarriages treated with IVIg or without; however, there was a significant improvement of live births when IVIg was given to women with secondary recurrent miscarriages ($p=0.03$)
	[214]	Meta-analysis	IVIg versus placebo or no treatment	303 women with idiopathic recurrent abortions from 8 RCTs	No benefit of IVIg on recurrent pregnancy loss
	[215]	Meta-analysis	IVIg	246 women with recurrent spontaneous miscarriages (at least 2) from 5 RCTs; secondary recurrent miscarriages are defined as those in women that had at least a previous successful birth	No significant difference between women with primary recurrent miscarriages treated with IVIg or without; not enough patients to conclude something about women with secondary recurrent miscarriages but there was a trend towards improvement
	[216]	RCT	29 women received IVIg, 29 placebos; IVIg was administered from weeks 5–10 weekly at 0.8 g/kg every week, from weeks 10–20 at 0.8 g/kg every 2 weeks and from weeks 20–26 at 1 g/kg every 2 weeks; no IVIg as given after week 26	58 women with recurrent spontaneous miscarriages (at least 4); secondary recurrent miscarriages are defined as those in women who had at least a previous pregnancy that progressed to week 26 or more	No benefit in primary recurrent miscarriages but a trend towards improvement among women with secondary recurrent miscarriages
	[217]	Meta-analysis	IVIg in 125 patients, 115 received placebo	240 women with recurrent spontaneous miscarriages	No benefit of IVIg
	[217]	RCT	IVIg (Gammonativ) 20 g every 3 weeks, 5 courses after confirmation of pregnancy	41 women with recurrent spontaneous miscarriages	No benefit of IVIg neither for women with primary or secondary recurrent miscarriage
	[218]	RCT	22 patients received IVIg (Sclavo) 50 g over 2 days upon confirmation of pregnancy (weeks 5–7) and again 25 g 3 weeks later	46 women with recurrent spontaneous miscarriages	No benefit of IVIg
	[219]	RCT	47 patients received IVIg 0.5 g/kg every month starting up to 4 months before pregnancy and until weeks 28–32 of pregnancy; 48 patients received placebo	95 women with recurrent spontaneous miscarriages (2 or more)	More live births in women receiving placebo ($p=0.04$)

Table 5 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
	[220]	RCT	IVIg (Nordimmun, Novo-Nordisk, Gentofte, Denmark) 25–40 g per dose according to patient weight every 2 weeks until week 34 of pregnancy or placebo	34 women with secondary recurrent spontaneous abortion (subsequent to a birth or including at least one second trimester miscarriage)	More live births but not statistically significant in the IVIg group (52.9% against 29.4%)
	[221]	RCT	IVIg initial dose 30 g, then 20 g every 3 weeks until week 25 (Verum, Immuno GmbH, Heidelberg, Germany) or placebo	64 women with primary recurrent spontaneous abortion	No benefit of IVIg
Recurrent pregnancy loss in antiphospholipid syndrome	[222]	Meta-analysis	IVIg given in addition to heparin and aspirin	58 women with recurrent miscarriages due to antiphospholipid syndrome in 2 RCTs	Increased risk of pregnancy loss or premature birth in the group receiving IVIg
	[223]	Randomized trial	21 women received IVIg (IgVENA N; Sclavo, Siena, Italy) at the dose of 0.8 g/kg over 2 consecutive days as initial dose followed by 0.4 g/kg each month up to week 31; 19 women received aspirin 75 mg/day up to week 34 + heparin 5,700 IU/day up to week 37	40 women with at least 3 abortions due to antiphospholipid syndrome were treated since conception with IVIg or heparin + aspirin	More live births (84% against 57%, not significant difference) in the aspirin + heparin group ($p=0.06$)
	[224]	RCT	IVIg 2 g/kg (Gamimune-N, Bayer Corporation, West Haven, CT, USA) over 2 days every 4 weeks through 36 weeks' gestation	16 pregnant women (no more than 12 weeks' gestation) with recurrent miscarriages due to antiphospholipid syndrome received low-dose aspirin and heparin and received random IVIg or placebo	No benefit of IVIg
	[225]	Prospective two-center trial study	29 were treated with PD and LDA; 53 received IVIg 0.5 g/kg (Alphaglobin, Grifols International, Pisa, Italy) for 2 consecutive days, once a month from the 5th to the 32nd week of pregnancy	82 pregnant women with a history of recurrent fetal loss and APS	Live-birth rates were equivalent between groups (78% vs 76%), mean birth weight was higher in the IVIg group gestational hypertension and diabetes were found significantly more often in the PD group (14% vs 5%), respectively ($p<0.05$)
	[226]	Case series	Patients were treated with heparin (15), LDA (18), and CS (6); additionally, they received IVIg 0.4 g/kg for 5 days monthly from the first or early second trimester	19 pregnancies of 15 women with APS and recurrent fetal loss	The live-birth rate was 84%; compared to approximately 70% described in literature without IVIg
	[227]	Controlled trial	In phase III, they received heparin + LDA with or without IVIg	121 women with APS, who failed to achieve live births after 2 IVF attempts with heparin + LDA	The birth rate was 41% when IVIg was added and anti-PS or anti-PE involving IgG or IgM isotypes were present, as compared with 17% when H + A alone was administered; the IVF outcome did not improve when IVIg was administered in association with any other single APS antibodies

Table 5 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
	[228]	Controlled trial	IVIg 0.3 g/kg every 3 weeks until the 16th to 17th week of pregnancy	38 women after 3 or more consecutive first trimester spontaneous abortions and APS	Pregnancy proceeded beyond the first trimester in 34 of the patients (89.4%), and 31 patients (81.4%) gave birth to healthy infants at 37 to 42 weeks' gestation
	[229]	Case control	IVIg 0.5 g/kg for 2 days from the fifth week of pregnancy and repeated every 4 weeks until the 33rd week of gestation Data were compared to 70 matched uneventful pregnancies	14 women with a history of recurrent spontaneous abortion and APLA	No significant biometrical differences between the groups were seen; no fetal or neonatal growth retardation was seen
Premature rupture of membranes	[230]	RCT	IVIg (Pentaglobin, Biotest, Frankfurt/Main, Germany) 20 g, 24–48 h after premature rupture of membranes; thereafter, 10 g was administered in weekly intervals	18 women with premature rupture of membranes	Infants in treated group showed less laboratory and clinical signs compatible with prenatally acquired infection ($p<0.002$); less chorioamnionitis in treatment group ($p<0.036$)
Failure of *in vitro* fertilization	[231]	Meta-analysis	IVF along with or without IVIg	Women with IVF failure	Improvement in live-birth rate ($p=0.012$)
	[232]	RCT	IVIg (Gamimune 5%, Bayer Canada Inc., Etobicoke, Canada) 0.5 g/kg or placebo (saline), first infusion on the day of embryo transfer or during preceding 72 h, second infusion 4 weeks later upon evidence of embryonic heart activity	51 women after IVF failure	No significant improvement in implantation, pregnancy, or live birth rate

Pericardial diseases

Level of evidence C Pericardial involvement in Kawasaki disease may be seen in 6.3% to 24.5% of patients and may be complicated by cardiac tamponade despite IVIg therapy [17, 18], occasionally due to rupture of coronary aneurysms. There is a consensus that IVIg significantly decreases coronary aneurysms, but little is known regarding direct effect on the pericardium in the setting of mucocutaneous lymph node disease. It seems that septated pericarditis in Kawasaki disease response dramatically to IVIg but further research is warranted [19] (*strength of recommendation IIb*).

Low-dose IVIg therapy was found to be beneficial in 60% of lupus patients with pericarditis in a case series [20] (*strength of recommendation IIa*).

Chronic idiopathic pericarditis (CIP) appears in up to 25% of acute pericarditis cases. It may be associated with viral infections and autoantibodies [21]. There is limited evidence on the role of IVIg as an alternative therapy for prolonged steroid or colchicine treatment in CIP (*strength of recommendation IIa*).

Atherosclerosis

Atherosclerosis is believed to be mediated also by humeral and cellular immune mechanisms. There are accumulating data that support a role of IVIg in prevention of atherosclerosis. Possible mechanisms include decrease of matrix metalloproteinase 9 secretion from mononuclear cells [22], increase of IL-10 [12], and decrease of oxidized low-density lipoprotein uptake by macrophages [23]. Nevertheless, clinical trials are required in order to establish the relationship between IVIg use and atherosclerosis therapy.

Kawasaki disease

Level of evidence A It is the leading cause of acquired heart disease in the USA. Kawasaki disease is an FDA-approved absolute indication for IVIg therapy. The frequency of CA aneurysm development and associated morbidity and mortality have been dramatically decreased as a result of IVIg therapy when given within 10 days following the onset of fever. A single dose of 2 g/kg of IVIg over 10 H is usually

Table 6 The use of intravenous immunoglobulins in cardiac disease

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
Congestive heart failure (CHF)	[14]	RCT	Octagam (Octapharma) 0.4 g/kg per day for 5 days followed by monthly dose of 0.4 mg/kg for 5 months, compared with placebo	40 patients with symptomatic CHF (NYHA II/III) and ejection fraction (EF) <40% due to idiopathic dilated cardiomyopathy (42.5%) or secondary to ischemic heart disease; 20 patients (9 idiopathic DCM, 11 coronary artery disease) received IVIg; 20 patients received placebo	IVIg induced significant increase of EF by means of 5 EF units, regardless of the cause of CHF, compared to no significant change of EF in the placebo group; improved quality of life in 73% compared to 40% in placebo group; p value< 0.05
Dilated cardiomyopathy (DCM)	[13]	RCT	Gamimune N, 10% (Bayer Corporation), 1 g/kg IV each day on 2 consecutive days, compared to placebo	62 patients with new-onset DCM and EF ≤40% (with symptoms for less than 6 months); both idiopathic DCM and myocarditis patients were included; 33 patients received IVIg, and 29 patients were treated with placebo	Mean EF improved from 0.25±0.08 to 0.41±0.17 following 6 months for all patients; there was no significant difference in EF improvement between IVIg and placebo group
Peripartum cardiomyopathy (PPCM)	[233]	Retrospective study, case series	2 g/kg of IVIg given as 1 g/kg q.d. on 2 consecutive days along with conventional therapy, compared to conventional therapy alone	17 patients with PPCM; 6 received IVIg; all with NYHA class II–IV and EF<40%, within 6 months from delivery	In the control group, 1 patient died (9.09%), and others had a mean improvement of EF by 13±13 EF units, compared to 26±8 EF units in the IVIg group; p value 0.042
Myocarditis	[234]	Case series	Total dose of 1 to 2 g/kg IVIg over 48 h (Venilon, Venoglobulin-IH, and Polyglobin-N preparations were used); all patients received conventional therapy	9 patients: 6 patients with acute myocarditis, 3 patients with acute dilated cardiomyopathy; NYHA III and IV	Mean EF improved significantly, from 19.0± 7.5% to 35.4±9.1% following IVIg treatment; P value<0.01
	[235]	Prospective nonrandomized trial	IVIg (Immuno AG, Vienna), total dose of 2 g/kg over a maximum of 24 h; some of the IVIg groups were treated with an additional dose of 1 g/kg a week later, compared with conventional therapy	46 patients with acute onset disease and severely depressed EF; 21 patients received IVIg; a control group of 25 patients was collected from retrospective files	There was no significant change of survival in the IVIg group compared to control; IVIg group had a higher fractional shortening than control during 3- to 6-month follow-up period; the control group failed to normalize EF; p value 0.033
Chronic idiopathic pericarditis (CIP)	[21]	Case series	Five monthly cycles of 0.4 g/kg per day for 5 consecutive days, followed by administration every 2 months	4 patients with CIP	Remarkable response in 3 patients, and a long-standing remission with no need for further steroid treatment; 1 patient with partial response
Pericardial diseases	[19]	Case report	Total dose of 2 g/kg of IVIg, and 100 mg/kg per day of acetylsalicylic acid for 14 days	1 patient with Kawasaki disease, left anterior descending artery aneurysm and septated pericardial effusion	2 weeks following treatment initiation, there was disappearance of the pericardial effusion and no change of the coronary aneurysm
	[17]	Case report	IVIg treatment starting at the 16th day following initial presentation, total of 2 g/kg, and 30 mg/kg per day of MP for 5 days	1 patient with Kawasaki disease, complicated by cardiac tamponade	Failure of treatment and need for salvage pericardiocentesis
	[20]	Case series	Low-dose IVIg therapy—approximately 0.5 g/kg every 5±2 weeks for 6±6 courses	62 lupus patients, of which several developed pericardial disease	60% of affected patients had resolution of pericardial involvement

Table 6 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
Kawasaki disease (KD)	[236]	Meta-analysis	Low (≤80 mg/kg) and high doses (>80 mg/kg) of aspirin and low (≤1 g/kg) to high doses (>1 g/kg) of IVIg over 3–5 days	Review of all published papers from 1967 to 1993; 30–60 days of follow-up	The rates of coronary aneurysms were significantly reduced due to IVIg therapy compared to aspirin alone; high-dose IVIg had lower aneurysm rates compared with low-dose therapy; higher aspirin dose did not alter outcome; p value<0.0001
	[237]	Meta-analysis of RCT	Patients received: (1) various doses of IVIg, plus aspirin, versus placebo; (2) different doses of IVIg (0.1, 0.2, 0.4 g/kg for 5 days); (3) IVIg 0.4 g/kg for 5 days Vs 2 g/kg once; (4) comparison between 4 types of preparations	16 RCTs of patients with KD	(1) Significant decrease in new CAAs, fever, and hospitalization at 30 days with IVIg RR (95% CI)=0.74 (0.61 to 0.90) but only trend at 60 days (p=0.06); (2) dose comparisons showed a decrease in the number of new CAAs with increased dose; (3) less CAA for 2 g/kg once RR (95%)=4.47 (1.55 to 12.86); (4) no difference
	[238]	Multicenter RCT	IVIg 0.4 g/kg for 4 days, with or without aspirin	153 patients (78 with KD, 75 controls)	Reduction of echocardiogram-proven CAA from 23% to 8% at 2 weeks (p=0.01) and from 18% to 4% at 7 weeks (p=0.005)
	[239]	Case control study	IVIg 2 g/kg per day at 1–5 or 5+ days from fever onset	178 patients with KD (89 in each group)	Patients treated within 5 days had shorter fever duration (p<0.001) and less CAA at 1 year (p=0.02)
	[240]	RCT	IVIg 2 g/kg per dose and aspirin; four different brands were used in four groups: Venoglobulin-S (brand A; Alpha Therapeutics, Los Angeles, CA, USA), Gamimune_ N (brand B; Bayer Therapeutics, Elkhart, IN, USA), Intraglobin F (brand C; Biotest Pharma, Dreieich, Germany), "CBSF" human immunoglobulin (brand D; Scottish National Blood Transfusion Service Protein Fractionation Center, Edinburgh, Scotland, UK)	435 patients with KD	Patients receiving brand C had higher rates of CAAs (p= 0.01), nonresponsiveness (p=0.001) and giant aneurysm (p=0.008)
	[241]	RCT	Patients were divided to 2 groups receiving IVIg 1 or 2 g/kg, plus aspirin	242 children with KD	There was no significant difference in the incidence of CAL (p>0.05)
	[242]	Multicenter prospective RCT	Group A: Tx with IVIg 2 g/kg and additional 2 g/kg for nonresponders; group B: IVIg 1 g/kg, and additional dose first 1 g/kg then 2 g/kg for nonresponders; IVIg used: Venilon (Teijin Pharma, Japan), Venoglobulin-IH (Venesis, Japan) or Polyglobin-N (Bayer Yakuhin, Japan)	109 patients with KD divided to 2 groups	No significant difference in CAA between the patients; discriminate analysis suggested that 52.4% of the patients in group A could be treated with 1 g/kg IVIg only

Table 6 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
	[243]	Multicenter RCT	Single infusion of 2 or 0.4 g/kg for 4 days; both received aspirin (100 mg/kg per day through the 14th day of illness, then 3 to 5 mg/kg per day)	549 children with KD	Single-dose patients had less fever (p=0.001), inflammatory markers, and CAA (p=0.004)
Rheumatic fever (RF)	[244]	RCT	IVIg (Intragam, from Common wealth Serum Laboratories) 1 g/kg on days 1 and 2 and 0.4 g/kg on days 14 and 28	59 patients with RF, diagnosed according to Jones criteria; 27 patients received IVIg and 32 patients received placebo	IVIg did not affect the natural history of RF during 52 weeks of follow-up
Congenital heart block	[27]	Case series	1 gm/kg IVIg (Sandoglobulin; Novartis, Bern, Switzerland), at 14th and 18th weeks of gestation; PD (40 mg/day) from the 14th week, which was tapered down to 10 mg/day	8 pregnant women with past history of an affected child with neonatal lupus	1 child was born with erythematosus skin rash, and 1 child had congenital heart block—interestingly, his mother was the only patient that refused PD intake
Awaiting for cardiac transplantation	[245]	Controlled trial	1 to 3 monthly courses of IVIg 2 g/kg administered in 4 divided daily doses or high-dose IVIg therapy (3 g/kg) in poorly responsive patients; all patients received monthly 0.5–1.0 g/m^2 cyclosporine	16 sensitized patients with left ventricular assist device (LVAD) awaiting cardiac transplantation; results were compared to plasmapheresis (n=4) and to cyclosporine alone (n=28)	Within 1 week of infusion of IVIg, the reactivity of IgG antibodies for allogeneic HLA class I molecules was reduced by a mean of 33%; high-dose IVIg for unresponsive patients resulted in a mean reduction of 20%; IVIg has earlier onset of action and greater efficacy than plasmapheresis; waiting time for donation was significantly reduced from 7.1 to 3.3 months; p value<0.05
	[246]	Retrospective, nonrandomized, controlled trial	IVIg, 10 g daily for 3 days or conventional therapy following LVAD transplantation	51 nonsensitized patients with CHF, who received left ventricular assist device transplantation received either IVIg (n=26) or conventional therapy (n=25)	Low-dose IVIg therapy failed to reduce sensitization rate in nonsensitized LVAD patients who received blood transfusion during bridge time to cardiac transplantation
	[247]	Case series	IVIg 2 g/kg given 1 day before the Norwood procedure, repeated 3 weeks and 4 months later	7 infants with hypoplastic left heart syndrome who underwent Norwood procedure with cryopreserved allograft pulmonary artery patch	IVIg did not prevent sensitization of the previously unsensitized patients

recommended along with a high dosage of aspirin [24]. Failure of IVIg treatment in Kawasaki disease and the need for several consecutive IVIg doses is usually caused by delayed initiation of treatment [17]. Detailed treatment algorithms may be found elsewhere [25] (*strength of recommendation I*).

Rheumatic fever

Level of evidence B Because there is no efficient treatment for established rheumatic carditis, several agents has been proposed in an attempt to change the natural history. IVIg has failed to change clinical outcome and disease progression and therefore is not recommended for treatment of acute rheumatic fever (*strength of recommendation III*).

Congenital heart block in neonatal lupus erythematosus

Level of evidence C Neonatal lupus erythematosus is a rare disease that is associated with anti-Ro and anti-La autoantibodies [26]. A single case series of eight subjects had

nonconclusive results regarding the effect of IVIg and PD in prevention of congenital heart block [27] (*strength of recommendation IIb*).

Cardiac transplantation

Level of evidence C IVIg has anti-idiotypic properties, as well as human leukocyte antigen molecules that may neutralize high panel reactive antibodies in sensitized patients awaiting cardiac transplantation. There is some evidence for IVIg benefit in patients with left ventricular assist device who are awaiting cardiac transplantation (strength of recommendation IIa). Nevertheless, IVIg did not reduce sensitization in previously unsensitized patients who underwent Norwood procedure (*strength of recommendation III*).

The following conditions refer to (Table 7).

Ophthalmic IgA bullous disease

Level of evidence C Linear IgA bullous disease may affect the eye (in 67% of patients) and may present as chronic cicatrizing conjunctivitis. Systemic disease may be treated with systemic CS and dapsone. In poorly responsive patients, IVIg treatment may be used, although its use should be further investigated (*strength of recommendation IIa*).

Mucous membrane pemphigoid

Level of evidence C Mucous membrane pemphigoid (MMP) may involve the eye. There is some evidence for the beneficial effect of IVIg in MMP that involves the eye. IVIg may provide more rapid control of symptoms and prevents remissions during long-term follow-up [28, 29]. This notion should be supported by larger randomized trials (*strength of recommendation IIa*).

Ocular Behcet's disease

Level of evidence C There are some but limited data regarding the potential benefit of IVIg use in Behcet's disease. Further study is required. Nevertheless, IVIg should be carefully considered in patients resistant to conventional immunosuppressive therapy (*strength of recommendation IIa*).

Optic neuritis

Level of evidence A The natural history of optic neuritis in multiple sclerosis patients is not altered by IVIg transfusion, neither clinically nor radiologically. Therefore, IVIg is not recommended in that setting (*strength of recommendation III*).

Inflammatory pseudotumor of orbit

Level of evidence C There is anecdotal evidence for the possible beneficial role of IVIg in the treatment of inflammatory pseudotumor of orbit (*strength of recommendation IIb*).

Birdshot retinochoroiditis

Level of evidence C Birdshot retinochoroiditis is a rare inflammatory disease (bilateral autoimmune posterior uveitis of idiopathic origin). Without immunosuppressive treatment, a progressive visual deterioration will occurs in 80% of patients [30]. There is supporting evidence for the use of IVIg, especially in patients unresponsive to other therapies (*strength of recommendation IIa*).

Orbital myositis

Level of evidence C It is caused by inflammatory process of unknown etiology, which is confined to the orbit. There are very limited data on the effect of IVIg in patients with orbital myositis. Such treatment might be considered in symptomatic patients, resistant to other therapies (*strength of recommendation IIa*).

Refractory uveitis

Level of evidence C Most cases of refractory uveitis (RU) are associated with autoimmune mechanisms. There are some data supporting the use of IVIg in resistant RU, although more research is required in order to establish clinical guidelines (strength of recommendation IIa).

Graves' ophthalmopathy

Level of evidence B It seems that IVIg is as efficient as CS in the treatment of Graves' ophthalmopathy. Nevertheless, despite similar clinical response to treatment, IVIg was associated with fewer side effects and the study group showed more tolerance towards it. Therefore, we conclude that IVIg should be considered in CS intolerance (*strength of recommendation I*).

Paraneoplastic visual loss

Level of evidence C There is limited evidence for the benefit of IVIg in cancer-associated retinopathy. Nevertheless, since spontaneous recovery usually does not occur, IVIg may be used in progressive visual compromise in addition to CS or plasmapheresis (*strength of recommendation IIb*).

The following conditions refer to (Table 8).

Table 7 The use of intravenous immunoglobulins in ophthalmic disease

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
Ophthalmic IgA bullous disease	[248]	Case report	Monthly IVIg treatment, 4 g/kg per month, with graduate discontinuation following clinical improvement	1 patient with chronic cicatrizing conjunctivitis due to linear IgA bullous disease with poor response to topical or systemic CS	Improvement of clinical symptoms with maximal effect 10–12 days following infusion; decrease of circulating IgA anti-97-kDa epidermal protein
Mucous membrane pemphigoid (MMP)	[28]	Nonrandomized controlled trial	IVIg, 2 g/kg per cycle, cycles were repeated every 2–4 weeks, compared to conventional immunosuppressive therapy	16 patients that were equally divided to control and IVIg group	Remission was achieved after 4 months in IVIg group vs 8.5 months in control group; IVIg had less recurrence and decreased progression; p value<0.05
Ocular Behcet's disease	[91]	Case series	IVIg 0.4 g/kg per day: 5 times in first week, 3 more in the next months and once every 20 days for total of 3 months	4 patients refractory to CS and cyclosporine A	Control of acute inflammation and preservation of remission for 1 year; marked improvement of visual acuity
Optic neuritis	[249]	RCT	27 patients were treated with IVIg (Gamimune N; Bayer Pharmaceutical Division, West Haven, CT, USA) 0.4 g/kg per day for 5 days followed by 3 monthly single cycles vs placebo (n=28)	55 patients with multiple sclerosis and visual loss due to optic neuritis	No difference between treatment groups was observed; there was no absolute reversal of persistent visual loss; the trial was terminated by the National Eye Institute
	[250]	RCT	IVIg 0.4 g/kg per day (Immunoglobulin SSI liquid; Statens Serum Institute, Copenhagen, Denmark), infused on days 0–2, and 1 to 2 months later (n=34) vs placebo (n=34)	68 patients with recent visual accuracy loss; 34 patients received IVIg (of which 15 had multiple sclerosis), compared with 34 patients who received placebo (of which 8 patients had multiple sclerosis)	No immediate or delayed effects were observed; there was no change in visual acuity, MRI findings and visual evoked potential results
Inflammatory pseudotumor of orbit	[251]	Case report	IVIg 2 g/kg divided over 4 days	1 patient with inflammatory pseudotumor of the orbit, resistant to systemic CS, and radiation therapy	Both clinical and radiographic improvement within days
Birdshot retinochoroiditis	[252]	Case series	IVIg 0.4 g/kg per day for 4 days; then 0.6 g/kg per day for 2 days, every 4 weeks	37, of which 18 were followed up	Visual acuity of 53% of patients' eyes has increased by 2.6±1.5; in 29% of patients, visual acuity remained stable, and in 18% of eyes VA have decrease
	[30]	Case series	IVIg 1.6 g/kg every month for 6 months, followed by 1.2–1.6 g/kg every 6–8 weeks	18 patients	In patients with visual acuity of 20/30, there was increase in visual acuity in 53.8% of eyes and decrease of acuity in 7.7% while there was no change in the remaining eyes
Orbital myositis	[253]	Case report	IVIg (Venimmun) 0.3 g/kg per day for 3 days	1 patient intolerant to CS treatment and poor clinical response	Both clinical and tomographic resolution within 2 weeks
Refractory uveitis	[254]	Case series	IVIg (Baxter Healthcare, Glendale, CA, USA), 0.5 g/kg per day for 3 days each month; median of 7.5 cycles	10 patients with poor response to immunosuppression (some cases were idiopathic, others were secondary to sarcoidosis, Behcet, inflammatory bowel disease, and birdshot retinochoroiditis)	50% sustained improvement of visual acuity, 20% have required a reduced doses of immunosuppressive therapy without disease progression; the patient with sarcoidosis had improved vision and reduced need for immunosuppression, although that effect was not sustained 4.5 months following

Table 7 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
					treatment discontinuation; the Behcet patient showed marked improvement
	[255]	Case series	IVIg, 1–2.5 g/kg per cycle over 3 days; cycles were repeated every 2–4 weeks initially and every 5 to 6 weeks after effect was observed; treatment time averaged at 16.8 months	5 patients unresponsive to conventional therapy, of which 1 patient had juvenile idiopathic arthritis and 1 patient had psoriatic arthritis; 1 patient had retinal vasculitis and APLA; the other 2 cases were idiopathic	In 60% (2 idiopathic cases, 1 patient with vasculitis and APLA), treatment was effective in controlling inflammation, and visual acuity remained stable or improved
Graves' ophthalmopathy	[256]	Prospective nonrandomized	35 patients were treated with IVIg and 27 with CS	62 patients with Graves' ophthalmopathy	76% response in IVIg-treated patients compared to 66% in CS group, in a manner that was statistically insignificant; side effects were more common in patients receiving CS therapy
	[257]	RCT	21 patients were treated with 6 cycles of 1 g/kg IVIg for 2 days every 3 weeks; 19 patients were treated with oral prednisolone (starting dose 100 mg/day)	40 patients	No marked difference between IVIg (62% response) and prednisolone (63% response); both groups had significantly improved proptosis, visual acuity, decrease of intraocular pressure, and decrease of eye muscle area
Paraneoplastic visual loss	[258]	Case series	2 patients were treated with IVIg 0.4 mg/kg per day for 5 days; 1 patient received single-dose d/t treatment intolerance	3 patients	1st patient improved from distinguishing hand movement to 20/40 and 20/50 OS; improved visual fields 2nd patient, no improvement 3rd patient, improved visual field without change in visual acuity
	[259]	Case report	IVIg, as well as radiotherapy and surgical resection	1 patient with melanoma-associated retinopathy	Improvement in visual fields over 1 year of follow-up

Lupus nephritis

Level of evidence B A few case reports and a single RCT clearly indicate the efficacy of IVIg in the treatment of lupus nephritis. In all cases, patients had a beneficial response to IVIg and a significant improvement of renal function was noted. Therefore, IVIg is recommended as an alternative treatment in lupus nephritis or in cases that conventional immunosuppressive treatment fails (*strength of recommendation I*).

Renal transplant rejection

Level of evidence C Although evidence for the use of IVIg in renal transplant rejection is limited to case reports and case series results showed that IVIg may be effective for treating acute or chronic renal transplant rejection. IVIg may improve renal function and reverse Ab-mediated rejection. IVIg may be considered among the treatment options generally together with immunosuppressive therapy (*strength of recommendation I*).

ANCA-associated rapidly progressive glomerulonephritis (RPGN)

Level of evidence C There is weak evidence indicating significant benefit from the use of IVIg in antineutrophil cytoplasmic antibody (ANCA)-associated RPGN. Several case series and case reports showed that IVIg may improve renal function and therefore is recommended as a potential therapy for ANCA-associated RPGN (*strength of recommendation I*).

Table 8 The use of intravenous immunoglobulins in kidney diseases

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
Membranous nephropathy	[260]	Retrospective uncontrolled trial	IVIg 0.4 g/kg every 21 days (mean duration of treatment was 15 months equal to 21 cycles)	13 adult patients (8 males, 5 females) with primary membranous glomerulonephritis	5 patients had complete remission 5 patients had partial remission 3 patients no clinical remission but presented marked reduction in proteinuria
	[261]	Case series	IVIg 0.4 g/kg per day for 3 days every 21 days (3 courses), then once every 3 weeks for 10 months	9 patients with biopsy-confirmed idiopathic membranous nephropathy	5 patients with normal renal function: 4 had complete remission, 1 had partial remission 4 patients with moderate renal insufficiency: 1 had complete remission, 2 had partial remission, 1 had no response
	[262]	Retrospective analysis	IVIg 0.1–0.15 g/kg per day for 6 days, 1–3 courses	86 with primary membranous glomerulonephritis	30 patients were treated with IVIg: 13 patients had complete remission; 11 patients had partial remission; 3 patients had continued nephrotic state with renal dysfunction; 3 patients reached end-stage renal disease
IgA nephropathy	[263]	Single-arm, nonrandomized study	IVIg 2 g/kg monthly for 6 months	14 patients with progressive IgA nephropathy	6 patients received IVIg; the mean loss of renal function and proteinuria were significantly reduced in the IVIg group (p=0.024, p= 0.015, respectively)
	[63]	Open prospective cohort study	IVIg 2 g/kg per month for 3 months followed by IMIg for another 6 months	11 patients with moderate IgA nephropathy	Proteinuria, glomerular filtration rate, and histologic index of activity were significantly decreased
BK-virus-associated nephropathy in renal allograft recipients	[264]	Case series	IVIg 2 g/kg over 2–5 days + immunosuppression	8 renal allograft recipients with BK-virus-associated nephropathy	88% of the patients were dialysis free and had stable renal function after follow-up of 15 months
	[265]	Case report	IVIg 0.6 g/kg, 5 doses repeated every 4–6 weeks	A pediatric renal transplant patient recipients with BK-virus-associated nephropathy	Stabilized renal function, reduced viral load, and resolved histological findings were noted after IVIg treatment
ANCA-associated rapidly progressive glomerulonephritis (RPGN)	[266]	Case series	IVIg 0.4 g/kg per day for 5 days + CS ± CP after IVIg	Twelve patients with MPO-ANCA-associated RPGN (7 men, 5 women)	After IVIg treatment, a significant reduction was noted in white blood cell count (p<0.05), in C-reactive protein values (p<0.001), in Birmingham vasculitis; Activity Score (p<0.001) and in the rate of change in 1/Cre (p<0.05)
	[58]	Case series	IVIg 0.4 g/kg per day for 5 days + immunosuppressive therapy	30 patients with MPO-ANCA-associated RPGN (male 17, female 13)	After IVIg, significant reduction in CRP (p<0.001), improvement in serum creatinine in 63% of patients; at 3 months, disease activity was completely reduced; at 6 months, renal survival rate was 92% and life survival was 93%
	[267]	Case report	IVIg (Omr-IgG-am5%IV) 0.5 g/kg per day for 4 days after immunosuppressive therapy	A 68 year-old woman with RPGN	Significant improvement in renal function after IVIg treatment

Table 8 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
	[268]	Case reports	IVIg	A 66-year-old male and a 14-year-old boy with MPO-ANCA-associated RPGN	Significant improvement in both patients including renal function after IVIg treatment
Renal transplant rejection	[269]	Prospective pilot trial	IVIg 1 g/kg per dose every week for 4 weeks + rituximab 1 week after last IVIg infusion	6 pediatric renal transplant recipients with chronic antibody-mediated rejection	4/6 responded to IVIg with significant improvement in glomerular filtration rate ($p<0.05$); 2/6 no response
	[270]	Case report	IVIg 0.5 g/kg every other day for 4 cycles + rituximab + plasmapheresis	A 46-year-old female renal transplant recipient with antibody-mediated rejection	Improvement in renal function
	[271]	Case report	IVIg 0.15 g/kg within 72 h of transplantation, and 0.1 g/kg every 2 weeks for 4 doses, followed by monthly infusions for 2 doses + plasmapheresis + monoclonal anti-T lymphocyte antibody therapy	A 14-year-old renal transplant recipient with antibody-mediated rejection	Improvement in renal function and reverse of Ab-mediated rejection
	[272]	Case series	IVIg 2 g/kg	7 renal transplant recipient with antibody-mediated rejection	IVIg-induced reversion of acute rejection in all patients and reduced donor-specific anti-HLA alloantibody levels
Lupus nephritis	[273]	RCT	During 18 months, 5 received IVIg 0.4 g/kg once a month, 9 continued CP	14 patients with proliferative lupus nephritis	Treatment with IVIg as maintenance therapy was safe and effective as CP
	[274]	Case series	IVIg, 0.4 g/kg for 5 days, of ISIVEN (Istituto Sierovaccinogeno Italiano I. S.I.S.p.A, Italy).	7 lupus nephritis patients who failed to respond to at least PD and CP	All patients had a beneficial response to IVIg; all had significant decrease in proteinuria
	[275]	Case report	IVIg 2.8 g/kg, one dose	A 39 year-old female SLE patient with lupus serositis and nephritis	Clinical improvement and significant decrease in proteinuria.
	[276]	Case report	IVIg 12.5 g/day for 5 successive days after CS and plasmapheresis treatment	A 34-year-old Japanese female patient with rapidly progressive lupus nephritis associated with anti-MPO antibodies	Significant improvement of renal function after IVIg treatment

BK-virus-associated nephropathy in renal allograft recipients

Level of evidence C The use of IVIg in BK-virus-associated nephropathy in renal allograft recipient is limited only in a few case reports. Nevertheless, in these cases, IVIg showed significant efficacy and with concomitant reduction of immunosuppression it may be considered as one of the treatment options in this disease (*strength of recommendation I*).

IgA nephropathy

Level of evidence B Results coming from a single-arm nonrandomized study and a prospective cohort study showed that IVIg may be effective in treating severe IgA nephropathy and therefore it may be considered as a possible treatment option. However, RCTs are needed to confirm this efficacy (*strength of recommendation I*).

Membranous nephropathy

The efficacy of IVIg in membranous nephropathy was studied in few retrospective trials and a case series. Results from these studies indicate that IVIg may be effective in induction of remission. Although there is no strong evidence, IVIg may be considered as an additional option in treatment of membranous nephropathy (strength of level of evidence C; *recommendation I*).

The following conditions refer to (Table 9).

Autoimmune blistering diseases

Pemphigus vulgaris

Level of evidence B There is some evidence that IVIg have steroid-sparing effect and may be effective as monotherapy and/or adjunctive therapy in patients with previously severe unresponsive pemphigus vulgaris (*strength of recommendation IIa*).

Pemphigus foliaceus

Level of evidence C Adjunctive to standard immunotherapy treatment with IVIg may cause improvement in clinical course and may have steroid-sparing effect in previously steroid-dependent patients with refractory pemphigus foliaceus (*strength of recommendation IIa*).

Bullous pemphigoid

Level of evidence C In some severe cases of bullous pemphigoid, IVIg was found to be effective as monotherapy and adjunctive therapy as well; it had steroid-sparing effect and led to improvement of quality of life (*strength of recommendation IIa*).

Mucous membrane pemphigoid

Level of evidence C There is some evidence that IVIg monotherapy may be at least as effective as standard immunosuppressive treatment and lead to quick therapy response and better quality of life (*strength of recommendation IIa*).

Epidermolysis bullosa acquisita, linear IgA disease, pemphigoid gestationis

Level of evidence C The sparse data of positive effect of IVIg on severe cases of epidermolysis bullosa acquisita, linear IgA disease, and pemphigoid gestationis were published (*strength of recommendation IIa*).

Summary In autoimmune blistering diseases, the treatment with IVIg may be effective and has to be implicated in cases with severe disease, resistant to conventional therapy or those who experienced severe complications of such therapy.

Other immune-mediated dermatoses

Stevens–Johnson syndrome and toxic epidermal necrolysis

Level of evidence C The randomized studies have not been performed and the current knowledge about effectiveness of IVIg in SJS and TEN is based on results of multiple prospective noncontrolled studies, retrospective case series, and case reports. The data are limited and inconclusive (*strength of recommendation IIb*).

Atopic dermatitis

Level of evidence B The current data based on single, randomized, controlled, and evaluator-blinded trial and number of prospective noncontrolled studies suggest that IVIg may be effective as monotherapy in pediatric patients and as adjunctive therapy in adults. However, in view of the low-cost effectiveness of IVIg, this treatment should be used in cases of severe disabling atopic dermatitis (*strength of recommendation IIa*).

Urticaria

Level of evidence C A number of case reports and case series describe the beneficial effect of IVIg in chronic idiopathic and autoimmune urticaria, but randomized controlled studies are still lacking. The use of IVIg has to be limited to severe unresponsive cases of chronic urticaria or in case of severe complications of conventional treatment (*strength of recommendation IIa*).

Psoriasis

Level of evidence C Only three cases of severe resistant psoriasis with psoriatic arthritis responsive to treatment with high-dose immunoglobulin were reported. We conclude that there is now evidence of effectiveness of IVIg in psoriasis (*strength of recommendation IIb*).

Pyoderma gangrenosum

Level of evidence C IVIg was successfully used in few cases of previously unresponsive pyoderma gangrenosum, but its systematic use cannot be recommended (*strength of recommendation IIa*).

Miscellaneous dermatoses

Level of evidence C Several case reports and case series showed IVIg to be effective for nephrogenic fibrosing dermopathy, pretibial myxedema, and Arndt–Gottron scleromyxedema, but still well-controlled studies are lacking. We suppose that IVIg can be used in severe cases of these rare conditions, unresponsive to conventional treatment (*strength of recommendation IIa*).

The following conditions refer to (Table 10).

Table 9 The use of intravenous immunoglobulins in dermatologic diseases

Results/response	Number of patients	Intervention including dose and IVIg preparation used	Study design	Ref.	Disease
21/21 reached sustained remission; mean time to clinical response 4.5 months; maintenance therapy for a mean 22.7 months; compared to pretreatment period the study subjects received a lower dosage of CS and immune-suppressive therapy, had fewer side effects, recurrences, and relapses, needed fewer hospital admissions and days of hospital stay ($p<0.001$), and reported better quality of life ($p<0.0001$)	21 patients with severe pemphigus vulgaris unresponsive to corticosteroid and immune-suppressive agents	Monotherapy 2 g/kg given in 3 days in 4-week interval until complete healing, afterwards after 6, 8, 10, 12, 14, and 16 weeks if patient is disease free; end point—disease free with a 16-week interval between the 2 infusion cycles; adjunctive to other systemic therapy, not effective in the beginning of trial	Uncontrolled trial	[277]	Pemphigus vulgaris
10/12 (83%) responded, 6/12 (50%) had complete remission and 4/12 (33%) partial response; 72% decline of pemphigus antibody levels and steroid-sparing effect	12 patients with severe unresponsive pemphigus vulgaris	IVIg for 6 months as adjuvant to immune-modulating therapy	Uncontrolled trial	[278]	
No new lesions and 72% decline of pemphigus antibodies levels after 1 week, 80% reduction of extent of existing lesions in 5/6 patients after 2 weeks, 41% reduction of steroid doses after 3 weeks	6 patients with active pemphigus vulgaris, unresponsive to at least 2 months of CS therapy	IVIg 2 g/kg in 5-day cycles (as 5% solution, Venoglobulin S; Alpha Therapeutics Co, LA, CA, USA) concurrent with CS and cyclophosphamide 100–150 mg/day	Uncontrolled trial	[279]	
Significant reduction of total PD dose ($p=0.004$), duration of PD therapy ($p=0.003$), and number of relapses ($p<0.001$); CS was discontinued over a mean period of 4.3 months	15 patients with steroid-dependent pemphigus vulgaris, mean follow-up of 6.2 years	IVIg 1 to 2 g/kg given in 3 doses on 3 consecutive days as a 4- to 5-h infusion at a frequency of every 3 to 4 weeks adjunctive to CS (no other immunosuppressive therapy was allowed); intervals were increased to 6, 8, 10, 12, 14, and 16 weeks, if clinical response was achieved	Retrospective analysis	[280]	
38/39 on adjunctive therapy improved; in monotherapy group, no change in 2 patients, worth in 1	42 patients with pemphigus vulgaris	IVIg 2 g/kg per month in 37 patients; 0.3 g/kg per day in 4 patients, 0.25 g/kg per day in 1 patient; Sandoglobulin® in 10, Puimmun® in1, NA in 31 adjunctive in 39, monotherapy in 3	Review of published case reports	[239]	
6/7 did not respond; 1/7 had partial response with >50% improvement (but died 1 month after IVIg cycle of pneumonitis)	7 patients with pemphigus vulgaris	As adjunctive therapy in the dose of 2 g/kg per cycle, 4/7 patients received Venoglobulin®; other 3 patients received Gammagard/Gammar P.I.V/Gamimune; mean duration of treatment was 7 months	Case series	[281]	
11/11 had effective clinical response in mean of 5.3 months, clinical remission for a mean period of 18.6 months after discontinuation of IVIg; After IVIg, the study subjects received a lower dosage of CS ($p=0.001$), had fewer side effects ($p=0.002$), recurrences, and relapses ($p=0.001$), had fewer hospital admissions and days of hospital stay ($p<0.01$), and had better quality of life ($p=0.001$) compared to pretreatment period	11 patients with refractory pemphigus foliaceus	IVIg 2 g/kg given over 3 days in 4-week interval until complete healing, afterwards after 6, 8, 10, 12, 14, and 16 weeks if patient is disease free; end point—disease free with a 16-week interval between the 2 infusion cycles; adjunctive to other systemic therapy, previously not effective	Uncontrolled trial	[282]	Pemphigus foliaceus

8/8 significant reduction of antidesmoglein antibodies after 4 months of treatment (p NA), nondetectable titers after 13 months, serological remission after additional observation period of 5 months	8 patients with severe pemphigus foliaceus	IVIg	Uncontrolled trial	[283]	
CS gradually discontinued over a mean period of 2.8 mo, with resulting reduction of PD total dose (p=0.005), total duration of PD treatment (p=0.02) and number of relapses (p=0.002) according to pre-IVIg therapy.	7 steroid dependent pemphigus foliaceus patients.	In the beginning of the trial adjunctive to CS and as monotherapy afterwards.	Uncontrolled trial	[284]	
All improved	28 patients with pemphigus foliaceus	Adjunctive IVIg 1 to 2 g/kg per month, 0.27 g/kg per month in 1, continued for several weeks to more than 5 months	Review of published case reports	[239]	
15/15 clinical response within mean of 2.9 months; all patients demonstrated fewer hospital admissions, fewer relapses and recurrences, significant steroid-sparing effect (were tapered over a mean period of 3.3 months), and quality of life improvement compared to pre-IVIg therapy (p<0.0001)	15 patients with recurrent bullous pemphigoid despite oral PD and systemic immune-modulating treatment	IVIg 2 g/kg over 3 days by 4–5-h infusion adjunctive to oral PD, given every 4 weeks, until clinical stabilization; intervals were gradually increased to 6, 8, 10, 12, 14, and 16 weeks (mean number of cycles 14.7)	Uncontrolled trial	[285]	Bullous pemphigoid
12/17 (70%) improved; 5/17 (30%) had no change; in some patients, high-dose IVIg had systemic steroid-sparing effect; the lack of response was observed in low-dose or single-effusion cases; early treatment, multiple treatment cycles, and concomitant immunosuppressive treatment led to longer and more sustained remissions	17 patients with severe bullous pemphigoid	15 patients received high-dose IVIg 2 g/kg per month for 1 month (12 patients) to 3 months (1 patient); 2 patients received 0.1 and 0.3 g/kg per day for 5 days (low dose), 10 patients as monotherapy and 8 adjunctive to immunosuppressive therapy	Review of published case reports	[286]	
1/3 complete response after 4 cycles, maintained with 5 additional cycles; 2 patients had no response	3 patients with bullous pemphigoid	Adjunctive therapy with 2 g/kg per month of Venoglobulin® in 2 and Carimune® in 1 of 3 patients for mean 7 months	Case report	[281]	
19/22 improved on adjunctive therapy, 8/12 improved on monotherapy within 2 weeks–4 months	34 patients with bullous pemphigoid	Adjunctive 22, monotherapy in 12 2 g/kg per month in 32 patients, 0.1 g/kg per day for 5 days and 0.3 g/kg per day for 5 days in 2 patients; Venoglobulin® in 11, Sandoglobulin® in 4, NA in 23 continued up to 14 months	Review of published case reports	[239]	
Clinical response in 7/7 patients, treated with IVIg, after a mean period of 4.5 months, sustained remission after a mean treatment period of 26.9 months, improvement of quality of life after IVIg therapy (p<0.001); reduction of antibody titers in both groups (p=0.015), but faster in IVIg group (p=0.03)	7 patients (mean age of onset 55.5) on IVIg monotherapy vs. 7 random patients (mean age of onset 55) with severe (+3) oral pemphigoid; treatment period 12 months	Monotherapy with 1 to 2 g/kg per month IVIg vs. conventional immunosuppressive treatment (PD and dapsone or AZA or MTX or tacrolimus or CP); adjunctive local treatment with sublesional injections of triamcinolone acetonide (proven not to be systemically absorbed by serum cortisol levels) was given to patients in both groups	Controlled trial	[287]	Mucous membrane pemphigoid
Significant improvement, reduction of relapses, duration and total dosage of corticosteroid therapy and quality of life after IVIg (p NA)	15 patients with severe mucous membrane pemphigoid	IVIg 1 to 2 g/kg per month	Uncontrolled trial	[284]	

Table 9 (continued)

Results/response	Number of patients	Intervention including dose and IVIg preparation used	Study design	Ref.	Disease
All patients improved within 2–6 months on combination therapy and within 4–6 months on monotherapy, steroid-sparing effect in adjunctive therapy group	43 patients with mucous membrane pemphigoid	IVIg 1–3 g/kg over 3–5 days for 2–4-weeks; adjunctive/monotherapy 28/15.	Review of published case reports	[239]	
Improved 3/3 on adjunctive and 2/3 monotherapy, 1/1 UV protection	7 patients with epidermolysis bullosa acquisita 16–59 years old, all males	IVIg 0.4 g/kg per day for 5 days, 2–6 weeks (4), 2 g/kg per day 2 weeks (1), 0.04 g/kg per day for 5 days 3–4 weeks (1), 1.2 g/kg per month (1) Polyglobulin® in 1, Sandoglobulin® in 3, NA 3; adjunctive therapy 3, monotherapy 3, 1 UV protection for 1–4 months	Review of published case reports	[239]	Epidermolysis bullosa acquisita
All improved	3 patients 45–67 years old with linear IgA disease	Sandoglobulin® 0.4 g/kg per day over 5 days in 1 patient; 2 patients received 4 g/kg per month regiment (preparation NA); 2 patients received CS as additional treatment	Review of published case reports	[239]	Linear IgA disease
Complete response after 5 cycles of IVIg (3.5 months), IVIg continued for additional 10.5 months	1-week-old newborn with linear IgA disease	Adjunctive therapy with Venoglobulin® 1 g/kg every 2–4 weeks for 14 months	Case report	[281]	
Steroid-sparing effect, maintained with cyclosporine and low-dose prednisolone; cyclosporine was stopped 16 months after delivery	17-year-old female with pemphigoid gestationis, developed at 20 weeks gestation in her 1st pregnancy	2 g/kg per month for 2 months adjunctive to CS	Case report	[288]	Pemphigoid gestationis
Objective response in all patients within a mean of 2 days, skin healing within 8.3 days, slow healing in patients with underlying diseases, an overall survival rate of 100%	12 patients with SJS (mean age 44)	Commercially available IVIg at a mean dose of 0.6 g/kg per day for an average of 4 days as monotherapy	Retrospective multicenter study	[289]	Stevens–Johnson syndrome
The average duration of fever was 8 days in IVIg-treated vs. 14 in non-IVIg-treated group (p=0.06); the mean stay in hospital was 12 days in IVIg-treated vs.15 days in non-IVIg-treated group (p=0.5)	Total of 12 patients (mean age 6 years), 7 IVIg-treated and 5 non-IVIg-treated	IVIg as single infusion at 1.5–2.0 g/kg given on an average of 3 hospital days	Retrospective series report	[290]	
No mortality, arrest of disease progression in 1–5 days (mean 2.83), re-epithelialization in a mean of 7.33 days (range 5–13); the average duration of hospital stay was 12.5 days	12 patients (average age 27.2 years, 4 children 7–12 years old); the average affected body area was 57.5%	IVIg 0.5–1.0 g/kg per day for 4–5 days adjunctive to standard care protocol, infusion started on average 1.58 days	Uncontrolled trial	[291]	Toxic epidermal necrolysis
90% of patients survived; one patient with previous history of severe heart disease died as a result of cardiac arrest during the first day of treatment	10 patients with TEN with predicted mortality rate 35% according to SCORTEN	IVIg 0.4 g/kg per day for 5 days started within 3 days from the onset of TEN	Prospective single center uncontrolled	[292]	
Progression of epidermal detachment in 22/34, more deaths than predicted by prognostic SCORTEN score (11 (32%) instead of 8.2 (24%)), most deaths in elderly with renal impairment	34 patients with a mean of 4.3 days after onset of SJS (n=9), SJS/TEN (n=5), TEN (n=20)	IVIg 2 g/kg within 2–5 days (30 patients treated with Tegeline (Laboratoire francais du Fractionnement et des Biotechnologies, France), 2 with Sandoglobulin® (Novartis, France), 2 with Gammagard ® (Baxter, France), only Gammagard did not include sucrose)	Uncontrolled trial	[293]	

Mortality rate was 20% in IVIg-treated patients vs. 50% in non-IVIg group (overall mortality of 33%)	9 patients with TEN—all treated with CS; 5/9 received IVIg as adjunctive therapy	IVIg 0.75–1 g/kg per day for 3 days adjunctive to intravenous prednisolone 0.25–0.5 g/day for 1–3 days	Retrospective series report	[294]	
All survived	3 patients with 30–70% epidermal detachment	IVIg 0.5 g/kg per day for 4 days (2 patients), 1 patient was switched after 24 h to 0.6 g/kg per day for 2 days due to further deterioration	Case series	[295]	
7/7 survived, a cessation of blistering in 7/7 patients within an average of 2 days; in published cases, time to objective response could be ascertained in 20 patients: cessation of blistering after an average of 2.5 days; patients with concomitant CS treatment were noted to have a longer time to objective response	7 pediatric patients with SJS and 28 published pediatric cases of SJS (12), SJS/TEN (5), and TEN (11) treated with IVIg	7 patients IVIg (Gamimune) in an average dose of 2 g/kg over 4 days (on days 1, 2, 4, and 6) initiated an average of 2.7 days after onset, in 5 cases adjunctive to CS in 28 published cases, an average total dose of 2.5 g/kg initiated 3.75 days after blister onset	Retrospective case series and review of published case reports	[296]	
Time to objective response was 2.3±1.2 days; duration of IVIg treatment was 4±0.9 days; objective response rate was 90%; survival rate was 88%; time to complete healing was 15±9.5 days; the odds of survival decreased per year of life (p=0.02) and increasing epidermal detachment (p=0.03); more underlying disease in the group of nonsurvivors (p=0.03)	48 patients with TEN (mean age 44), with skin detachment in 44.8±22.5% and mucous membrane involvement in 91.7% of cases	Commercially available IVIg at mean dose of 0.7 g/kg per day for a mean of 4 days given as monotherapy 7.3±6 days from onset of TEN	Retrospective multicenter	[297]	
83% reduction of mortality (1 patient died instead of 5.8 expected based on SCORTEN)	16 patients with TEN	IVIg for 4 days (15 patients 1 g/kg per day and 1 patient 0.4 g/kg per day); 2 patients received IVIg without sucrose	Retrospective series report	[298]	
The average time to arrest of progression was 2.1 days; complete re-epithelialization was 8.1 days and length of hospitalization 13.6 days; no mortality	8 pediatric patients with TEN with mean surface involvement of 67%	Monotherapy of IVIg 0.5–0.75 g/kg per day for 4 consecutive days, started with average delay of 3.2 days after blisters onset	Retrospective series report	[299]	
No difference in length of stay, mechanical ventilation, severity of inflammatory response or incidence of sepsis, wound progression, time to healing, and mortality	16 TEN patients with initial rash involving 65±29%, treated with IVIg vs. 16 patients with TEN initial rash involving 65±27% not treated with IVIg	IVIg (Gamimune® N, Bayer Inc., Toronto, CA) 0.2 to 0.7 g/kg per day according to discretion of attending physician on duty, as 5% or 10% solution according to availability, for 4±1 day	Retrospective	[300]	
No difference of SCORAD index and in global evaluation of disease severity by patients at day 30	10 adult patients (mean age 28) with sever atopic dermatitis	IVIg 1 g/kg per day (Sandoglobulin®, Sandoz, France) immediate or delayed by 1 month (meanwhile intensive therapy with emollients and topical CS (limited to class II 60 g/month)), for 2 days in 8-h infusion, as monotherapy	RC evaluator-blinded trial	[301]	Atopic dermatitis
Improvement in skin score (mEASI) was apparent in responders (4/6 patients) from 2 to 3 months and continued to improve over a 6-month period; after 7 months, there was a significant reduction of the overall mEASI; CD69-expressing T cells decreased to 60% from baseline; no change of TNF-a and IFN-g	6 adult patients with severe stable atopic dermatitis	Flebogamma® 5% 2 g/kg per month given in 2–5 days for 6 months as adjunctive treatment, followed for 3 months	Open, single center, prospective	[302]	
3/3 patients improved skin scores, allowing reduction of steroid dose	3 adult patients with severe atopic dermatitis and steroid-related side effects	Alphaglobin® (Grifols, UK) or Sandoglobulin ® (Novartis, UK) 2 g/kg per month in 3–5 days adjunctive to CS	Case report	[303]	

Table 9 (continued)

Results/response	Number of patients	Intervention including dose and IVIg preparation used	Study design	Ref.	Disease
		Aza, Hxc			
9/10 were available for analysis: 6/9 showed slight improvement of skin lesions; 2/9 were unchanged and 1/9 worsened; there were no steroid-sparing effect, change in mean IgE, lymphocyte response to PHA, Candida, tetanus, and anti-CD3 antibody, and change in RAST positivity to negativity	10 patients (7–64 years old): 1 patient with hyper-IgE syndrome and 9 patients with atopic dermatitis	Adjunctive to CS in 6/10 Venoglobulin® I (10%) 2 g/kg per month for 7 months	Open, single center	[304, 305]	
9/10 patients less than 6 years old improved on monotherapy; 1 patient with WAS failed to improve after 1 treatment cycle; 17/22 adults received adjunctive therapy; 10/17 (59%) improved; the longest time to response was 3–4 months	32 patients (8 months to 64 years old) with atopic dermatitis	2 g/kg per month for 1 to 11 cycles, 1 patient with WAS 1 g/kg per month for 1 month; 14/32 patients received IVIg as monotherapy, 5 patients Bayer Biological Co., 6 patients Flebogamma®, 10 patients Venoglobulin I ®, 3 patients Sandoglobulin®/ Alphaglobulin®, 8 patients preparation NA	Review of published case reports	[305]	
9 of 10 patients responded: 3 patients with complete remission sustained 3 years later; 2 patients with temporary complete remission; 4 patients improved subsequent to treatment; total urticaria activity score assessed by physician and by patient with the use of visual analog score at 2 and 6 weeks improved significantly ($p<0.01$) without significant change of the positivity of autologous serum injection test	10 patients with severe chronic autoimmune urticaria	0.4 g/kg per day for 5 days as 3% solution in normal saline on the first day, followed by a 6% solution on the succeeding 4 days (Sandoglobulin®, Novartis, UK); sympatientomatic treatment with cetirizine 20 mg/day was taken by all patients	Case series	[306]	Chronic urticaria
After the 1st application of IVIg, urticaria score was reduced to 1, maintained with repeated administrations of IVIg in intervals of 4 weeks	A 63-year-old woman with a 2-year history of chronic urticaria with urticaria score of 4/8 despite H1-and H2-blockers	Low-dose IVIg 0.2 g/kg every 4 weeks adjunctive to standard antihistamine therapy	Case report	[307]	
95% resolution over 3.5 months without concomitant therapy	A 28-year-old female with 41-month history of severe chronic urticaria	1 cycle of Venoglobulin® 2 g/kg in 5 days as monotherapy	Case report	[281]	
5 of 8 responded: 3 remission (2 after one and 1 after 3 cycles); 2 patients improved; responders improved with 3 or fewer infusions; 3 patients failed to improve after 2–6 cycles of IVIg; ASST was not a predictor of response to IVIg	8 adult patients with steroid-dependent refractory delayed pressure urticaria (concomitant with chronic urticaria 8/8, angioedema 4/8, cholinergic urticaria 1, and dermographism 1)	2 g/kg per month (Scottish National Blood Transfusion Service) over 2 to 3 days, followed by antihistamines and CS	Uncontrolled trial	[308]	Delayed pressure urticaria
After 3 cycles tolerated visible light and 15 min of intense solar exposure, SU has disappeared after 1 year	55-year-old woman suffered from resistant solar urticaria for 3 years	IVIg	Case report	[309]	Solar urticaria
Optimal improvement with combination of IVIg, antihistamines, and PUVA	A female patient with resistant solar urticaria	IVIg 2.5 g/kg over 3 days	Case report	[310]	
Taper off of CS and prolonged remission; recurrence and remission of symptoms were associated with changes of IVIg lot and source	A 54-year-old man	IVIg 0.4 g/kg every 3 weeks (Panglobulin® or Gamimune N® according to availability) adjunctive to CS	Case report	[311]	Angioedema with hypereosinophilia syndrome
2 patients experienced dramatic improvement in both their joints and skin and a fall in inflammatory markers; 1 patient had improvement in arthritis but little change in skin involvement	3 patients with treatment-resistant psoriasis and psoriatic arthritis	IVIg (Octagam®, Octapharma, Coventry, UK) 2 g/kg over 3 to 4 days adjunctive to conventional treatment; in 2 cases, improvement was sustained with additional cycles of IVIg; in 1 case, information is not	Case series	[312]	Psoriasis

		available			
7 of 10 patients demonstrated clearance of lesions; in 6/7 of cases, the efficacy maintained with repeat IVIg infusions	10 patients with severe refractory pyoderma gangrenosum	IVIg 2 g/kg per month in 3 days, 9/10 in conjunction with CS and MMF and/or cyclosporin; IVIg was stopped after 2 to 3 cycles in case of ineffectiveness	Case series	[313]	Pyoderma gangrenosum
Stabilization of pyoderma gangrenosum and steroid-sparing effect in both patients	Case 1 with a 6-year and case 2 with a 3-year history of multidrug-resistant pyoderma gangrenosum	IVIg 2 g/kg per month for 6 months adjunctive to CS	Case report	[314]	
Improvement of range of joints motion and laxity of skin after 1 month but no further improvement after the 2nd and the 3rd cycles of IVIg	A 61-year-old male with a 4-month history of NFD	IVIg 2 g/kg in 5 days for 3 months	Case report	[315]	Nephrogenic fibrosing dermopathy
Clinical improvement in all patients after 2–9 months with reduction of skin thickness by US evaluation (4/7), reduction of mucopolysaccharide skin content (3/7), disappearance of lymphocytic skin infiltration and IgG deposition (2/7)	7 patients affected by Grave's ophthalmopathy and pretibial myxedema	IVIg Endoglobulin® 2 g/kg every 3 weeks as monotherapy	Case series	[316]	Pretibial myxedema
8 patients had complete (2) or partial (6) response, but in all the effect was transient, requiring reinfusion and maintenance therapy	10 patients with scleromyxedema—8 cases proven by skin biopsy, 2 had inconclusive biopsy results but had classic clinical findings and a characteristic gammopathy	IVIg in dose 0.4–1.0 g/kg per day for 2–5 days for a total 2 g/kg every month for 6 months as monotherapy after failure of other treatment modalities	Case series	[317]	Arndt–Gottron scleromyxedema
All patients had cutaneous improvement as well as improvement in ureteral stricture, vocal strength, and dysphagia	3 patients with scleromyxedema	IVIg 0.4 g/kg per day for 5 days every 5 weeks (Gammagard; Baxter Healthcare Corp, Hyland Immuno, Glendale, CA, USA)	Case report	[318]	
First patient had significant reduction in skin scores (36/60 to 11/60) for 1 year only; second had a dramatic sustained response with continued Tx (interval subsequently increased to 10 weeks)	2 patients with scleromyxedema and severe skin disease	IVIg 0.4 g/kg per day for 5 days, monthly	Case report	[319]	
Improvement after the first treatment, continuous skin softening and reduction of induration, sustained response to treatment after 20 courses	A 48-year-old female with long-standing scleromyxedema unresponsive to high-dose CS and immunosuppressive (CP, melphalan) treatment	IVIg 2 g/kg in 2 days (Intratect®; Biotest, Dreieich, Germany) every 4 weeks, adjunctive to PD 10 mg/day	Case report	[320]	
Progressive clinical improvement over several months allowing discontinuation of PD but rapid deterioration afterwards with lethal CVA despite reinstating PD and CP	An 81-year-old female with scleromyxedema and IDDM	IVIg (Gamimune N, 10%, Bayer) 1.5 g/kg (dose reduced due to CHF) every 4 weeks and oral PD 30 mg/day	Case report	[321]	
A positive response after 2 cycles	An 82-year-old female with a 12-year history of scleromyxedema unresponsive to various preceding therapies	Venimmun® N (ZLB Behring, Germany) 0.5 g/kg for 5 days at 4-week intervals as monotherapy	Case report	[322]	
Marked clinical improvement, maintained with repeated IVIg infusions	A 56-year-old woman with scleromyxedema	IVIg (Sandoglobulin®) 2 g/kg over 5 days as monotherapy	Case report	[323]	
Complete clearance of skin lesions, sustained effect after 1 year without treatment	A 47-year-old female with 8-year history of tumorous variant of scleromyxedema and a history of ineffectiveness of melphalan and PD therapy	5 courses of IVIg 0.3 g/kg for 5 days every 4 weeks adjunctive to melphalan 4–2 g/day and PD 30–10 mg/day, 5 additional cycles as monotherapy 1 year later	Case report	[324]	

Table 9 (continued)

Results/response	Number of patients	Intervention including dose and IVIg preparation used	Study design	Ref.	Disease
Improvement in all but relapse in 1 patient, 2 weeks to 6 months for full response, most needing 6–8 weekly cycles	10 patients, 30–79 years old with scleromyxedema	IVIg 2 g/kg per month given over 5 days; Octagam® (2 patients), Sandoglobulin® (3 patients), Gammagard ®SD (1 patient), unknown (2patients); adjunctive to PD (2 patients) and thalidomide (1 patient) or as monotherapy (7 patients)	Review of published case reports	[325]	
Regrowth of eyelashes, eyebrows, and body and scalp hair after second dose, significant hair regrowth with 5–6 cm of scalp hair	8-year-old girl with CVID and alopecia universalis	IVIg 0.4 g/kg every 4 weeks	Case report	[326]	Alopecia universalis

Kaposi's sarcoma

Level of evidence C A patient with polymyositis and Kaposi sarcoma had remission of both conditions on IVIg therapy (*strength of recommendation IIb*).

Metastatic melanoma

Level of evidence C Stabilization of metastatic melanoma was shown in the small group of patients after addition of IVIg to standard therapy (*strength of recommendation IIb*).

Chemotherapy-induced oral mucositis

*Level of evidence C*IVIg was shown to be effective in preventing severe recurrent chemotherapy-induced oral mucositis in two patients treated with methotrexate (*strength of recommendation IIa*).

Thymus carcinoma

Level of evidence C Anecdotal case report describes complete remission of metastatic malignant thymoma after four cycles of IVIg given to myasthenic patient (*strength of recommendation IIb*).

Thymoma and immunodeficiency (Good syndrome)

Level of evidence C After thymectomy, two patients with Good syndrome were maintained with IVIg for developed immunodeficiency; one of them developed Kaposi sarcoma after 3 years (*strength of recommendation IIb*).

The following conditions refer to (Table 11).

Summary There are still no randomized controlled trials evaluating efficacy of IVIg and it cannot be recommended for treatment of epithelial or other solid malignancies.

Diabetes mellitus

Level of evidence C There is some evidence that IVIg therapy can improve the Neuropathy Impairment Score in patients with diabetic demyelinating polyneuropathy (*strength of recommendation IIa*). A few case reports describe regression of symptoms of proximal diabetic neuropathy, diabetic amyotrophy, and cranial nerve neuropathy in different diabetic patients treated with IVIg (*strength of recommendation IIa*). We conclude that evidence for the use of IVIg in diabetic neuropathies is poor and its systematic use cannot be recommended.

Table 10 The use of intravenous immunoglobulins in oncological diseases

Results/response	Number of patients	Intervention including dose and IVIg preparation used	Study design	Ref.	Disease
Considerable improvement of KS skin lesions after 2 weeks, disappearance of 6 of 8 skin lesions after 1 month; after 3 cycles, only 1 remnant skin lesion; after 2 years of monthly treatment, no relapse of KS or progression of polymyositis	45-year-old patient with polymyositis, who developed KS when given immunosuppressive therapy for polymyositis	IVIg 0.4 g/kg per day for 5 days (Sandoglobulin®, Sandoz, Switzerland) adjunctive to low-dose PD	Case report	[327]	Kaposi's sarcoma (KS)
2 of 9 (22%) patients had stabilization of disease (one for 8 months)	9 patients with metastatic melanoma	IVIg 1 g/kg (VIGAM® LIQUID, BPL, UK, contains 0.5 g sucrose per gram of immunoglobulin) given over a 1- to 3-day period at a maximum dose of 25 g/day for up to 8 h, every 3 weeks (during 3 or 6 months in case of nonprogression according to CT/MRI) adjunctive to standard therapy	Uncontrolled trial	[328]	Metastatic melanoma
No mucositis after MTX treatment followed by IVIg in both cases	15-year-old male and a 5-year-old girl, who developed grade 3 mucositis after every course of MTX	0.2 g IVIg/kg applied 27 h after the 24-h MTX infusion	Case report	[329]	Chemotherapy-induced oral mucositis
Complete remission of thymoma after 4 cycles of IVIg confirmed by FDG-PET	A patient with metastatic malignant thymoma and myasthenic crisis	IVIg	Case report	[330]	Thymus carcinoma
Case 1 developed immunodeficiency 2 years after the resection of thymoma, maintained with IVIg and low-dose CS; case 2 was maintained with IVIg and was stable but developed Kaposi sarcoma 3 years afterwards	Case 1—a 51-year-old woman Case 2—an 89-year-old man	Monthly IVIg 0.4 g/kg	Case report	[331]	Thymoma and immunodeficiency (Good syndrome)

Hashimoto's encephalopathy

Level of evidence C A rare case of autoimmune encephalopathy during thyrotoxic phase of Hashimoto's disease only partially responded to immunosuppressive therapy with adjuvant intravenous immunoglobulin (*strength of recommendation IIb*).

X-linked adrenoleukodystrophy

Level of evidence B Therapeutic efforts including dietary therapy and immunomodulation with IVIg fail to improve prognosis in patients with X-linked adrenoleukodystrophy and BMT remains the only treatment that can reverse early neurological manifestations and adrenal impairment of ALD (*strength of recommendation III*).

Waterhouse–Friderichsen syndrome

Level of evidence C No evidence supports the use of IVIg in Waterhouse–Friderichsen syndrome due to meningococcal sepsis (*strength of recommendation III*).

Autoimmune polyendocrine syndrome

Level of evidence C No evidence supports the use of IVIg in autoimmune polyendocrine syndrome type 2 (*strength of recommendation IIb*).

The following conditions refer to (Table 12).

Acute disseminated encephalomyelitis

Level of evidence C There is weak evidence coming out from several case reports that IVIg may be a useful treatment option either as a combination therapy with CS or in cases that steroid treatment fails (*strength of recommendation I*).

Adrenoleukodystrophy

Level of evidence B Taking into consideration the limited evidence (one RCT) and the unfavorable effect of IVIg treatment, at this point, IVIg should not be used as treatment of adrenoleukodystrophy (*strength of recommendation III*).

Amyotrophic lateral sclerosis

Level of evidence C No benefit was observed from the use of IVIg in two case series. Considering the weak evidence and the negative outcome, IVIg is not recommended for the treatment of amyotrophic lateral sclerosis (*strength of recommendation III*).

Autism

Level of evidence C The use of IVIg in autism is only limited to case series and the effect is questionable. IVIg is not recommended at the moment for the treatment of autism (*strength of recommendation III*).

Chronic inflammatory demyelinating polyneuropathy

Level of evidence A Several RCTs evaluated the effectiveness of IVIg. The results of these studies are strongly pointing to the useful effect of IVIg in patients with chronic inflammatory demyelinating polyneuropathy. IVIg should be considered as an additional option in combination with other immunosuppressive agents (*strength of recommendation I*).

Opsoclonus myoclonus

Level of evidence C In this rare syndrome, IVIg was reported in several case reports and a retrospective study proved that it induced significant response. Although there is no strong evidence, IVIg may be considered as an additional option in treatment of opsoclonus myoclonus (*strength of recommendation I*).

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections PANDAS

Level of evidence B Results coming from one small RCT testing the effect of IVIg showed significant improvement in symptoms; therefore, IVIg is recommended as an additional option for treatment of PANDAS (*strength of recommendation I*).

Multiple sclerosis

Level of evidence A Data from several RCTs and a meta-analysis showed significant differences between IVIg and placebo favoring the use of IVIg in relapsing–remitting multiple sclerosis (MS). On the other hand, a recent RCT including 127 patients with relapsing–remitting MS treated with IVIg or placebo showed no significant difference in the proportion of relapse-free patients among treated groups. Another recent RCT including 231 patients showed that IVIg can delay progression of disease in primary chronic progressive MS but no significant difference in progression was noted for secondary chronic progressive MS. To conclude, IVIg may be used as an alternative therapy in relapsing–remitting MS and in primary chronic progressive MS when standard immunosuppression therapy fails (*strength of recommendation IIb*).

Table 11 The use of intravenous immunoglobulins in endocrine disorders

Results/response	Number of patients	Intervention including dose and IVIg preparation used	Study design	Ref	Disease
21 of 26 patients showed improvement of the mean Neuropathy Impairment Score (NIS) from 61.5±26.0 to 33±29.6 ($p<0.001$); improvement of NIS was more frequent in patients with a conduction block (100%) vs. in those who did not (66.7%; $p=0.03$); relapses occurred less in the responders who had a conduction block (9.1%) vs. in those who did not (50%; $p=0.04$)	26 patients with DDP evaluated at baseline, at the end of 4 weeks of IVIg therapy, afterwards every few months, mean follow-up period of 25 months.	IVIg 0.4 g/kg for 5 days	Prospective open label	[332]	Diabetic demyelinating polyneuropathy
Reached 80% reduction of pains and significant recovery of muscle strength	A 57-year-old man with type 2 diabetes and painful proximal diabetic neuropathy with muscle weakness and atrophy	IVIg 0.4 g/kg for 5 days	Case report	[333]	Proximal diabetic neuropathy
All defective cranial nerve findings disappeared during the 1st month and did not recur during 8 months of follow-up	A 55-year-old woman, with 12-year history of DM, developed simultaneous right VII and left III, IV, and VI cranial nerve pulses	IVIg 0.4 g/kg for 5 days	Case report	[334]	Cranial nerve neuropathy in diabetes mellitus
5 days after IVIg easy fatigability of thigh disappeared and of the strength of shoulder girdle muscle improved; 1 year after IVIg treatment, there was normal muscle strength and significant improvement of atrophy	A 45-year-old man with IDDM and diabetic amyotrophy	IVIg 0.4 g/kg per day for 5 days	Case report	[335]	Diabetic amyotrophy
Rapid improvement of fasting serum glucose levels, stabilization of renal function, and decrease in the donor-specific class II antibodies	A 44-year-old man with long-standing poorly controlled IDDM	3 doses of 0.5 g/kg per day of IVIg, started on day 14 posttransplant and given every other day adjunctive to standard posttransplant therapy, plasmapheresis, and rituximab	Case report	[336]	Pancreas allograft rejection
Partial response to IVIg and complete resolution of weakness after CP, asymptomatic after 1 year without treatment	A 17-year-old man with known IDDM and a subclinical Hashimoto's thyroiditis and a new onset of asymmetric weakness and atrophy in arms	Monthly infusions of IVIg 0.4 g/kg per day for 5 consecutive days followed by 6 cycles of CP 1 g/m^2	Case report	[337]	Multifocal motor neuropathy, type 1 diabetes, and Hashimoto's thyroiditis
Within 10 weeks after IVIg, muscle weakness and sensory disturbances disappeared, but tendon reflexes stayed slightly depressed; the patient was treated with IVIg every 3 months due to IVIg-dependent course	A 64-year-old man with clinical and laboratory findings supportive for MMN, high titers of anti-GM1-Abs and subclinical Hashimoto's thyroiditis	IVIg 0.4 g/kg per day for 5 days, repeated every 3 months due to IVIg-dependent course of the disease	Case report	[338]	Multifocal motor neuropathy and Hashimoto's thyroiditis
Partial response to CS and IVIg and antiepileptic medication (probably due to lowering of seizure threshold by antithyroid drugs and beta-blockers); continued with immunosuppressive therapy (high-dose CS and AZA) but relapsed after 2 months, recovered after thyroidectomy	A 34-year-old woman with encephalopathy and thyrotoxic Hashimoto's thyroiditis	IVIg 2 g/kg in 3 days adjunctive to high-dose CS and plasmapheresis	Case report	[339]	Thyrotoxic autoimmune encephalopathy
See ophthalmology section					Grave's ophthalmopathy

Table 11 (continued)

Results/response	Number of patients	Intervention including dose and IVIg preparation used	Study design	Ref	Disease
All had normalization of VLCFA within 3 months, but neurological status continued to deteriorate in both groups	6 of 12 patients with X-linked childhood and adolescent adrenoleukodystrophy received IVIg in addition to diet and GTOE supplement	IVIg 1 g/kg in 8–12 h (Gamma globulin; Merieux, France) every 15 days for 3 months and every month for a year, thereafter; both groups received very-long-chain fatty acids (VLCFA)-restricted diet and supplement of 40 mg/day glycerol trioleate and erucic acids (GTOE)	RCT	[340]	Adrenoleukodystrophy
3/9 improved; 3/9 remained stable; 3/9 deteriorated and died	9 adult patients with various X-ALD phenotypes	15 cycles of 1 g/kg 7 S-immunoglobulin (Venimmun, Behring, Germany)	Uncontrolled trial	[341]	
Recovery of adrenal function but dependence on dialysis 18 months later	A 20-year-old man with Waterhouse–Friderichsen syndrome and bilateral renal cortical necrosis secondary to meningococcal sepsis	Neither protocol nor IVIg preparation is available; IVIg adjunctive to aggressive treatment with antibiotics, CS, vasopressors, plasmapheresis, and dialysis	Case report	[342]	Waterhouse–Friderichsen syndrome
During IVIg treatment, normalization of thyroid function, some nonovulatory menses, and reduction of antibody titers were observed	A female with autoimmune polyendocrine syndrome type 2	IVIg	Case report	[343]	Autoimmune polyendocrine syndrome

Guillain–Barré

Level of evidence A There is strong evidence, several randomized controlled trials, and a meta-analysis that prove that IVIg is of benefit in improving the disability grade in patients with Guillain–Barré syndrome. No significant difference between IVIg and PP was found. IVIg should be considered as a treatment option in Guillain–Barré syndrome (*strength of recommendation I*).

Paraproteinemic neuropathy (IgM)

Level of evidence A There is no reliable evidence to recommend the use of IVIg in paraproteinemic neuropathy. A restricted number of RCT's and a systematic review showed only modest benefit with IVIg in the short term (*strength of recommendation IIb*).

Lambert–Eaton myasthenic syndrome

Level of evidence B A single small RCT showed significant improvement in patients suffering from Lambert–Eaton myasthenic syndrome with the use of IVIg compared to placebo. Therefore, it is acceptable to consider the use of IVIg in this rare and severe neurological syndrome (*strength of recommendation I*).

Stiff-person syndrome

Level of evidence B Data from a small randomize control trial and several case reports showed that the use of IVIg led to significant improvement in patients with stiff-person syndrome and was superior to placebo. IVIg should be considered as a treatment option in this syndrome especially if the first-line treatment fails (*strength of recommendation I*).

Intractable childhood epilepsy

Level of evidence A Two RCTs investigated the efficacy of IVIg in patients with intractable childhood epilepsy compared with placebo. Results from these studies do not support benefit from the use of IVIg. Therefore, IVIg is not recommended for the treatment of intractable childhood epilepsy (*strength of recommendation III*).

Critical illness polyneuropathy

Level of evidence C There is no reliable evidence (level of evidence C-III) to recommend the use of IVIg in the treatment of critical illness polyneuropathy (*strength of recommendation III*).

Table 12 The use of intravenous immunoglobulins in neurological diseases

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
Opsoclonus myoclonus	[344]	Case reports	IVIg 3 doses of 0.3 g/kg over 4 months + rituximab	2 patients with postinfectious opsoclonus myoclonus syndrome	Significant clinical improvement without relapses
	[345]	Case report	IVIg 0.4 g/kg per day for 5 days + prednisolone + clonazepam	A 41-year-old woman with idiopathic opsoclonus myoclonus syndrome	Complete recovery
	[346]	Case report	IVIg 30 g/day for 5 days with 5 repeated doses after 2 months + CS	A 36 year-old man with parainfectious opsoclonus myoclonus syndrome	Accelerated recovery
	[347]	Case report	IVIg + ACTH + CS	A patient with childhood-onset opsoclonus myoclonus	Partial recovery
	[348]	Case report	IVIg initially 5.5 g and 6 additional courses at a dosage of 2.5 g and 7 courses at a dosage of 5 g every 2 to 3 weeks + ACTH	A 22-month-old girl with neuroblastoma-associated opsoclonus myoclonus	Partial recovery
	[349]	Case report	IVIg + ACTH	A 27-year-old woman with severe opsoclonus myoclonus	Complete recovery
	[350]	Case report	IVIg 1 g/kg for 2 days with 12 additional doses given every 4–6 weeks	An 18-month-old black girl with neuroblastoma-associated opsoclonus myoclonus	Complete recovery
	[351]	Case report	High-dose IVIg	A 14-month-old male with infantile opsoclonus myoclonus	Complete recovery
	[352]	Retrospective study	IVIg + CS	9 patients with idiopathic and paraneoplastic opsoclonus myoclonus	Idiopathic opsoclonus myoclonus: 2/9 complete recovery, 1/9 partial recovery, 2/9 remission Paraneoplastic opsoclonus myoclonus: 3/9 no response, 1/9 partial recovery
PANDAS	[353]	RCT	IVIg I g/kg per day for 2 days vs PP vs placebo	29 children with severe infection-triggered exacerbations of obsessive-compulsive disorder (OCD) or tic disorders, including Tourette syndrome	At 1 month, significant improvement in global impairment ($p=0.0009$), obsessive- compulsive symptoms ($p=0.006$), anxiety ($p=0.001$), depression (0.002); at 1 year, more than 80% of patients receiving IVIg or PP remained improved
Multiple sclerosis (MS)	[354]	RCT	IVIg 0.2 g/kg–0.4 g/kg every 4 weeks for 48 weeks vs placebo	127 patients with relapsing–remitting multiple sclerosis (RRMS)	At 1 year, there was no significant difference in the proportion of relapse-free patients among treated groups
	[355]	RCT (primary and secondary chronic progressive MS)	IVIg 0.4 g/kg per month for 24 months vs placebo	231 patients with primary (PPMS) and secondary (SPMS) chronic progressive MS	IVIg can delay progression of disease in primary chronic progressive MS; no significant difference in progression was noted for secondary chronic progressive MS; no improvement in neurological functions with IVIg

Table 12 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
	[356]	RCT (secondary progressive MS)	Monthly IVIg 1 g/kg for 27 months vs placebo	34 patients with secondary progressive (SP) MS	No reduction in the relapse rate or the progression of disability
	[357]	Retrospective study (relapsing–remitting MS)	IVIg treatment at a mean time of 3.4±1.8 years at a mean dose of 15.5± 8.3 g/month	308 patients with RRMS	69% reduction of mean annual relapse rate was observed after IVIg treatment initiation
	[358]	RCT (secondary progressive MS)	IVIg 1 g/kg per month for 27 months vs placebo	318 patients with secondary progressive multiple sclerosis	No effect on the time to confirmed progression on the EDSS, annual relapse rate, and the change in T2 lesion load on MRI
	[359]	Meta-analysis	IVIg 0.15–2 g/kg for 12–24 months vs placebo	4 RCT (265 patients with RRMS)	Significant beneficial effect: on the annual relapse rate (p=0.00003), on the proportion of relapse-free patients ($p=2.1\times10^{-8}$)
	[360]	RCT	IVIg 0.15–0.2 g/kg per month for 2 years vs placebo	148 patients with RRMS	Progression of disability was reduced in 24% of the patients with therapeutic efficacy to be noted in the first 6 months of the treatment
	[361]	RCT (relapsing remitting MS)	IVIg 0.4 g/kg for 5 days followed by once every 2 months for 2 years vs placebo	40 patients with RRMS	Reduction in yearly exacerbation rate (p= 0.0006 (overall))
	[362]	RCT (relapsing remitting MS)	IVIg 1 g/kg for 2 days every 4 weeks for 24 weeks vs placebo	17 patients with relapsing–remitting or relapsing progressive multiple sclerosis	11 had no exacerbations during IVIg treatment compared with only 6 on placebo (p=0.05)
Guillain–Barré syndrome (GBS)	[363]	Systematic review meta-analysis	IVIg 0.2–1 g/kg per day for 2–6 days vs PP vs immunoabsorption vs supportive care	11 RCT (913 patients)	Improvement on the disability grade scale with intravenous immunoglobulin (IVIg), weighted mean difference WMD of 0.02 (95% confidence interval (CI) 0.25 to 0.2); no significant difference between IVIg and plasma exchange
	[364]	Open-labeled study	IVIg 0.4 g/kg per day for 5 days	11 patients younger than 15 years old, diagnosed with moderate or severe GBS	After 2 weeks, 72.7% of patients improved by one or more grades and 36.4% improved by 2 or more grades, measured on the Hughes' functional grade FG scale
					After 4 weeks, 81.8% of patients improved by one or more grades and 63.6% of patients improved by 2 or more grades
	[365]	RCT	IVIg 0.4 g/kg per day for 3 or 6 days	39 patients with Guillain–Barré syndrome	No significant difference in time to assisted walking in the 2 groups (p=0.08); significantly shorter time

Table 12 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
					to assisted walking in ventilated patients in the 6-day group (p=0.04)
	[366]	RCT (IgG anti-GM1-positive subgroup)	IVIg vs plasmapheresis	24 patients with Guillain–Barré syndrome	IVIg-treated patients had: significantly lower Hughes grade scores 1, 3, and 6 months after onset (p=0.03); higher probability to regain independent locomotion at 6 months (p=0.044); more frequent rapid recovery within 4 weeks (p=0.03)
	[367]	RCT	IVIg 0.4 g/kg per day for 5 days vs plasma exchange	379 adult patients with Guillain–Barré syndrome	IVIg is equivalent to plasmapheresis in reducing the amount of disability at 4 weeks after treatment
	[368]	RCT	IVIg 0.4 g/kg per day for 5 days vs plasma exchange	150 patients with Guillain–Barré syndrome	53% of patients treated with IVIg improved compared to 34% in the PP group (p=0.024)
Paraproteinemic neuropathy (IgM)	[369]	Systematic review	IVIg or interferon alpha or plasma exchange	5 trials (97 patients with IgM antimyelin-associated glycoprotein paraproteinemic neuropathy)	2 trials with 33 patients suggest that IVIg may sometimes produce short-term benefit (in terms of improvement in Modified Rankin Scale at 2 weeks and 10-m walk time at 4 weeks) and is relatively safe
	[370]	Crossover RCT	IVIg 2 g/kg over 1 to 2 days vs placebo	22 patients with paraproteinemic demyelinating neuropathy	After 4 weeks, the overall disability significantly decreased during the IVIg period (p=0.001) compared to the placebo period where it was unchanged; the mean difference between the treatment effects was significant (p = 0.05)
	[371]	Crossover RCT	IVIg vs placebo given monthly for 3 months	11 patients with demyelinating polyneuropathy associated with monoclonal IgM antibodies	Modest benefit with IVIg
Amyotrophic lateral sclerosis	[372]	Case series	IVIg 0.4 g/kg per day for 5 days followed by monthly 2-day infusions + CP	7 patients with amyotrophic lateral sclerosis	All patients worsened according to MRC and/or bulbar and/or Rankin scores
	[373]	Case series	IVIg monthly for 3 months	9 patients with rapidly progressive amyotrophic lateral sclerosis	All patients worsened after 3 months with decrease in mean total muscle scores (megascores)
Lambert–Eaton myasthenic syndrome	[374]	Crossover RCT	IVIg 1 g/kg per day for 2 days vs placebo	9 with Lambert–Eaton myasthenic syndrome	IVIg showed significant improvements in limb, respiratory, and bulbar muscle strength measures (p=0.017 to 0.038) and a significant decline in serum calcium channel antibody titers (p=0.028)

Table 12 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
Stiff person syndrome	[375]	Case series	IVIg	3 patients with active disease and/or disease refractory to treatment with diazepam and/or CS	Improvement after treatment
	[376]	Uncontrolled pilot study	IVIg	3 patients with stiff-man syndrome	Improvement after treatment
	[377]	Case report	IVIg	A patient with refractory stiff-man syndrome	Long-term remission after treatment
	[378]	Crossover RCT	IVIg 2 g/kg once a month for 3 months vs placebo	14 patients with stiff-person syndrome and anti-GAD65 antibodies	According to stiffness scores, IVIg was superior compared to placebo in direct treatment effect (p= 0.01) and in first-order carryover effect (p=0.001)
Adrenoleukodystrophy	[379]	RCT	IVIg 1 g/kg per day every 15 days for 3 months and every month for 1 year + VLCFA-restricted diet + GTOE vs VLCFA-restricted diet + GTOE	12 X-linked adrenoleukodystrophy	No significant differences in deterioration of neurological symptoms in the 2 groups according to EDSS score
Intractable childhood epilepsy	[380]	RCT	IVIg 0.1–0.4 g/kg (7 infusions in 6 weeks total time) vs placebo	61 patients with refractory epilepsy (46 with partial epilepsy)	No significant difference between the groups studied; no relationship between IVIg dose and efficacy
	[381]	Crossover RCT	IVIg 0.4 g/kg (Sandoglobulin) 2 infusions each with an interval of 2 weeks vs placebo	10 patients aged 4–14 years with Lennox–Gastaut syndrome	2/10: immediate reduction in their high-frequency and invariable seizure activity from 42% to 100% and a less abnormal EEG 8/10: unchanged general condition, no EEG changes
Critical illness polyneuropathy	[382]	Retrospective chart analysis	IVIg 0.3 g/kg per day for 3 days	16 patients with critical illness polyneuropathy following multiple-organ failure and gram-negative sepsis	8/16 patients of multi-organ failure with sepsis without the development of critical illness polyneuropathy had been treated with IVIg immediately after the diagnosis of sepsis 7/16 who eventually developed critical illness polyneuropathy were not treated with IVIg
	[383]	Case series	IVIg	3 patients with critical illness polyneuropathy	No improvement after treatment
Rasmussen's encephalitis	[384]	Case series	IVIg, CS, CP, therapeutic PP (TPE), protein A, immunoglobulin G (IgG), immunoadsorption (PAI)	15 patients with Rasmussen encephalitis (14 with childhood and one with adolescent onset)	In 11 patients treated with IVIg, 1 had reduction of seizure frequency by >50% and improvement of neurologic condition or resolution of status epilepticus and 2 had reduction of seizure frequency by up to 50%; in the rest, 5 had no effect and in the 3 effect was not assessable
	[385]	Case report	IVIg 0.4 g/kg per day for 5 days once a month	A 45-year-old woman with adult-onset Rasmussen encephalitis	Improvement after IVIg therapy with a >75% reduction in seizures and

Table 12 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
					mild improvement in neurologic performances
	[386]	Case reports	IVIg 0.4 g/kg per day for 5 days once a month	2 patients with advanced adult-onset Rasmussen's encephalitis	Significant improvement in seizure control, hemiparesis, and cognition
	[387]	Case series	IVIg ± high-dose CS	19 patients with Rasmussen's encephalitis	8/9 patients receiving IVIg had some reduction of seizure frequency and mild improvement in hemiparesis
Chronic inflammatory demyelinating polyradiculoneuropathy	[388]	Crossover RCT	IVIg 1 to 2 g/kg over 1 to 2 days every 3 weeks for 24 weeks vs placebo	117 patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	54% of patients treated with IVIg and 21% treated with placebo improved according to INCAT disability score (p=0.0002); IVIg patients had a longer relapse time compared with placebo (p=0.011) in the extension phase
	[389]	Crossover RCT	IVIg 2 g/kg over 1 to 2 days vs oral prednisolone for 6 weeks	24 patients with CIDP	Both treatments showed marked improvement in INCAT disability scores after 2 weeks; no significant difference between the 2 treatments
	[390]	RCT	IVIg 1 g/kg per day for 2 days vs placebo	53 patients with untreated CIDP	Average muscle score (AMS) was significantly improved in the IVIg group (p= 0.0006) at day 42; IVIg significantly improved nerve conduction; according to Hughes' functional disability scale IVIg group showed better improvement than placebo (p=0.019)
	[391]	Crossover RCT	IVIg 0.4 g/kg per day for 5 days vs placebo	30 patients with definite or probable CIDP of chronic progressive (16 patients) or relapsing (14 patients) course	At 4 weeks, significant improvement with IVIg in neurological disability score (NDS; P< 0.0001) in clinical grade (CG; P< 0.002) and in grip strength (GS; P< 0.001); significant improvement in summed MCV (P< 0.0001) and in summed (CMAP) amplitudes (P< 0.03)
Myasthenia gravis	[392]	Systematic review	IVIg vs no treatment or placebo or plasma exchange	6 RCT (n=371)	There is insufficient evidence to determine the efficacy of IVIg in myasthenia gravis
	[393]	RCT	IVIg 2 g/kg over 2 days vs placebo	51 patients with worsening weakness due to myasthenia gravis	According to quantitative myasthenia gravis (QMG) score at day 14, there was a significant improvement in the IVIg group (p=0.047) which continued at day 28
	[394]	RCT	IVIg 2 g/kg vs placebo	15 patients with myasthenia gravis	No significant differences between the 2 groups were

Table 12 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
					noted at day 42 according to QMG score
	[395]	Crossover RCT	IVIg 0.4 g/kg for 5 days vs plasma exchange	12 patients with generalized moderate to severe myasthenia gravis on immunosuppressive treatment for at least 12 months	After 1 and 4 weeks of treatment, a significant improvement was noted according to QMG score in both groups; no significant difference between them
	[396]	Case series	IVIg 0.04 g/kg per day for 5 days and maintenance every 6 weeks	10 patients with severe generalized myasthenia and an acute deterioration unresponsive to conventional therapy	Significant improvement according to Osserman scale at 1 year ($P<0.001$) in all patients
Acute disseminated encephalomyelitis	[397]	Case report	IVIg 2 g/kg once and repeat bolus of 150 g on week 3 and 4; previews treated with CS with no response	A 20-year-old male with postvaccination acute disseminated encephalomyelitis	Rapid response with partial recovery over 1 year
	[398]	Case series	IVIg 2 g/kg over 2 days or MP or IVIg 2 g/kg over 2 days + MP	6 children with severe acute disseminated encephalomyelitis	1 patient treated with IVIg and 10 patients treated with CS alone had complete response; from 5 patients treated with combined therapy, 2 had complete response and 3 partial or no response
	[399]	Case series	IVIg 0.4 g/kg per day for 5 days	5 adult patients, 3 of them affected by classic disseminated encephalomyelitis and 2 by a postinfectious myelitis	Marked functional improvement in all patients starting from day 5 with maximum effect at 3 weeks
	[400]	Case report	IVIg + CS for 3 days	A child with atypical acute disseminated encephalomyelitis	Complete response
	[401]	Case report	IVIg + CS	A 3-year-old boy with severe acute disseminated encephalomyelitis	Complete response
	[402]	Case reports	IVIg 30 g/day for 5 days and 3 additional monthly courses of 30 g + CS IVIg 50 g/d for 2 days + CS.	2 adult women with acute disseminated encephalomyelitis	Complete response in both patients
Autism	[403]	Case series	IVIg 0.04 g/kg monthly for 6 months	7 patients with childhood autism	No statistically significant changes on behavioral measures after 6 months

PANDAS pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

Rasmussen's encephalitis

Level of evidence C There is weak evidence indicating significant benefit of IVIg in Rasmussen's encephalitis either used as monotherapy or combined with other therapies. It should be considered as one of the treatment options in this disease (*strength of recommendation I*).

Myasthenia gravis

Level of evidence A Several RCTs and a meta-analysis examined the efficacy of IVIg in patient with myasthenia gravis. Results are conflicting. A recent meta-analysis concluded that there is insufficient evidence to determine the efficacy of IVIg in myasthenia gravis. IVIg may be used as treatment for myasthenia gravis

Table 13 The use of intravenous immunoglobulins in immunodeficiencies

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
X-linked agammaglobulinemia (XLA)	[404]	Retrospective trial	IVIg was given at doses of >0.25 g/kg every 3 weeks (mean individual residual IgG levels of 700 mg/dl); 24 patients received IVIg from the "Etablissements de Transfusion Francais," others Sandoglobulin (Novartis Institute, Basel) and Endoglobulin (Immuno France, Marseilles) for 3,690 cumulated months	31 patients with XLA at mean age of 24 months followed for a median time of 123 months	The incidence of bacterial infections requiring hospitalization fell from 0.4 to 0.06 per patient year ($p<0.001$); the incidence of bacterial infections requiring hospitalization was lower for the periods when patients had residual level of IgG>800 mg/dl than for the period of levels <800 mg/dl ($p<0.001$); however, viral or unidentified infections still developed (enteroviral meningitis 3, exudative enteropathy 3, aseptic arthritis 1); at last follow-up, 30 patients were alive at median age of 144 months (range, 58 to 253)
	[405]	Retrospective trial	Patients were treated with different regiments of IVIg between 1965 and 1990; 20 patients were treated before any IVIg was available, 14 patients received IMIg in dose of <0.1 g/kg every 3 weeks; 9 patients were treated at dosages up to 0.2 g/kg every 3 weeks; 15 patients received IVIg at dosages between 0.35 and 0.6 g/kg every 3 weeks (patients receiving different replacement regiments were assigned to more than one group if they received respective regiment for a minimum of 1 year)	29 patients with XLA	A significant increase in trough serum IgG ($p=0.0001$) and a significant decrease in the incidence of pneumonias ($p=0.038$) and number of days spent in the hospital in high-dose IVIg group compared with other groups ($p=0.005$); improvement in therapeutic outcome was particularly evident when high-dose IVIg was started before the age of 5; bacterial meningitis, chronic pulmonary disease, and bronchiectasis occurred in IMIg but not in any of IVIg groups
	[406]	Retrospective trial	IVIg 0.3–0.4 g/kg every 3 to 4 weeks	23 patients with XLA treated with IVIg for a mean period of 6.8± 4.1 years	Significant decrease of the incidence of pneumonia requiring treatment or hospitalization ($p=0.006$) and hospitalizations due to pneumonia ($p=0.08$)
	[407]	RCT	GamaSTAN 20 ml in 2 IM injections every 4 weeks vs. 0.15 g/kg IVIg every 4 weeks (Cutter Laboratories, Inc., Berkeley, CA, USA) during 242 months of treatment	22 patients with antibody deficiency (9 with XLA); 14 (5 with XLA) received IVIg, 13 (7 with XLA) received ISg; 7 patients (3 with XLA) received both ISg and IVIg in separate courses	Less acute infections per month of treatment in IVIg group ($p<0.01$; in XLA subgroup, mean 0.8 vs. 2.7); in patients who received separate courses of both IVIg and SIg, infection rate was lower on IVIg ($p<0.05$; in XLA subgroup, mean 0.3 vs. 4.7)
	[408]	RDB crossover	Standard-dose IVIg (adults 300 mg/kg and children 0.4 g/kg every 4 weeks) for 9 months, followed by 3-month washout period and	41 patients with primary hypogammaglobulinemia (19 patients with XLA)	High-dose therapy significantly reduced the number (mean, 3.5 vs. 2.5 per patient ($p=0.004$) and 4.3 vs. 3.4 in XLA

Table 13 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
			high-dose IVIg (adults 0.6 g/kg and children 0.8 g/kg every 4 weeks) or vice versa (Immunoglobuline IV, Sanquin Blood Supply Foundation, the Netherlands)		subgroup) and duration (median, 33 vs. 21 days (p=0.015), in XLA subgroup 28.5 vs. 19 days) of infections
Wiscott–Aldrich syndrome (WAS)	[409]	Retrospective trial	IVIg 0.18–0.58 g/kg every 2–4 weeks and antibiotic prophylaxis with acyclovir and/or fluconazole in some cases	21 patients with WAS	Only 4 episodes of sever acute bacterial infection in 451 patient months after splenectomy
Hyper-IgE syndrome (Job syndrome)	[410]	Case series	IVIg	3 adult patients with hyper-IgE syndrome	Marked improvement in tendency to infections
	[411]	Case report	Monthly IVIg and interferon gamma three times a week since age 3; he received also prophylaxis with antibiotic and fluconazole	15-year-old boy with hyper-IgE syndrome	Good control of disease
	[412]	Case report	IVIg 2 g/kg (Venoglobulin I-Alpha Therapeutic Corporation, Los Angeles, CA, USA) monthly for 7 courses	Patient with hyper-IgE syndrome	No improvement
	[413]	Case series	IVIg	8 children with recurrent infections, failure to thrive, hypergammaglobulinemia and IgG2 subclass deficiency	Clinical resolution
	[414]	Case series	IVIg (Sandoglobulin) 6–12 g monthly	3 members of a family (2 children, 1 adult) with recurrent severe respiratory infections and IgG2 subclass deficiency	Clinical resolution
IgG subclass deficiencies	[415]	Case report	IVIg monthly 7 courses	A-6-year old child with chronic rhinosinusitis, nasal polyps and IgG3 deficiency	Clinical improvement
	[416]	Case report	IVIg monthly	A 2-year-old child with recurrent sinopulmonary infections and IgG2 deficiency	Clinical improvement
	[417]	Cases report	IVIg 10–15 g every 3 weeks for 6 months	2 patients with treatment-resistant osteomyelitis of the jaw, one with IgG2 deficiency, and the other with IgG3 deficiency	Clinical improvement in both patients
Specific antibody deficiency	[418]	Retrospective study	Part of this patients received IVIg	75 patients with recurrent infections and low response to pneumococcal polyvalent vaccine	Reduction in number of infections
	[203]	Series report	IVIg	9 children with recurrent sinopulmonary infections and poor response to *Haemophilus influenzae* type b capsular polysaccharide	Reduction of infections upon start of IVIg treatment and recurrence after discontinuation
	[419]	Case report	IVIg	Patient with Smith–Lemli–Opitz syndrome, frequent infections and absent response to Pneumovax	Same frequency of infections, less severity

Table 13 (continued)

Disease	Ref.	Study design	Intervention including dose and IVIg preparation used	Number of patients	Results/response
Hyper-IgM syndrome (HIGM)	[420]	Case control study	IVIg was administered every 4 weeks and serum IgG levels were consistently maintained above 4 or 5 g/l in most patients	29 patients with HIGM due to activation-induced cytidine deaminase deficiency, suffering from recurrent infections	After IVIg therapy was initiated, frequency of infections markedly decreased
	[421]	Case control	IVIg	9 patients with HIGM and recurrent infections	Regression in the manifestations of infection
	[422]	Case control	IVIg, 0.25–0.3 g/kg every 4 weeks for 1 year	6 patients with HIGM and recurrent infections	Severity and frequency of infections decreased significantly
	[423]	Case report	IVIg with antibiotics, chloroquine, and PD	A 6-year-old with HIGM and severe recurrent respiratory infections	Mild improvement with a decrease in the inflammatory infiltrate in thoracoscopic biopsy
	[424]	Case report	IVIg and prophylactic antibiotic therapy	A 6 years old with CD40 ligand deficiency, chronic neutropenia, and HIGM	Management of neutropenia, better quality of life with decreasing occurrence of infection
	[425]	Case report	IVIg	A 5-month-old boy with HIGM and severe pneumonia refractory to antibiotics	His pneumonia improved; after that, he had no recurrent infections
Transient hypogamma of infancy (THI)	[426]	Case report	IVIg every 4 weeks	1-year-old girl with THI and *Staphylococcus aureus* sepsis refractory to antibiotics	Gradual improvement
	[427]	Case report	Treated with antibiotics and IVIg	1-year-old boy with THI and recurrent sepsis	Fewer infections
Severe combined immunodeficiency (SCID)	[428]	Case control	Monthly IVIg	45 children surviving BMT for SCID	Effective as adjuvant for BMT
Common Variable Immune Deficiency (CVID)	[429]	Case series	The number of pneumonia episodes was compared prior to and after initiation of IVIg maintenance therapy for 6.6±5.2 years (0.3–0.4 g/kg every 3 to 4 weeks)	50 patients with confirmed CVID	Prior to IVIg therapy, 84% of patients had an episode of pneumonia, and 22% had recurrent pneumonias; following IVIg administration, 22% of the patients have acquired pneumonia; this change was found to be statistically significant ($p<0.001$)
	[33]	Case series	Data were collected retrospectively; all the patients were treated by 3 modalities: no IVIg, low-dose IVIg (0.2 g/kg every 3 weeks), and standard-dose IVIg (0.4 g/kg every 3 weeks)	7 patients diagnosed with CVID	Number of infections per patient-year was 5 in the no-IVIg period, 2.79 in the low-dose period ($p=0.002$), and 1.53 in the standard-dose period ($p=0.02$); lower respiratory tract infections were markedly decreased due to IVIg therapy
	[32]	Case series	IVIg (Sandoglobulin and/or Nordimmune), 0.4 g/kg every 3 to 4 weeks; the follow-up period was 41.5± 35.4 months	26 patients diagnosed with CVID	IVIg therapy was associated with significant decrease of annual hospitalization due to pneumonia: from 88.5% to 46% ($p=0.0025$); a significant decrease of total hospital admissions was also observed (from 3.4 to 0.7 per year, $p<0.0005$)

severe acute exacerbations (*strength of recommendation IIa*).

The following conditions refer to (Table 13).

X-linked agammaglobulinemia

Level of evidence B Retrospective analyses revealed that IVIg is beneficial in terms of reduction of acute and chronic infections and days of stay in the hospital. Intravenous route is preferred over intramuscular administration of immunoglobulin and the number and severity of complications are inversely correlated with the dose of IVIg (*strength of recommendation I*).

Wiscott–Aldrich syndrome

Level of evidence C Despite relatively low evidence of effectiveness of IVIg, the majority of WAS patients are treated with IVIg, which appears to be effective in reduction of acute and chronic infections in these immunodeficient patients (*strength of recommendation IIa*).

Hyper-IgE syndrome (job syndrome)

Level of evidence C There is weak evidence that IVIg is useful in the treatment of hyper-IgE syndrome. IVIg may be tried in cases in which recurrent live-threatening diseases cannot be controlled by antibiotic prophylaxis (*strength of recommendation IIb*).

IgG subclass deficiencies

Level of evidence C There is scarce evidence that IVIg is useful in the treatment of IgG subclass deficiencies. Most of the experience reported is patients with IgG2 deficiency. In our opinion, when antibiotic treatment is not effective, IVIg would be a reasonable alternative (*strength of recommendation IIb*).

Specific antibody deficiency

Level of evidence B This is a heterogeneous group. Specific deficiency of antibodies after vaccination has been found to correlate with infection susceptibility. Most of the published experience regarding IVIg is in patients with deficiency of antibodies to capsular polysaccharide. IVIg has been reported to be beneficial in some cases. This is not surprising as antibodies to bacterial capsular polysaccharide are contained in IVIg [31]. The evidence for the use of IVIg in specific antibody deficiency is not strong but might be warranted when recurrent infection is present and it is possible to demonstrate low antibody responses to a relevant vaccine (*strength of recommendation IIa*).

Hyper-immunoglobulin-G syndrome

Level of evidence B The hyper-IgM syndrome (HIGM) is a rare hereditary immune deficiency, characterized by a low or nil level of IgG and IgA and a normal or increased level of IgM, predominately affecting boys. Its clinical manifestations are dominated by recurrent infection, notably of the digestive tube, the ears, nose, and throat and the lungs. IVIg may be considered to treat patients with HIGM and recurrent infections (*strength of recommendation I*).

Transient hypogammaglobulinemia of infancy

Level of evidence C Transient hypogammaglobulinemia of infancy is characterized by a prolongation and accentuation of the physiologic hypogammaglobulinemia normally occurring during the first 3 to 6 months of life and recovers spontaneously between 18 and 36 months of age. Infants with transient hyogammaglobulinemia of infancy (THI) may remain asymptomatic or develop recurrent sinopulmonary infections, but severe or life-threatening infections are rare. In general, supportive and antimicrobial therapies are sufficient management for the treatment of specific infections in patients with THI. In cases in which infections are severe or refractory to conventional therapy, IVIg is sometimes considered although literature reports are lacking (*strength of recommendation I*).

Severe combined immunodeficiency

Level of evidence B SCID is a severe form of heritable immunodeficiency in which both “arms” of the adaptive immune system are defected. These babies, if untreated, usually die within 1 year due to severe recurrent infections. Treatment with BMT is successful, and IVIg is used as an adjuvant for this therapy (*strength of recommendation I*).

Common variable immune deficiency

Level of evidence C Common variable immune deficiency (CVID) is an idiopathic hypoimmunoglobulinemia. World Health Organization diagnostic criteria are well established [32]. Both B and T cells dysfunction have been observed [33]. There are both theoretical logic and experimental evidences that support IVIg administration in CVID (*strength of recommendation IIb*).

Primary phagocytic defect

Many different genetic diseases will ultimately result in primary phagocytic defect: cyclic neutropenia, severe congenital neutropenia, Shwachman–Diamond syndrome, leu-

kocyte adhesion deficiency, Rac2 deficiency, interferon-γ and IL-12 defects, chronic granulomatous disease, myeloperoxidase deficiency, Chediak–Higashi syndrome, and neutrophil-specific granule deficiency [34]. An extensive PubMed-based search revealed little if any information regarding the efficacy of IVIg in the above entities.

IgA deficiency

IgA deficiency may be associated with preventable anaphylaxis or anaphylactoid reaction following IVIg transfusion [35]. This adverse reaction is encountered in patients with selective IgA deficiency and high titer of anti-IgA antibodies. In those patients, anaphylaxis can be avoided by the use of IgA-depleted IVIg preparation [36].

Discussion

This article summarizes most of the studies dealing with IVIg administration that were publicized until recently. We have included an array of clinical conditions, some in which the use of IVIg is expected according to their pathogenesis, such as primary immunodeficiencies and rheumatic diseases, and others somewhat less obvious indications including cardiac and oncologic diseases. In some diseases, the usage of IVIg was found to be highly recommended (with a level of evidence A and strength of recommendation I): Kawasaki disease, acquired hypogammaglobulinemia, juvenile rheumatoid arthritis, hemolytic disease of the newborn, acute immune thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, and Guillain–Barré syndrome. For many other diseases, treatment with IVIg was found effective as well, but this was less well established, either due to a lack of well-designed studies or due to conflicting evidence among them. In some diseases, there is a strong recommendation against using IVIg (with a level of evidence A and strength of recommendation III): stem cell/bone marrow transplantation, inclusion body myositis, recurrent pregnancy loss due to antiphospholipid syndrome, optic neuritis, and intractable childhood epilepsy. Nevertheless, the effectiveness of IVIg in such a large span of diseases fortifies the accumulating evidence that many pathological conditions are autoimmune mediated.

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