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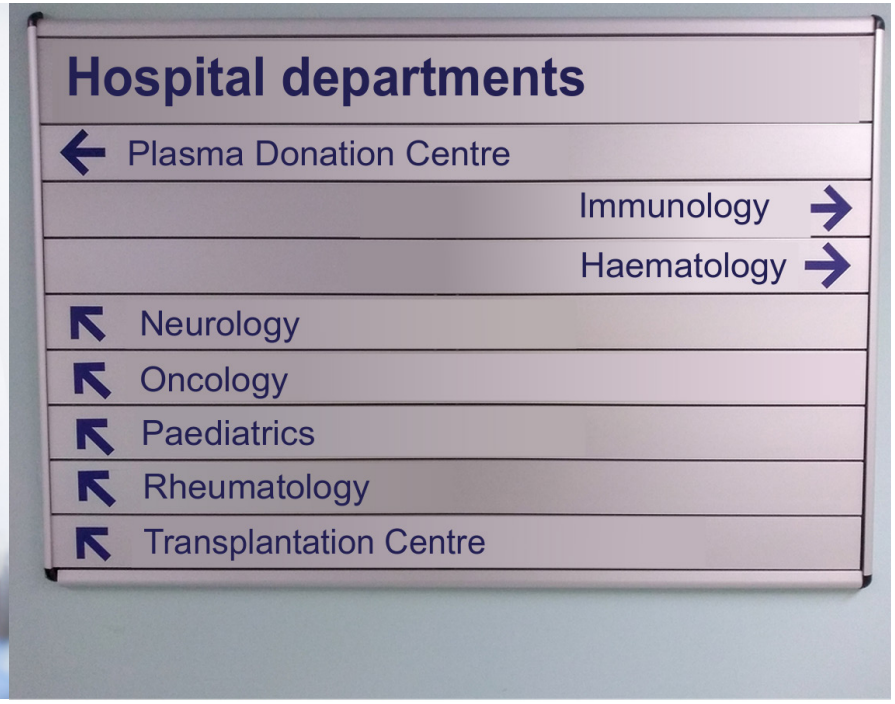
Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

POLYVALENT IMMUNOGLOBULINS – PART 1: A RAPID REVIEW

SUPPLEMENT 2



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HEALTH TECHNOLOGY ASSESSMENT

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POLYVALENT IMMUNOGLOBULINS – PART 1: A RAPID REVIEW

SUPPLEMENT 2

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COLOPHON

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1 IMMUNOGLOBULINS ON THE BELGIAN MARKET

1.1 Overview of Immunoglobulin products registered in Belgium

Products		Firm	administration
Gammanorm®	1g/6ml, 1.65g/10ml, 3.3g/ 20ml	Octapharma	Subcutaneous
Gamunex®	10g/100ml	Grifols	Intravenous
Hizentra®	1g/5ml, 2g/10ml, 4g/20ml	CSL Behring	Subcutaneous
Iqymune®	2g/20ml, 5g/50ml, 10g/100ml, 20g/200ml	CAF-DCF	Intravenous
Multigam®	1g/20ml, 2.5g/50ml	CAF-DCF	Intravenous
Nanogam®	1g/20ml, 2.5g/50ml, 5g/100ml, 10g/200ml, 20g/400ml	CAF-DCF	Intravenous
Octagam®	2g/20ml, 2.5g/50ml, 5g/100ml, 10g/100ml, 10g/200ml, 20g/200ml	Octapharma	Intravenous
Panzyga®	10g/100ml	Octapharma	Intravenous
Privigen®	2.5g/25ml, 5g/50ml, 10g/100ml, 20g/200ml	CSL Behring	Intravenous
Sandoglobulin®	6g/200ml	CSL Behring	Intravenous

Source: BCFI website on 1 October 2019

Note: not all registered products are reimbursed

1.2 Overview of stock ruptures since January 2018 till October 2019

Products		Firm	Supply problem start date	Expected end date
Gamunex®	10% 100ml	Grifols	August 1, 2017	July 2, 2018
Gammanorm®	3,3g/ 20ml	Octapharma	Jun 11, 2019	Jul 31, 2019
Iqymune®	2g/20ml, 5g/50ml, 10g/100ml, 20g/200ml	CAF-DCF	Dec 21, 2018	Oct 31, 2019
Panzyga® [a]	10g/100ml	Octapharma	Apr 15, 2019	Dec 31, 2019[a]

Source: FAMPH website: https://banquededonneesmedicaments.fagg-afmps.be/#/query/supply-problem/human ; a) since January 2020 there is an interruption of commercialisation of Panzyga® in Belgium

1.3 Overview of Market Withdrawals since 2008

Products		Firm		Year withdrawn from market
Multigam®	10 g / 200 ml, and all 10% formulations	CAF-DCF	IVIg	2018-2019
Kiovig®	all formulations	Baxter AG	IVIg	2015
Gammagard®	all formulations	Baxter AG	IVIg	2013
Sandoglobulin®	1g/50ml; 3g/100ml	CSL Behring	IVIg	2014
Subcuvia®	all formulations	Baxter AG - Shire	SCIg	2013
Vivaglobin®	all formulations	CSL Behring	SCIg	2013

Source: FAMPH communication

2 EXTRACTION TABLES OF SYSTEMATIC REVIEWS AND RCTS

2.1 Extraction table of moderate to good quality SRs on safety

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
Thromboembolic events (TEEs)										
Ammann et al. Intravenous immune globulin and thromboembolic adverse events: A systematic review and meta-analysis of RCTs	2016	To assess the effect of IVIg treatment on the risk of serious TEEs (acute myocardial infarction, ischemic stroke, or venous thromboembolism)	31 RCTs, Studies with a high risk of detection of reporting bias for AEs were excluded	October 2015	Mixed: autoimmune and/or inflammatory conditions, secondary immune deficiency, infection, sepsis and/or systemic inflammatory response syndrome, hematopoietic stem cell or organ transplantation, infertility and pregnancy outcomes, Alzheimer's disease, and others. Mean age 47	IVIg vs placebo, no treatment or standard treatment. IVIg as adjuvant therapy was also included	1ary outcome: Rate of serious TEEs. Arterial and venous TEES were analysed as 2ary outcomes	Safety: 0,52% of patients treated with IVIg, versus 0,44% in the control group). Risk difference of 0,0% (95%CI: -0,7%; 0,7%). No sig evidence of heterogeneity across studies. No increase in risk seen either when arterial and venous TEEs were analysed separately. (31 RCTs, n=4129).	The risk of TEEs with IVIg appears to be low. However caution is needed due to the mean age of the population (young) and the potential underreporting of AEs in the included studies	High (8/11)
Necrotising enterocolitis (NEC)										
Yang et al. The effect of immunoglobulin treatment for hemolysis on the incidence of necrotizing enterocolitis – a meta-analysis	2016	To study the risk of NEC in hemolytic patients	5 observational studies (no RCTs), of high quality according to JADAD	December 2015	Hemolytic infants	IVIg versus controls (not described in detail)	Rate of NEC and mortality	The risk of NEC in hemolytic patients is significantly higher with IVIg versus the control (OR: 4.53; 95% CI, 2.34-8.79; p < 0.00001), but no significant differences were seen in mortality. (95% CI, 0.15-5.13; p = 0.87)	IVIG treatment for hemolysis may significantly increase the risk of NEC in infants. But it does not increase the risk of mortality.	Moderate (6/11)

2.2 Extraction table of moderate to good quality SRs for indications reimbursed in Belgium

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
PRIMARY IMMUNODEFICIENCY DISEASE (PID)										
Wood et al. Recognition, clinical diagnosis and management of patients with PID: a systematic review	2007	Evidence based info on recognition, diagnosis and management	RCTs, case-control, cohort 4 RCTs comparing doses or administration: (Eijkhout 2001, Roifman 1987, Roifman 2003, Chapel 2000)	June 2006	PID	IVIg vs placebo or no treatment: No RCTs low vs high dose IVIg: 2 RCTs (Eijkhout 2001, Roifman 1987) administration forms: 1 RCT on IVIg vs SCIG (Chapel 2000); 1 RCT on IVIg-C vs IVIg-SD (Roifman 2003)	Increased life expectancy Reduction in rate of (bacterial) infection	Efficacy: No pooling of data. Focus on results from RCTs No RCTs on life expectancy Reduction of infections: 1 RCT showed no sign. difference between High vs Low dose (Roifman 1987, n=12) and 1 did show sign. dose response (Eijkhout 2001, n=43) SCIg and IVIg equal infection reduction (Chapel 2000, n=30)	Increased doses of IVIg improve outcome measures with regard to infection frequency and severity, but whether they impact mortality remains to be established	Moderate (4/11)
Orange et al. Impact of through IgG on pneumonia incidence in PID: meta-analysis of clinical studies	2010	Impact of IVIg through IgG on pneumonia incidence	RCTs and observational: 2 cross-over RCTs (Chapel 2000; Roifman 1987) 15 observational	September 2009	PID treated with IVIg	Dose-response: high dose vs low dose (Roifman 1987) IVIg vs SCIg (Chapel 2000)	Pneumonia Incidence IgG Through level	Efficacy No separate meta-analysis based on RCTs Each additional 100mg/kg dose increment was associated with a sign. reduction in Pneumonia incidence (IRR=0.726; CI:0.65-0.81) ➔ reduced by 27% (17 studies, n=676)	The meta-analysis provides evidence that pneumonia risk can be progressively reduced by higher IgG trough levels (up to at least 1000mg/dl)	Moderate (6/11)
Abolhassani et al. Home-Based Subcutaneous	2012	comparing efficacy and safety of IVIg and SCIg	Retrospective (n=20) and prospective cohort studies	January 2012	1ary or 2ary antibody deficient patients	SCIg versus IVIg	Serum IgG trough levels: MA	Efficacy: Serum IgG through level mean difference= 1.00,	Showed significant preference	Moderate (5/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
Immunoglobulin vs. Hospital-Based Intravenous Immunoglobulin in Treatment of Primary Antibody Deficiencies: Systematic Review and Meta-Analysis			(n=25) and RCTs (n=2) (Chapel et al. 2000 (n=30); Desai et al. 2009 (n=12))				Serious bacterial infections: MA Systemic AEs: MA Local AEs, hospitalization, health related QoL, treatment satisfaction and convenience, missed days of work/school cost: no MA, no systematic description	range (0.84–1.15; p<0.01) (17studies) serious infection rate: OR=0.59 (0.36–0.97; p<0.04) indicated non-sign preference of SCIg over IVIg (9 studies, n=269) <u>Safety:</u> Systemic AEs: OR= 0.09 (0.07–0.11; p<0.001) (15 studies, n=376) patients) indicates a significant preference for SCIg. Local AEs: no meta-analysis. Description of study results of different trials.	of SCIg over IVIg.	
Lingmann Framme and Anders Fasth Subcutaneous Immunoglobulin for Primary and Secondary immunodeficiencies: an Evidence-Based Review	2013	comparing IVIg and SCIg regarding efficacy, safety, health-related QoL and health economics	RCTs and observational <u>PID:</u> 2 RCTs (Chapel 2000; Desai 2009) 17 non-randomized studies <u>SID:</u> 1 retrospective study 5 HTAs	June 2012	PID or SID with patients ongoing Ig substitution	SCIg vs IVIg	1ary: serious bacterial infections; 2ary: N. of annual infections, days with fever, days with antibiotics and IgG trough levels; HRQoL: (SF-36 health survey in adults and the Child Health Questionnaire in children) AEs.	No meta-analysis because of lack of info on standard deviations and low level of evidence. Only descriptive analysis. <u>Efficacy:</u> SBI (based on 3 observational studies, n= 58 patients): no SBI found. Annual infection (5 studies, n=96 of which 2 RCTs n=41): no comparison made HRQoL (4 observational studies): better in patients with home-based SC	Both SC and IV immunoglobulin substitution offer protection from serious bacterial infections and have good safety	High (8/11), The quality of evidence as assessed by the GRADE score was found to be low for all outcomes (only for outcomes reported in RCTs, it was moderate: annual infection).

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
								immunoglobulin substitution compared with those who received hospital-based IVIg substitution SCIg has higher through level as reported in all studies (11 studies, n=284 of which 2 RCTs n=41): no statistical analysis <u>Safety:</u> Serious AEs (5 studies, n=118 of which 1 RCT n=30): none reported Local AEs: more frequent with SCIg (descriptive no comparison made) .		
Shabaninejad et al. Comparative study of IVIg and SCIg in adult patients with PID: systematic review and meta-analysis	2016	Efficacy and safety of SCIg	RCTs and observational For efficacy: 1 crossover RCT (Chapel 2000) For safety: 5 RCTs (Empson 2012, Wasserman 2010, Gelfand 2006, Ochs 2006, Schiff 1997)	March 2015	Adults with PID	SCIg versus IVIg	Serum Ig level infection rate AEs	<u>Efficacy:</u> SCIg achieves higher serum Ig levels: meta-analysis (15 studies, n=446) Mean diff = 0,336 (0,205-0,467; p<0,01); similar rates for infections; no meta-analysis possible- descriptive analysis <u>Safety:</u> Systemic AEs: OR= 0,497; 0,180-1,371; p=0,1 (13 studies, n=431)	Because of limitations of the included studies no definite conclusion on effectiveness was possible; results suggest superiority of SCIg in comparison to IVIg	Moderate (5/11); meta-analysis mostly based on observational studies

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
Secondary hypogammaglobulinemia (SID) - MULTIPLE MYELOMA and CHRONIC LYMPHOCYTIC LEUKEMIA (Hematological Cancers)										
Raanani et al. Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation (Cochrane)	2008	Efficacy of prophylactic administration of IVIg for MM, CLL	RCTs only, 4 on CLL (Boughton 1995; Chapel 1994c; Cooperative CLL 1988; Molica 1996); 4 on MM (Chapel 1994; Musto 1995; Salmon 1967; Hargreaves 1992); 1 both on CLL and MM (Sklenar 1993) 1 both on MM and low risk non-Hodgkin lymphoma (Gluck 1990)	2007	Patients with hematological malignancies - CLL or MM	IVIg vs placebo or no intervention: 7 RCTs, 2 crossover studies not included in meta-analysis	1ary: All cause mortality Clinically documented infections 2ary: AEs	<u>Efficacy:</u> All-cause mortality at 1y: no sig. different between IVIg and control, RR 1.36 (95% CI 0.58 to 3.19) (2 RCTs, n=163) IVIg reduced the risk for developing clinically documented infections by 51%; RR: 0.49 (95% CI 0.39 to 0.61) (3 RCTs, n=205) <u>Safety:</u> IVIg caused a sig. increase in AEs events, RR:2.37 (95% CI 1.74 to 3.24) (3 RCTs, n=205), but when focussing on AEs requiring discontinuation, this was not sig. RR:5.43 (95%CI 0.70-42.24) (2 RCTs, n=124)	Use may be considered in CLL and MM patients with hypogammaglobulinemia and recurrent infections, for reduction of clinically documented infections.	High (10/11)
Secondary hypogammaglobulinemia (SID) – POST HAEMOPOIETIC STEM CELL TRANSPLANTATION (HSCT)										
Raanani et al. Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell	2008	Efficacy of prophylactic administration of IVIg for patients undergoing BMT or HSCT given IVIg (and not as treatment of	RCTs only: 18 RCTs comparing polyvalent IVIg to placebo, no treatment, other doses,… + 3 RCTs comparing polyvalent to CMV-Ig	2007	Patients undergoing BMT or allogeneic and autologous HSCT 1 RCT autologous transplantation only (Wolff 1993) 16 RCTs (including 3 RCTs on CMV-IG)	IVIg vs placebo: 1 RCT (Sullivan 2000), IVIg vs. no intervention: 10 RCTs 1 RCT both different doses and placebo used as	1ary: All-cause mortality; clinically documented infections; 2ary: Microbiologically documented infections; Bacteremia;	<u>Efficacy:</u> Comparing to placebo or no treatment: No difference in the risk for all-cause mortality (RR:0.99 (95% CI 0.88 to 1.12). (8 RCTs, n= 1418) No reduction in the occurrence of	Routine prophylaxis is not supported neither for allogenic or autologous HSCT	High (10/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
transplantation (Cochrane)		suspected or documented infections).			allogenic transplantation only 4 RCTs included autologous and allogenic	comparators (Cordonnier 2003) Different products Gamimmune®, Gammagard®, Sandoglobuli®: 2 RCTs IVIg different doses: 3 RCTs 1 study both different products and different doses evaluated (Raiola 2002)	Infection-related mortality; Acute and chronic GVHD, veno-occlusive disease and interstitial pneumonia in allogeneic bone marrow transplants; Disease relapse; AEs	clinically documented infections, RR 1.00 (95% CI 0.90 to 1.10). (5RCTs, n=699) Significantly reduced risk interstitial pneumonitis by 36% (RR 0.64, 95% CI 0.45 to 0.89), (7 RCTs n= 990) => sensitivity analysis showed loss of significance when studies of inadequate randomisation were excluded No decrease in occurrence of acute GVHD, RR 0.93 (95% CI 0.83 to 1.04)(7RCTs, n=989) Safety: Significantly increased risk for developing VOD, RR 2.73 (95% CI 1.11 to 6.71), (4 RCTs, n=447)		
Secondary hypogammaglobulinemia (SID) – SOLID ORGAN TRANSPLANT										
Hodson Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane	2007	assess the benefits and harms of IgG, anti CMV vaccines or interferon for preventing symptomatic CMV disease in solid organ transplant recipients	6 RCTs on IVIg (n=189) 12 RCTs with hyperimmune CMV-Ig (n=704)	Dec 2005	All ages, ≥1 solid organ transplantation (kidney, liver, lung, heart, pancreas)	IVIg vs placebo (1 RCT) IVIg vs no treatment (5 RCTs), Ig vs antiviral therapy (4 RCTs) Ig as add-on to antiviral therapy (4 RCTs)	1ary: incidence of symptomatic CMV disease all-cause mortality 2ary: incidence of all CMV infections (symptomatic and asymptomatic),	Efficacy Compared to no treatment or placebo: no stat. significant differences for both IVIg and CMV-Ig. IVIg CMV disease: 5 RCTs, n= 175; RR:0.83 (95% CI 0.54, 1.28)	No indications for IgG in the prophylaxis of CMV disease in recipients of solid organ transplants	High (9/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
							acute rejection, graft loss, death, opportunistic infections, harms.	CMV infection: 3 RCTs, n=111 ; RR:0.81 (95%CI 0.61, 1.07) All-cause mortality: 1 RCT, n=34; RR:0.47 (95%CI=0.02, 10.6) No sig. impact on 2ary outcomes <u>CMV-Ig</u> CMV disease: 11 RCTs, n=595; RR= 0.79 (95%CI 0.55, 1.13) CMV-infection: 12 RCTs, n=664; RR= 0.97 (95%CI 0.80, 1.19) All-cause mortality : 7 RCTs, n= 468; RR= 0.58 (95%CI 0.32, 1.05) Compared to antiviral medication: Sig. reduction in the risk of CMV disease with antiviral medication alone (ganciclovir or acyclovir) vs IgG alone (4 RCTs, n=392; RR 0.68, 95% CI 0.48 to 0.98). Ig as add-on to antivirals: no sig. impact on outcomes <u>Safety:</u> One patient experienced		

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
								hemolysis and one patient stopped Ig because of mental state deterioration		
CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY										
Etimov et al. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy *(Cochrane)*	2013	To evaluate efficacy and safety of IVIg in CIDP	(quasi) RCTs: 8 RCTs (Vermeulen 1993; Mendell 2001; Hughes 2008; Nobile-Orazio 2012) of which 4 cross-over (Dyck 1994; Hahn 1996;Thompson 1996;Hughes 2001) Zinman 2005, Van doorn 1990 not included because of low quality	December 2012	Definite or probable CIDP (progression of weakness exceeding 8 weeks)	IVIg vs placebo (5 RCTs), plasma exchange (1 RCT) or corticosteroids (1 RCT on prednisolone and 1 RCT on intravenous methylprednisolone (IVMP)	1ary: proportion of participants with a sign. improvement in disability within six weeks after the onset of treatment 2ary: change in mean disability score, change in Medical Research Council sum score, AEs	Efficacy: IVIg vs placebo: Sign. improvement in disability scale RR 2.4 (95%CI 1.72 to 3.36) (5 RCTs, n=269) IVIG vs prednisolone, improvement in disability: NS (RR=0.91, 95% CI 0.50 to 1.68, 1 RCT, n=32). IVIg vs IVMP, improvement in disability: NS (RR 1.46, 95% CI 0.4 to 5.38). IVIg vs PE: no info on 1ary outcome-Neurological Disability Scale (1 RCT, n=19). Safety: Increased risk vs placebo (RR=2.61, 95% CI 1.80 to 3.78), 3 RCTs, n=308). Severe AEs: NS (RR=0.82, 95%CI 0.36 to 1.87, 3 RCTs, n=315). 1 IVIg treated with symptoms resembling aseptic meningitis	The evidence from RCTs shows that IVIg improves disability for at least two to six weeks compared with placebo, with an NNTB of three.	High (10/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
								Compared to PE, prednisolone, IVMP: NS for general and serious AEs. 1 IVIg treated died after cardiac arrest 1 month after treatment, 1 IVIg died three months after treatment due to respiratory failure		
Gaebel et al. Intravenous immunoglobulin for the treatment of CIPD: a systematic review and meta-analysis	2010	evaluate the clinical effectiveness and safety of IVIg	Controlled clinical trials, MAs, SRs, and HTAs. 9 RCTs (Vermeulen 1993; Mendell 2001; Hughes 2008; Zinman 2005, van Doorn 1990; Dyck 1994; Hahn 1996;Thompson 1996;Hughes 2001)	2009	Any age with definite or probable CIDP	IVIg vs. placebo (6 RCTs: Vermeulen 1993; Mendell 2001; Hughes 2008; Doorn 1990; Hahn 1996;Thompson 1996) IVIg vs. PE 2 RCTs (Zinman 2005; Dyck 1994) IVIg vs. prednisolone 1 RCT (Hughes 2001)	1ary: effect in disability as determined by the study itself Proportion of patients with a response to treatment as defined by the study itself 2ary: different measures of disability as well as QoL AEs.	Efficacy: IVIg vs. placebo: A sign effect, with a standardized mean difference of 0.65 (95% CI 0.23 to 1.08) in favour of IVIg (4 RCTs, n= 225) A sign effect on the proportion of patients responding to treatment (RR=2.74 (1.80–4.16, 4 RCTs, n=255) IVIg vs. PE or prednisolone: Descriptive analysis of different studies Safety: Descriptive analysis per study	IVIg therapy was statistically superior to placebo in reducing disability and impairment among patients with CIDP. The effectiveness of IVIg was similar to that of alternative treatment strategies (plasma exchange and oral prednisolone)	High (9/11)
Oaklander et al. Treatments for CIDP: an overview of systematic	2017	summarise the evidence from Cochrane and non-Cochrane systematic reviews	Corticosteroids (Hughes 2015), (IVIg) (Eftimov 2013), + 1 unpublished randomised open	October 2016	All forms of CIDP	Corticosteroids IVIg Plasma-exchange	1ary: change in disability after 12 or 6 months.	Efficacy: No update of meta-analysis Etimov 2013. For all outcomes see Etimov 2013	Moderate-quality evidence included in this overview supporting	High (9/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
reviews (Review) Cochrane			trial (Camdessanché 2014) plasma exchange (Mehndiratta 2015), other immunomodulatory treatment (Mahdi-Rogers 2013) for neuropathy associate with IgA and IgG Para proteins (Stork 2015).			Other immunomodulatory treatments		1 unpublished RCT (n= 35) compared IVIg to oral prednisone: disability RR 1.65, 95% CI 0.94 to 2.90). Safety: Serious AEs occurred in 3 IVIg patients and no participants who received prednisone (RR 6.63, 95% CI 0.37 to 199.59 More AEs with IVIg (82 out of 167; 49%) than with placebo (25 out of 141;18%)'; RR: 2.62 (95% CI 1.81 to 3.78) No sign. diff for serious AEs (RR 0.82, 95% CI 0.36 to 1.87).	the short-term efficacy of IVIg and PE, but evidence is limited by the small numbers of trials, the low numbers of participants and the short duration of follow-up, which was in many cases limited to four to six weeks.	
TOXIC SHOCK SYNDROME (STREPTOCOCCAL)										
Alejandra et al. Intravenous immunoglobulins for treating patients with severe sepsis and septic shock (Cochrane)	2013 (update of 1999, 2002, 2010)	To estimate the effects of IVIg as adjunctive therapy in patients with bacterial sepsis or septic shock	RCTs: 17 on adults 8 on neonates	January 2012	Adults: 17 RCTs (n=1958); 10 RCTs on standard IVIg, 7 on IgM-enriched New-borns: 8 RCTs (n = 3667) 5 on standard IVIg) (3831 participants) including a large polyclonal IVIg trial on infants	15 on polyclonal IVIGs vs Placebo or no treatment 10 on IgM enriched Ig vs placebo or no treatment	1ary: All-cause mortality 2ary: Bacteriological failure rate; Development of organ failure; Length of hospital stay among survivors; Mortality from septic shock;	Adults: sign. reductions in mortality Standard polyclonal IVIg (RR 0.81; 95% CI 0.70 to 0.93; 10 trials, n = 1430) Enriched polyclonal IVIG (RR 0.66; 95% CI 0.51 to 0.85; 7 trials, n =528). Non-sign reduction when only trials with low RoB were analysed:	Both standard and (IgM)-enriched polyclonal Ig decreased the number of deaths in adults but not in infants. However, no reductions in adult deaths were seen with polyclonal IVIg when focusing on	High (10/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
					with sepsis that was published in 2011 3 IgM-enriched n = 164))		AEs.	(RR 0.94; 95% CI 0.74 to 1.18; 5 trials 3 on standard and 2 on IgM enriched, n=945) Neonates: no sig. reduction of mortality Standard polyclonal IVIg (RR 1.00; 95%CI 0.92 to 1.08; n = 3667) IgM-enriched polyclonal IVIg (RR 0.57; 95% CI 0.31 to 1.04; n = 164) Safety: AEs reported in 7 RCTs on adults and 4 RCTs on neonates. Described per study, no analysis. In neonates: 1 trial reported on 2 infusion-related AEs, 2 other trials did not find any AE and 1 trial did not find a difference between IVIg and placebo In adults: in 4 trials allergic reactions were found, of which in one trial they recorded Shock. In the other 3 trials no AEs linked to IVIg were found.	high-quality trials only.	
Parks et al Polyspecific Intravenous Immunoglobulin in Clindamycin-treated Patients With Streptococcal	2018	evaluating the use of adjunctive IVIg in STSS + effect of IVIg on mortality rates in the subgroup of patients with STSS whose antibiotic	RCTs and nonrandomised: 1 RCT (Darenberg 2003) 4 nonrandomised (Kaul 1999, Carapetis 2014,	December 2017	Subgroup of adults and children with STSS who received clindamycin (n=165). Not all included studies, only	IVIg vs placebo: 1 RCT (Darenberg 2003 (n=18) IVIg vs standard care 4 Nonrandomized studies (n=147) of	1ary: risk ratio (RR) for death at 30 days	Efficacy: Pooled analysis of 5 studies: IVIg was associated with a reduction in mortality rate from 33.7% to 15.7% (RR, 0.46; 95% CI, 0.26–0.83; P = 0.01) n=165,	In association with IVIg, mortality fell from 33.7% to 15.7% with remarkable consistency across the single randomized and four	Moderate (7/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
Toxic Shock Syndrome: A Systematic Review and Meta-analysis		therapy included clindamycin	Linner 2014, Adalat 2014)		included STSS patients with clindamycin treatment (overall n=216)	which 1 used historical controls (Kaul et al 1999) and the other 3 used concurrent patients who did not receive IVIg as controls		Safety: No info on AEs	nonrandomized studies	
KAWASAKI SYNDROME										
Oates-Whitehead et al. IVIg for the treatment of KD in children. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD004000	2003	To evaluate the effectiveness of IVIg in treating, and preventing cardiac consequences, of KD in children	RCTs only: 16 overall. All published before 2000	April 2003	Children between the ages of 0-18 diagnosed with Kawasaki disease.	IVIg vs placebo or no treatment Different doses of IVIg IVIg + salicylate vs salicylate alone Single dose IVIg vs multiple dose IVIg Different types of IVIg	1ary: Death CAAs Myocardial function abnormalities 2ary: Duration of fever AEs Length of hospital stay.	Efficacy: Death: Only 1 death reported in the IVIg 400,g/kg group during subacute phase due to an aneurysm (1 study; n=549) CAAs IVIg vs placebo (MA all): strong evidence of a benefit with IVIg compared to placebo. (7 RCTs/10 comparisons; n=970) Duration of fever (MA): Evidence of a sign. reduction with IVIg (2 RCTs/3 comparisons; n=262) Duration of hospitalisation: Evidence of a sign. reduction with IVIg (2 RCTs; n=253) Safety: No sign. increase in AEs observed in any of the 9 RCTs (n=1787) which captured this	This SR found good evidence that IVIg treatment within the first 10 days of symptoms reduces CAAs in children with KD	High (9/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
								outcome. No severe AEs were reported.		
Chen, Ma et al. Treatment of KD disease by different doses of Ig: a MA of efficacy and safety; Transl Pediatr;1(2):99-107	2012	To assess the efficacy and safety of different doses of Ig in the treatment of KD.	28 RCTs (n=2596)	NA	Children with KD; who had received Ig therapy and undergone echocardiography within 2 weeks after treatment.	1gr/kg over 1-2 days vs 2 gr/kg on a single infusion (9 RCTs). 1gr/kg over 1-2 days vs 400 mg/kg for 4-5 days (11 RCTs). 2gr/kg over 1-2 days vs 400 mg/kg for 4-5 days (9 RCTs).	1ary: Incidence of CALs 2ary: time for fever disappearance AEs.	Efficacy: Sign. lower incidence of CALs during the acute phase (RR 0,76; 95%CI: 0,54, 1,06; p<0,05), and 6 months after treatment (RR 0,49; 95%CI: 0,18, 1,30; p<0,009) with a single infusion of the higher dose. No sign. differences found on CALs between the 1gr/kg for 1-2 days and the 400mg/kg for 4-5 days regimens. Mean time to resolve fever sign. lower for the two high-dose regimes, compared to the 400mg/kg over 4-5 days. Safety: No sign difference in the rate or severity of AEs	Similar efficacy for KD between the Ig groups at doses of 1 g/(kg/d) for 1-2 days and 2 g/(kg/d) for single use. Fever disappearance time in the two groups is shorter than that in the treatment group at 400 mg/(kg/d) for 4-5 days.	Moderate (6/11)
Chan, H.; Chi, H.; You, H.; et al. Indirect-comparison meta-analysis of treatment options for patients with refractory KW. BMC Pediatr - Volume 19,	2019	To compare different standard treatment options (i.e. infliximab or IVMP) vs 2nd IVIg infusion, in patients with	12 studies (9 RCTs)	August 2018	Refractory KD patients according to the Japanese MoH or the American Heart Association	-2nd infusion of IVIg vs infliximab -2nd infusion of IVIg versus IVMP (no separation between RCTs and observational for this	1ary: reduction in (CALs) and treatment resistance. 2ary antipyretic effects and AEs	Efficacy: 2nd infusion IVIg vs inflix: No sign. differences in reducing the incidence of CALs (RR 0,85; 95%CI: 0,43, 1,69; p=0,46) (3 RCTs, n=98). No sig, differences in treatment resistance	Inflix, IVMP, and 2nd IVIg infusion showed no sign. differences in the cardio protective effect or rate of treatment resistance. Inflix was more effective than 2nd IVIg infusion regarding	High (9/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
Issue 1, pp. 158		refractory KD				comparison. Therefore this comparison was excluded from our analysis)		(RR 0,43; 95%CI: 0,21, 0,89; p=0,667) Safety: Similar rate of AEs (RR 1,06; 95%CI: 0,69, 1,63; p=0,910).	antipyretic effects.	
Yang et al 2015. A MA of re-treatment for IV Ig-resistant KW disease. Cardiol Young - Volume 25, Issue 6, pp. 1182-90	2015	To assess the efficacy and safety of glucocorticosteroids vs a 2nd IVIg infusion in IVIg-resistant KD patients.	4 studies (2 RCTs)	Feb 2014	IVIg-resistant KD patients.	Glucocorticosteroids vs a second IVIg infusion	Coronary artery damage Time to recover body temperature	Efficacy: Body temperature in KD resistant patients more effectively restored with glucocorticosteroids vs a 2nd IVIg infusion (RR 0,39; 95%CI: 0,20, 0,74; p=0,004). No sig. differences found in incidence of CALs (RR 1,24; 95%CI: 0,28, 5,59; p=0,78).	Glucocorticosteroids more effective in controlling body temperature; but no sign, differences found in prevention of CALs	Moderate (6/11)
MULTIFOCAL MOTOR NEUROPATHY										
van Schaik IN et al. IVIg for MMN. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD004429.	2005	To evaluate the effectiveness of any dose of IVIg vs placebo in patients with a probable or definite MMN	RCTs only: 4 overall (n=34). The most recent published in 2001	March 2005 (updated in March 2007)	Patients with definite or probable MMN according to the published criteria. Patients with upper motor neuron features or bulbar signs, as well as other related conditions (e.g. other neuropathies), were excluded	IVIg vs placebo. IVIg given at different doses: A single treatment of 2 g/kg over 5 days (2 RCTs) 1 or 2 treatments de 2 g/kg over 5 days (1 RCT) 2,5g/kg/month for 3-6 months (1 RCT)	1ary: Proportion of patients experiencing an improvement in disability between weeks 2 and 4 after treatment, compared to baseline. 2ary: Muscle strength Frequency of AEs	Efficacy: Proportion of patients experiencing improvement in disability: RR = 3,00 (95%CI: 0,89; 10,12; p= 0,08); 7/18 with IVIg vs 2/18 with placebo (3 RCTs; n=18) Proportion of patients experiencing an improvement in muscle strength : RR = 11,00 (95%CI:2,86; 42,25; p=0,0005); 21/27 with IVIg vs 1/27	Limited evidence from RCTs showing a non-sign. trend towards improvement in disability with IVIg compared with placebo. Sign. improvement in muscle strength. No severe AEs observed	High (10/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
								with placebo (3 RCTs; n=27) No sign. results in the remaining 2ary outcomes. Safety: Proportion of patients experiencing treatment related AEs: RR = 10,33 (95%CI: 2,15; 49,77; p= 0,004); 15/21 with IVIg vs 1/21 with placebo (3 RCTs; n=21). All AEs were minor.		
GUILLAIN BARRE SYNDROME										
Hughes RAC et al. IVIg for GBS. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD002063.	2014	1. To examine the efficacy of IVIg in GBS. 2. To determine the most efficacious dose of IVIg for GBS. 3. To compare the efficacy of IVIg and plasma exchange (PE). 4. To compare the efficacy of IVIg+ PE vs PE alone for GBS	RCTs only: 12 overall (n=34). The most recent published in 2001	Dec. 2013	Children and adults with GBS of all degrees of severity.	IVIg vs PE (7 RCTs; n= 623 patients with severe GBS) IVIg+PE vs PE alone (1 RCT, n= 249). IVIg vs supportive care (3 RCTs, n= 75 children). 2-day vs 5-day IVIg treatment plan (1 RCT, n= 51 children). IVIg vs immunoabsorption (1 RCT, n= 48).	1ary: Improvement in disability grade at week 4 after randomisation. 2ary: Recovery of unaided walking; Time from randomisation until recovery of walking with aid; Time from randomisation until discontinuation of ventilation (for those ventilated); Mortality; Death or disability (inability to walk without aid after 12	IVIg vs PE: Efficacy 1ary efficacy: change in disability at 4 weeks: MD:-0,02 (95%CI:-0,25; 0,20; p=0,83). 5 RCTs, n=536 2ary efficacy outcomes: non sign. differences). 5 RCTs, n=536 Safety: AEs: RR: 0,84 (0,54; 1,30; p=0,43), but IVIg treatment more likely to be completed. 4 RCTs, n=388 IVIG vs supporting care: MD improvement: 1,42 (95%CI:2,57, -	Moderate quality evidence that, in severe disease, IVIg (within 2 weeks from onset) improves recovery as much as PE. AEs not sign. more frequent with either treatment. IVIg treatment sign. more likely to be completed than PE. Moderate quality evidence, showed that IVIg after PE does not offer sign. extra benefit. Low quality evidence, showed	High (9/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
						IVIg+ immunoabsorption vs immunoabsorption alone (1 RCT, n= 34)	months); Treatment-related fluctuation at 12 weeks AEs	0,27) 1 RCT, n=21 (mild cases) <u>IVIG+PE vs PE alone</u>: MD improvement: -0,2 (95%CI: -0,54;0,14). 1 RCT, n=249 <u>IVIG+immunoabsorption vs immunoabsorption alone:</u> MD improvement: -1,10 (95%CI: -1,88; -0,32). 1 RCT, n=34 <u>IVIG doses given over 2 hrs vs 5 hrs:</u> MD improvement: 0,27 (95%CI: -0,40; -0,94; p=0,43). 1 RCT, n=49.	that IVIg may improve recovery vs supportive care alone	
IDIOPATHIC THROMBOCYTOPENIA PURPURA										
Lioger et al. 2018. Efficacy and Safety of Anti-D Ig vs IVIg for IT in Children: Systematic Review and Meta-analysis of RCTs	2019	To evaluate the efficacy and safety of IVIg and anti-D Ig (anti-D) in paediatric ITP	RCTs only: 11 overall (n=558)	Sept 2016	Children under age 18 years with ITP	Different doses of IVIg vs (in 9/11RCTs) a standard single dose of 50 mcg /kg of anti-D Ig.	1ary: Proportion of children achieving platelet count responses and Bleeding response 2ary: Infusion reactions Hemolysis	<u>Efficacy:</u> Overall platelet response for acute: Sign. lower with anti-D versus IVIg. RR = 0,85 (95% CI: 0,77; 0,94; p= 0,0010); 7 RCTs; n=350) Overall platelet response for chronic: Lower with anti-D, but non sign. RR = 0,89 (95% CI: 0,65; 1,21; p=0,45); 1 RCT, n=34. <u>Safety:</u> Risk of general AEs: Less frequent with anti-D IV; Peto Odds ratio: 0,39 (95%CI:	Limited evidence from RCTs of poor quality shows that, IVIg led to a better response in terms of platelet count and may be preferred to anti-D Ig as a 1st-line treatment of ITP in children with acute haemorrhagic symptoms.	High (9/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
								0,25; 0,62; p< 0,0001); 24,6%with Anti-D Ig; 31,4% with IVIg. 7 RCTs; n=477) Serious AEs were reported for IVIg (i.e. 1 aseptic meningitis with generalized seizures 24 hours after infusion) and more risk for haemolysis with anti-D		
Qin et al. 2010. The efficacy of different dose intravenous Ig in treating acute idiopathic thrombocytopenic purpura: a meta-analysis of 13 randomized controlled trials	2010	To compare the effects of different dose IVIg for treatment of acute ITP	RCTs only: 13 overall (n=646)	Dec 2009	All patients with acute ITP	Low doses of IVIg (mostly 2g/kg/day over 5 days) vs high IVIg doses (mostly 0,4 or 0,5g/kg/day over 4-5 days)	Efficacy measures: Effective rate, Time of cessation of bleeding, Time of platelet count beginning to rise, Platelet count by 1st and 2nd weeks after treatment Time of platelet count to reach peak, Peak value of platelet count after treatment Rate of developing into chronic ITP AEs	<u>Efficacy:</u> No sign. differences found for any of the efficacy measures <u>Safety:</u> Low-IVIg doses associated with a sign reduced risk of AEs. OR: 0.39 (95% CI: 0.18–0.83); p=0.01.	Low-IVIg doses are as effective as high-IVIg doses and have fewer AEs, while not increasing the rate of chronic ITP development.	Moderate (6/11)

2.3 Extraction table of moderate to good quality SR for indications commonly recognised in other countries

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
Myasthenia gravis										
Gajdos et al Intravenous immunoglobulin for myasthenia gravis Cochrane	2012 (upd. of 2003 and 2007)	Efficacy of IVIg exacerbations or chronic MG	7 RCTs: Five trials evaluated IVIg for treatment of MG worsening or exacerbation (Gajdos 1997; Schuchardt 2002; (Gajdos 2005), (Zinman 2007) (Barth 2011) 2 trials for chronic (stable) MG: (Ronanger 2001; Wolfe 2002) The authors excluded one study (Liu 2009) because few data were available	Sept 2011	Exacerbations or worsening of generalised MG. Chronic generalised MG (severe but stable)	IVIG vs placebo (Wolfe 2002; Zinman 2007) IVIg vs Plasma exchange (Barth 2011; Gajdos 1997; Ronager 2001); IVIg: 1g/kg vs 2g/kg (Gajdos 2005); IVIg vs. Methylprednisolone (Schuchardt 2002)	Exacerbation 1ary : change in the score on a muscle strength scale day 7 and 15 (most often QMG score) Chronic: 1ary: improvement by at least 1 grade in a functional scale after 6 months. AEs	Efficacy: Compared to placebo: 1 study showed a mean difference in favour of IVIg (QMG Score) after 14 days of: -1.60 (95% CI - 3.23 to 0.03) : borderline significant Compared to PE: no difference in change in QMGS after 14 days Compared to Methylprednisolone: no difference in change in QMGS at 14 days (MD -0.42; 95% CI -1.20 to 0.36). Chronic: 2 RCTs did not report on 1ary outcome. Safety: AEs: 190 AEs were observed among 304 participants treated with IVIg in the six RCTs: fever or chills (13.8%), headaches (17.4%), nausea (6.9%), allergic reaction (1.3%), and others 11.5%.	Exacerbations: Some evidence of higher efficacy of IVIg vs placebo. No difference in efficacy vs PE No difference vs methylprednisolone (underpowered) Chronic: insufficient evidence from RCTs to determine whether IVIg is efficacious.	High (8/11)
Keogh Treatment for Lambert-Eaton myasthenic syndrome Cochrane	2011	Efficacy of all forms of treatment for Lambert-Eaton myasthenic syndrome (LEMS).	1 RCT on IVIg Double-blind cross-over (8 weeks, n=10 – low RoB) (Bain 1996)	October 2010	All adults and children diagnosed with LEMS	2g/kg IVIg vs placebo (0.3% albumin)	1ary: Myometric limb strength, respiratory and bulbar strength measures, and calcium channel antibody titres	Efficacy: Based on 1 RCT (n=10): Significant improvement in myometric limb strength after IVIg compared with placebo till 8 weeks	The possible beneficial effect of IVIg should be validated in further trials	Moderate (7/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
Ortiz-Salaz Human Immunoglobulin versus Plasmapheresis in Guillain–Barre Syndrome and Myasthenia Gravis: A Meta-analysis	2016	Efficacy and side effects over a short time period of PE vs IVIG in the management of autoimmune neurologic disorders	RCTs and observational studies MG: 4 RCTs: Barth D et al 2011; Gajdos P 1997; Rønager J 2001 ; Liu J et al 2010	Feb 2015	All ages, MG.	IVIg vs PE	1ary: Changes in the MG muscle score, or quantitative MG gravis score between day 1 and 15. AEs (analysis presented on the frequency of side effects, not on severity)	Efficacy: OR: 0.56; 95% CI: 0.22–1.40, P = 0.218 (3 RCTs, n= 201) Safety Frequency of AEs: OR: 0.65; 95%CI: 0.16–2.57 (4 RCTs, n=213)	There is no evidence on the clinical superiority (efficacy or safety) of IVIg vs PE Caution should be exercised in the interpretation of these results given the limitations in the quality of the evidence and the heterogeneity of the studies	Moderate (7/11)
CADTH (neurological conditions)	2018	What is the clinical effectiveness of the off-label use of intravenous immunoglobulin for the treatment of neurological or neuromuscular conditions	MG: 4 SRs Gadian et al 2017, INESSS 2017 and 2 with MA, Gajos 2012, Ortiz-Salaz 2016) and 2 RCTs (Barnett 2013 n=62, Alipour Faz 2017, n=24)	Oct 2017	any age with MG	IVIg versus Placebo (1RCT) IVIg versus PE (5 RCTs) IVIg versus methylprednisolon (1RCT)	Functional Outcomes (change in QMGS) QoL duration of hospital stay length of ICU stay after surgery AEs	Efficacy: IVIg was no better than placebo, no better than PE and methylprednisolone. Though on different time points (at 42-day follow-up, 21 day follow-up) some difference in favour of IVIg was seen. QoL did not sign. differ IVIg compared with PE 2 weeks post-treatment (1 RCT, n=62) Duration of Hospital stay and length of ICU after surgery did not sign. differ between IVIg and PE (1 RCT, n= 24) Safety: AEs: IVIg similar to PE, MA OR=0.654 (0.166 to 2.572), P = 0.543 (4 RCTs).	IVIg was reported to be no better than placebo or PE for the treatment of MG in 3 SRs, (Gajos 2012, Ortiz-salaz 2016, INESSS 2017) while one SR concluded that IVIg may improve response in patients with MG (Gadian 2017)	High (9/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
SOLID ORGAN TRANSPLANT										
Wan et al. The treatment of AMR in kidney transplantatio: an updated SR and meta-analysis	2018	Investigate all therapeutic strategies for AMR in kidney transplants	Controlled studies No RCTs on IVIg+PE vs placebo/no treatment. 2 retrospective studies on IVIg (Lee et al. 2016, Einecke 2016)	Feb. 2017	All ages with acute or chronic AMR in kidney transplant recipients	IVIg+PE vs no treatmen: Lee et al. 2016, n=75) IVIg+PE+Rituximab vs. no treatment: Einecke (n=71) Other comparisons made, but unable to report on the effect of IVIg alone or in combination.	1ary: graft survival (time-to-event data) 2ary: graft function change in serum creatinine, eGFR, creatinine clearance. AEs	Efficacy: Graft survival: no pooling possible HR of 0.26 (p<0.001, but reported no CIs) (no RCT, Lee 2016, n=75) No difference between PE+IVIg+rituximab and no treatment (RR=0.86 95%CI 0.6-1.22) (no RCT-Einecke 2016, n=71) Graft function: mean difference between groups of change in eGRF of 14 (95%CI: 12-16).(1 non RCT Lee et al 2016, n=75) Safety: AEs: only Lee et al. reported on AEs mortality and found 1 in the IVIg group vs 2 in the control arm.	IVIg and PE have become standard care for the treatment of acute AMR despite limited low-quality evidence (ethically difficult to assigning patients to no treatment, which is associated with high risk of graft loss)	High (9/11)
CADTH Rapid response review: off-label use of IVIG for Solid organ transplant rejection	2018	Clinical effectiveness of IVIG and SCIG for solid organ transplant rejection	HTAs, SRs, MAs, RCTs and non-randomised trials 1 RCT on IVIg+Rituximab (Moreso 2018) 1 non-randomised retrospective comparative study (Furmanzyck-Zawinska 2016)	Oct-2017	All ages with acute rejection and antibody-mediated rejection after solid organ transplantation Only info on kidney transplants	1 RCT on IVIg+rituximab vs placebo (n= 25) 1 non-randomised study on IVIg vs Methylprednisolione	1ary: graft function: change in eGFR and change in serum creatinine. 2ary: proteinuria, renal lesions, donor specific antibodies, Change in mean serum creatinine AEs	Graft function: Moreso et al. reported a non-sign. mean difference between groups (p=0.475), Change in mean serum creatinine: NS, change of 0.2 (± 2.1) in the IVIg + RTX group and 0.6 (± 1.1) in the placebo group (1RCT) Other 2ary outcomes: RCT showed non sig. effect in RCT Safety:	Limited to kidney transplants RCT showed no effect of IVIg + rituximab. The clinical effectiveness of IVIg for kidney transplants remains unclear.	High (8/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
								AEs did not different –no analysis (26 in the IVIg + RTX group and 28 in placebo) (1 RCT) AEs requiring hospitalisation did not differ- no analysis (5 in the IVIg + RTX group, and 4 in the placebo) (1 RCT)		
FETOMATERNAL TROMBOCYTOPENIA										
Rayment Antenatal interventions for fetomaternal alloimmune thrombocytopenia COCHRANE	2011	determine the optimal antenatal treatment to prevent fetal and neonatal haemorrhage and death	RCTs 4 RCTs in 3 publications (Berkowitz 2006, Bussel 1996, Berkowitz 2007)	Feb 2011	Pregnant women with a previous child affected by FNAIT	Relevant comparison: corticosteroid (n=20) vs IVIg (n=19) in pregnancies that had no prior sibling born with ICH (Berkowitz 2006) SR also covered other non-relevant comparisons: the addition of corticosteroids to IVIg (Bussel 1996a; Berkowitz 2006; Berkowitz 2007).	1ary: Fetal/neonatal death. Intracranial haemorrhage Platelet count at birth 2ary: Other bleeding. Miscarriage. Premature birth.	Corticosteroid versus IVIg (1RCT, n=39): no significant difference in outcomes Fetal/neonatal death (RR 0.95; 95% CI 0.06 to 14.13), Platelet count at birth (MD) -36.30 x 10*9/l , 95%CI -85.77 to 13.17). There were two ICHs in this group, but the trial did not report the treatment arm in which the two ICHs occurred. 2ary: No info	The optimal management of fetomaternal alloimmune thrombocytopenia remains unclear.	High (9/11)
Winkelhorst Antenatal management in fetal and neonatal alloimmune	2017	assess antenatal treatment strategies for FNAIT	RCTs as well as non-randomized studies 4 RCTs (Paridaans, 2015,	Dec 2015	Pregnant women with pregnancies at risk for FNAIT or fetuses/neonate	Corticosteroid (n=20) vs IVIg (n=19): Berkowitz 2006;	1ary: Intracranial Hemorrhage (ICH) Mortality	Pooling of results was not possible due to considerable heterogeneity. Descriptive analysis per study	Suggests that first line antenatal management in FNAIT is weekly	Moderate (5/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
thrombocytopenia: a systematic review			Berkowitz, 2007, Berkowitz, 2006, Bussel, 1996); 5 prospective and 17 retrospective studies		s diagnosed with FNAIT	IVIg plus a corticosteroid vs IVIg alone: Bussel 1996a (n=54) Berkowitz 2006 Berkowitz 2007 (n=73), Paridiaans 2015 (n=23).	Neonatal PLT Count Treatment-related complications		IVIg administration	
IMMUNOBULLOUS DISEASE- PEMPHIGUS VULGARIS, FOLICULAE										
Atzmony Treatment of Pemphigus Vulgaris and Pemphigus Foliaceus: A Systematic Review and Meta-Analysis	2015	Evaluate the efficacy, safety, steroid-sparing effect of available treatment modalities.	RCTs of any intervention 1 RCT on IVIg (Amagai 2009)	July 2014	PV or PF according to clinical features, histopathology, and immunofluorescence	IVIg to placebo (1 RCT, n= 61)	1ary: Proportion of patients achieving complete response (CR), Mean total cumulative glucocorticoid dose, Death. 2ary: Proportion of patients achieving disease control, time to disease control, time to achieve remission, proportion of patients relapse, and rate of withdrawal due to AEs.	Efficacy: No pooling of only IVIg. No possibility to report on predefined primary outcomes. Proportion of patients who did not need to escape from protocol: sign. higher in the composite IVIg group (400+200 mg) (RR 1.84, 95 % CI 1.11–3.05) and in the 400 mg IVIg group (RR 2.01, 95 % CI 1.21–3.33) vs the placebo group. Not sign. For the 200mg IVIg group compared with placebo (RR 1.67, 95 % CI 0.96–2.88). Safety: AEs similar in all treatment groups. 1 patient given 200mg IVIg died of hepatic failure as a result of hepC aggravation. Rates of withdrawal due to AEs could not be calculated	High-dose IVIg is effective in initiating and maintaining disease control	Moderate (4/11)

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
CADTH rapid Review: Off label use of IVIg for autoimmune or inflammatory conditions: a review of clinical effectiveness	2018	Clinical benefit and harms of IVIg or SCIg	HTAs, SRs, MAs, RCTs, non randomized studies 1 RCT (Amagai 2017, steroid resistant patients, n=56)	July 2017	Any age Immunobullous pemphigoid	IVIg 400mg/kg/day for 5 consecutive days) vs. placebo (1 RCT, n= 56)	1ary: DAS on day 15; 2ary: time to treatment reduction, oral steroid dosage, antibody titer, AEs	Efficacy: No pooling. 1ary: IVIg had a higher non sign. mean duration in 15-day disease activity score compared to placebo (p=0.089) 2ary: change in disease activity over time: only from day 1 to 15, IVIg had a sign. higher decrease than placebo. Not maintained through day 57. Time to treatment reduction: decreased 84.8% in IVIg vs. 53% in placebo (between group difference p=0.010) Oral steroid dose: placebo patients had sign. higher steroid dosage on day 15 compared to IVIg (p=0.042) Safety: No sign. diff between IVIg and placebo in AEs (p=0.143)	The authors concluded that IVIg may be therapeutically beneficial for steroid-resistant patients with pemphigus vulgaris, pemphigus foliaceus or bullous pemphigoid.	High (8/11)
DERMATOMYOSITIS and POLYMYOSITS										
Vermaak et al. The evidence for immunotherapy in dermatomyositis and polymyositis: a SR; Clin Rheumatol (2015) 34:2089–2095	2015	The effects of immunotherapy in adult patients with definite or probable dermatomyositis or polymyositis	2 RCTs (Dalakas et al. 1993 and Miyasaka et al. 2011)	Feb 2015	DM Refractory patients (Dalakas et al n=15) and Dermatomyositis (n=10) or polymyositis (n=16) resistant to treatment with corticosteroids (Miyasaka et al. n=26)	IVIg as add-on to corticosteroids vs. placebo (Dalakas, n=15) IVIg vs. placebo (Miyasaka et al, n=26)	1ary: Muscle strength score (after 6 months) 2ary: improvements in patient and physician global	Efficacy: No pooling. Descriptive analysis of the 2 RCTs -Sign. improvements in muscle strength from 76.6 ± 5,7 to 84.6 ± 4,6 in the IVIg group, vs no sign. difference in the placebo group (78,6 ± 6,3 to 78,6 ± 8,2) in three months (Dalakas et al 1993). -Non-sign. mean muscle score difference between IVIg and placebo after 8 weeks. (Miyasaka et al 2012, n= 26)	No clear conclusions could be drawn.	Moderate (7/11) Quality of included RCTs: high based on Jadad score

Study	Publication date	Objective	Included studies	Last search	Population	Intervention and comparison	Outcomes	Data-extraction/ results	Authors conclusion	Quality (AMSTAR)
							scores, physical function and muscle enzymes, AEs	<u>Safety:</u> Severe headaches (Dalakas et al 1993, n=2), but no discontinuation Miyasaka et al. reported AEs in 42.3 % of patients with 2 serious events in 1 patient (increased CK and muscle weakness)		
INESSS Efficacité, innocuité et modalités d'usage des immunoglobulines en neurologie : revue systematique	2017	To evaluate the efficacy and safety of Ig in children and adults with one of the 25 neurologic conditions analysed	2 RCTs (Dalakas et al.1993 and Miyasaka et al.2011)	Jan 2016	DM Refractory patients (Dalakas et al n=15) and Dermatomyositis (n=10) or polymyositis (n=16) resistant to treatment with corticosteroids (Miyasaka et al n=26)	IVIg as add-on to corticosteroids vs. placebo (Dalakas, n=15) IVIg vs. placebo (Miyasaka et al, n=26)	Muscle Strength score	<u>Efficacy:</u> No pooling. Descriptive analysis of the 2 RCTs MD in improvement in muscle strength between IVIg vs placebo after 3 months: 9.50 (95% CI 4.33 to 14.67) (Dalakas 1933) MD in improvement in muscle strength between IVIg and placebo after 8 weeks: 1,9 (95%CI - 4,8 to 8,5) non-sign. (Miyasaka 2012)	Discrepant findings Weak evidence	High (10/11) Quality of included studies (moderate RoB)

2.4 Extraction table of included RCTs in selected indications

Primary Immunodeficiency (PID)								
Author (year)	Country	Study design	Population, sample	Comparator	Statistical analysis	Outcome	Conclusion	Risk of bias
IVIg or SCIg vs placebo or no treatment: no RCTs found								
IVIg-SCIg								
Chapel 2000	UK and Sweden	Multicentre, crossover,	N=30 (IVIg naive patients or patient already	SCIg vs IVIg Cross-over after 1 year of treatment	No sample size calculation seemed	1ary: N. and severity of infections 2ary: Length of infections, days lost	<u>Efficacy:</u> No significant difference in infections: IVIg had a mean of	Unclear

Primary Immunodeficiency (PID)								
Author (year)	Country	Study design	Population, sample	Comparator	Statistical analysis	Outcome	Conclusion	Risk of bias
		Open label RCT	treated with IVIg)	dose differed per centre: 400mg/kg every 2 or 4 weeks in the UK 300mg/kg every 2 weeks in Sweden	possible==> an arbitrary number of 40 patients was predetermined Only patients that entered both treatment arms were analysed (n=26) Also analysis per country	from school or work due to infections, AEs, and acceptability of treatment	4.12 and SCIg 3.82 (p=0.766 UK and p=0.219 Sweden) No significant difference in length of infections, days lost <u>Safety:</u> AEs: SCIg had more local reactions (pain at redness at infusion site), but when focussing on systemic AEs, there was no difference (5% for IVIg and 3.3 for SCIg)	
Desai 2009	US	Pilot study, single site non- blinded, crossover	N=12 already on IgG therapy	SCIg vs IVIg at the same dose (no details) Crossover after 6 months (no washout)	No information on statistics	1ary: N. of acute serious bacterial infections (SBI) 2ary: Serum IgG concentrations, AEs, and patients' preferences	<u>Efficacy:</u> No SBI More infections during SCIg 26 (4.72/patient/yr) vs 18 infection episodes (3.27/patient/yr) (P = 0.038 by paired t test; P = 0.025 by Wilcoxon rank-sum test). The mean trough level was 1079 mg/dL (SD, 221) for IVIg, compared to 1160 mg/dL (SD, 164) for SCIg (P .004) 10 of the 11 patients indicated they would prefer subcutaneous therapy <u>Safety:</u> 2 serious AEs occurred, but none were judged ''related'' or ''possibly related'' to the study drug or treatment regimen.	Unclear
IVIg - SCIg dose response								

Primary Immunodeficiency (PID)								
Author (year)	Country	Study design	Population, sample	Comparator	Statistical analysis	Outcome	Conclusion	Risk of bias
Roifman 1987 (IVIg)	Canada	Crossover RCT	N=12 antibody deficiency and chronic lung disease	600mg/kg vs 200mg/kg crossover after 6 months (no washout)	No information on statistics	1ary: Incidence of infections 2ary: Serum IgG concentration, lung function, AEs	Efficacy: Similar incidence of infections between the two doses. The incidence of infection was lower when serum IgG was above 500mg/dl spirometric results were sign. higher in high-dose compared to low-dose (p<0.001)	Unclear
Eijkhout 2001 (IVIg)	Netherlands	Multicenter, double-blind, crossover RCT	n=43 adults and children PID and an IgG trough level of ≤4 g/L	300-400mg/kg every 4 weeks compared to 600-800mg/kg every 4 weeks 9 months per treatment, 3 months washout	No information on statistics	1ary: number and duration of infection 2ary: fever, hospital admissions, antibiotics use, through levels of serum IgG, AEs	Efficacy: High dose significantly reduced the number (3.5 vs. 2.5 per patient; P = 0.004) and duration (median, 33 days vs. 21 days; P = 0.015) of infections. Trough levels of IgG increased significantly during high-dose therapy. Safety: The incidence and type of side effects did not differ significantly.	Unclear
Wasserman 2017 (bioequivalence IVIg)	US, UK, Hungary	Multicenter, open-label, randomized, two-period, crossover bioequivalence trial, 38-48 weeks (adults) 23-28 weeks (pediatrics)	33 adults were randomised - 32 adults completed study 15 children (≥10 kg) were not randomised 14 children completed study	2 formulations of IVIg: Gammaplex 10% versus 5%, both dosed at 300–800 mg/kg per infusion every 21 or 28 days	PK endpoints defined based on all subjects who received regular doses and appropriate PK profile was obtained ==>30 adults and 13 children other endpoints based on intention-to-treat analysis	1ary: no clinical parameters; bioequivalence- area under the concentration versus time curve from time=0 to time=28 days 2ary: AUC at 21 days, PK parameters, AEs (general and product related)	Bioequivalence of Gammaplex 10% and Gammaplex 5% at the 28-day dosing interval. The Gammaplex 10% formulation was safe and well tolerated in pediatric and adult PID subjects. administration time for 10% is less than for 5% Safety: General AE were reported more frequently in high dose(44/47patients) compared to low dose (23/33patients); while product related AE appeared in similar proportions (16/47 versus 12/33)	Low

Primary Immunodeficiency (PID)								
Author (year)	Country	Study design	Population, sample	Comparator	Statistical analysis	Outcome	Conclusion	Risk of bias
					based on all patients with ≥1 infusion			
IVIg or SCIg administrations								
Bienvenu 2018 (new administration SCIg)	France	Multicentre, crossover, RCT non-inferiority trial, 3 months per period (6 months in total)	30 adult patients already on SCIg home treatment Two patients prematurely withdrew for adverse events and were not included in analysis	SCIg either weekly via a pump compared to every other day via a syringe (rapid push, RP)	intention-to-treat with sensitivity analysis on a per protocol subset incidence of infection via Poisson regression model	1ary: patient's life quality index via PID-specific life quality index (LQI) questionnaire. 2ary: Trough IgG, incidence rate of infections, costs, safety	<u>Efficacy</u>: Treatment interference on daily life (PID-LQI factor I) was higher with RP than with pump; no statistical difference on other LQI factors Serum IgG levels did not differ The overall 3-month incidence rate of infections was 1.00 [0.68; 1.47] for the pump period and 0.76 [0.49; 1.20] for the RP period (NS) Rapid push saved 70% of administration cost when compared to pump <u>Safety:</u> Two AE requiring study discontinuation (1 after pump and 1 after RP) Local reactions were similar in both administrations (71,8% experienced at least 1 local reaction of all 355 pump infusions and 67,2% for all 989 rapid push)	High
secondary Immunodeficiency-MULTPLE MYELOMA								

Author (year)	Country	study design	population, sample	Comparator	statistical analysis	outcome	conclusion	risk of bias
Vacca 2018	Italy	Single center, non-blinded RCT Mean duration of treatment with SCIg 18 months	46 patients randomised: >18 years, myeloma patients and secondary hypogammaglobulinemia 24 SCIg patients completed 6 months after which 3 withdrew based on AE	SCIg (n=24) at a monthly dose of 400mg/kg to 800mg/kg to keep through level above 500mg/dl control= no treatment (n=22)	student t-test, Chi², Wilcoxon correlation and Mann-Whitney U test	1ary: annual rate of severe infections 2ary: a) days of hospitalization due to severe infections; b) days under treatment with antibiotics; c) improvement of HRQoL, d) AEs	Efficacy: Significantly lower incidence annual infection rate ($p < 0.001$) as well as severe infection rate ($p< 0.01$) (only figures, no numbers) Infections lasted a mean of 62 days (26–87) for SCIg treated compared with 135 days (88–194) for those without treatment ($p < 0.01$) Mean days/year of hospitalization due to severe infections were 8 in SCIg- vs. 121 in the control group ($p <0.001$) Mean days with antibiotic: 28 for SCIg vs. 217 for the control ($p <0.001$). On most domains (except pain) a significant higher QoL score with SCIg Safety: 3 severe AE in SCIg treatment that required discontinuation (2 local reactions and 1 extensive skin reaction)	High

secondary Immunodeficiency-POST HAEMOPOIETIC STEM CELL TRANSPLANTATION (HSCT)								
Author (year)	Country	study design	population, sample	Comparator	statistical analysis	outcome	conclusion	risk of bias
Azik 2016	Turkey	Single centre, Open label RCT follow-up till 100 days after transplant	59 pediatric (range 6-15y) after allogenic BMT without infection	IVIg (400mg/kg) (n=27) compared to IgM enriched (Pentaglobin®)(4ml/kg) (n=32) The first dose of IVIG or Pentaglobin® was given before conditioning regimen and after transplant	assessment of distribution: Kolmogorov-Smirnov/Shapiro-Wilks test chi² and MannWhitney U	infection , frequency of CMV reactivation, CMV disease, acute GVHD, VOD, and AE within the first 100 days after transplant	Efficacy: no significant difference between IVIg and IgM enriched IVIg used on all outcomes 100 days after transplant: Bacteraemia episodes (65.6% in Ig-M enriched vs. 55.6% IVIg, $p=0.429$, septicaemia episodes (1 patient in Ig-M enriched vs. 2 in IVIg, $p=0.588$), local infection (43.7% vs. 55.6%, $p=0.635$), CMV reactivation (21.9% vs. 29.6%, $p=0.496$), acute GVHD (28.1% vs. 14.8%, $p=0.219$). Safety: VOD (3 patients in Ig-M enriched	Unclear

				was given on day +1, +8, +15, and +22. And then, it was given if IgG level was below 400 mg/dL.			IVIg vs. 2 IVIg in, p=1.0) or other AE (4 in Ig-M enriched vs 1 in IVIg (p=0,231)	

secondary Immunodeficiency-SOLID ORGAN TRANSPLANTATION								
Author (year)	Country	study design	population, sample	Comparator	statistical analysis	outcome	conclusion	risk of bias
Lederer 2014	US	Single center, double blind crossover RCT 36 weeks	11 adult patients with lung transplantation and hypogammaglobulinemia (IgG<500mg/dl)	IVIg (10%caprylate/chromatography purified-Gamunex®) 400mg/kg every 4weeks versus placebo (0.1% albumin) 12 weeks per treatment followed by a 12 week washout	intention-to-treat principle 1 dropout due to inability to comply with schedule Odds Ratios (generalised estimating equations) difference in continuous variables (linear mixed effects modelling) prior sample size calculation : n=10	1ary: number of bacterial infections 2ary: viral-fungal and all nonbacterial infections, hospital admissions, antimicrobial use, serious bacterial infections, through IgG level, acute rejection, spirometry and mortality AEs	<u>Efficacy:</u> Bacterial infections: 3 in IVIg and 1 in placebo OR=3.5, 95%CI 0.4-27.6, p=0.24 Any infection: 7 during IVIg and 3 in placebo, OR=2.7, 95%CI 0.95-7.6, p=0.06 IgG through level: higher during IVIg (mean of 765 vs. 486, p<0.001) no sign. difference in other outcomes. no acute rejection reported <u>Safety:</u> Infusion related AEs: 1 participant experienced chills, flushing and nausea serious AEs: 3 during IVIg (pancreatitis, vitreous haemorrhage, Ecoli pneumonia), 1 during placebo (hospital admission for thymoglobulin infusion) bronchoscopy was frequent but no difference between groups, cough and neck stiffness more common during IVIg	Low

Chronic inflammatory demyelinating polyradiculoneuropathy (CIPD)								
Author (year)	Country	study design	population, sample	Comparator	statistical analysis	outcome	conclusion	risk of bias
Markvardsen LH, 2013	Denmark	multicenter, double-blind, RCT 12 weeks	29 Patients in maintenance therapy with IVIg for CIDP (18–80 years) ➔IVIg-responders	SCIg (Subcuvia®16%) (n = 14) vs placebo (subcutanous saline) (n=15)	average change expressed as a % of pre-treatment level difference between change in scores unpaired t-test	1ary: change in muscle strength at isokinetic strength performance (IKS) 2ary: a modified Medical Research Council (MRC) performance, grip strenght,electrophysiological recordings, plasma IgG, AEs Preference for either SubC or IV treatment	Efficacy: Change in IKS: deteriorated significantly by 14.4 +-0.3% (P = 0.02) in placebo, it improved in the SCIg group by 5.5+-9.5% (P = 0.049)- (P = 0.004). All parameters improved in favour of SCIg compared to placebo: MRC, grip strength, 40-MWT and 9-HPT improved. Safety: AEs reported: 6 patients in SCIg, 2 in placebo 20/29 patients preferred SCIg over IVIg	Low
Markvardsen 2017	Denmark	Multicentre, crossover, single-blind, RCT, 20 weeks	20 randomized: patients with definite or pure motor CIDP, naive to immune modulatory therapy (between 18 and 80 years), 14 completed protocol (including crossover)	SCIg (0.4 g/kg/week) for 5 weeks or IVIg (0.4 g/kg/day) for 5 days After 10 weeks switch (minimum 5 weeks washout)	intention-to-treat with missing valued being 'last observation carried forward'. Per protocol subanalysis 2 way ANOVA or Friedman test (not normally distributed) paired t tests or wilcoxon ranked (not normally distributed) 17 patients	1ary: combined isokinetic muscle strength (cIKS). 2ary:disability, clinical evaluation of muscle strength and the performance of various function test AE	Efficacy: cIKS increased by 7.4+-14.5% (P = 0.0003) during SCIg and by 6.9+-16.8% (P = 0.002) during IVIg, the effect being similar (P = 0.80). Improvement of cIKS peaked 2 weeks after IVIG and 5 weeks after SCIg. Disability improved during SCIg treatment only. Muscle strength determined by manual muscle testing improved after 5 and 10 weeks during SCIg but only after 5 weeks during IVIg. In treatment-naive patients with CIDP, short-lasting SCIg and IVIg therapy improve motor performance to a similar degree, but with earlier maximal improvement following IVIg than SCIg treatment. Safety: AEs: 3 cases of haemolytic anaemia in IVIg treated. SCIg: 3 local skin reactions, 2 nausea	Unclear

Chronic inflammatory demyelinating polyradiculoneuropathy (CIPD)								
Author (year)	Country	study design	population, sample	Comparator	statistical analysis	outcome	conclusion	risk of bias
					being analysed for SCIg treatment and 15 for IVIg treatment			
Van schaik 2018	North America, Europe, Israel, Australia, and Japan	Multicentre, randomised, double-blind, placebo-controlled trial **(PATH study)** 25 weeks	172 patients >18y with definite or probable CIDP who responded to IVIg treatment	3 arms: High dose of SCIg 0.4 g/kg per week (IgPRo20, 20%) (n=58), Low dose of SCIg: 0.2 g/kg per week (IgPRo20, 20%) (n=57), Placebo (2% human albumin solution) per week (n=57)	primary outcome assessed via intention-to-treat and per protocol secondary outcome assessed via intention-to-treat sample size calculation: 58 per group	1ary: proportion of patients with a CIDP relapse or who were withdrawn for any other reason during 24w =>deterioration (ie, increase) by at least 1 point in the total adjusted INCAT score compared with baseline 2ary: time to relapse, INCAT score, mean grip strength for both hands, MRC sum score, ... AEs, exploratory outcomes: QoL, treatment satisfaction, work productivity	<u>Efficacy:</u> Relapse or withdrawn: placebo 63·2% (95%CI 50·9–75·4) low dose 39·0% (95%CI 27·7–53·1) high dose 33·7% (95%CI 22·8–47·8) (p=0.0007) Absolute risk reductions were 25% (95% CI 6–41) for low-dose versus placebo (p=0·007), 30% (95%CI 12–46) for high-dose versus placebo (p=0·001), and 6% (95%CI –11 to 23) for high-dose versus low-dose (p=0·32) <u>Safety:</u> Causally related AEs occurred in 47 (27%) patients (10 [18%] in the placebo group, 17 [30%] in the low-dose group, and 20 [35%] in the high-dose group). similar proportion of AEs in higher infusion rate compared to lower. no haemolysis or thrombosis occurred	Low

Sepsis-Toxic shock-invasive streptococcal group A infection (streptococcal toxic shock syndrome)								
Author (year)	Country	study design	population, sample	Comparator	statistical analysis	outcome	conclusion	risk of bias
Darenberg 2003	Sweden, Norway, Finland, the Netherlands	Multicentre (17 hospitals), double blind RCT	21 adult patients with suspicion or confirmed STSS with or without necrotizing fasciitis	IVIg: 1g/kg on day 1, 0,5g/kg on day 2 and 3 in combination with antibiotics(n=10) vs placebo (albumin) in combination with antibiotics (n=11)	mortality with t- test other outcomes with wilcoxon mann whitney U test early terminated because of slow recruitment (not enough statistical power) sample size calculation: 120 included	1ary: mortality at day 28 2ary: time to resolution of shock time to no further progression of cellulitis or necrotising fasciitis mortality at day 180 AEs	Efficacy: Mortality rate at 28 days was 3.8 fold higher in placebo compared to IVIg (NS, small sample size) 2ary outcomes: No statistical difference Safety: 6 severe AEs (deaths) and 12 AEs related to disease but not to IVIg	Unclear

Multi focal Motor Neuropathy								
Author (year)	Country	study design	population, sample	Intervention/Comparator	statistical analysis	outcome	conclusion	risk of bias
Hahn 2013	USA (Canada and Danemark also controbuted with patients)	Cross over, double blind, multicentre RCT Median treatment duration was 84 days (13–91) for IVIg and 28 days (7–86) for placebo.	44 patients: patients with a confirmed or probable diagnosis of multifocal motor neuropathy, already treated with IVIg for at least 3 months	IVIg at 0.4 to 2.0 g / kg over 5 days or less, every 2 to 4 weeks, (for a median of 84 days) vs placebo	ITT analysis performed. No patients lost to follow-up. Analysis of the co-primary efficacy endpoints performed by 2 separate, sequential hypothesis tests of the null hypothesis of no treatment effect against the one sided alternative hypothesis of superiority of IVIg at the 2.5% level of stat sig. To analyse the potential carry-over effect, the sum of the two blinded periods in each sequence was compared using the Wilcoxon rank sum test.	Two predetermined co-primary efficacy outcomes maximal grip strength in the more affected hand (by DynEx digital dynamometer), and disability (by upper limb portion of Guy's Neurological Disability Score). 2ary outcomes: 1.premature switching accelerated switch, 2.decline of ≥30%	Efficacy: Mean maximal grip strength of the more affected hand declined 31.38% with placebo and increased 3.75% with IVIg therapy (p=0.005). In 35.7% of participants, disability scores for upper limbs worsened during placebo, while these improved in 11,9% of participants with IVIg (p=0.021) 69% of patients switched prematurely from placebo to open-label IVIg. Safety:	Unclear

					The first blinded period in each sequence was also compared using Fisher's exact test.	in grip strength in the more and less affected hands, 3.maximal grip strength in the less affected hand, 4.overall disability sum score, 5.time required for the 9-hole peg board test with the dominant and non-dominant hand, 6. patient global impression of change score of disability. AEs	One severe AE (pulmonary embolism) and 100 non-serious reactions with IVIg therapy.	
Harbo 2008	Denmark	Cross over, single blinded RCT. Patients therapy for a period equal to 3 IVIg treatment intervals of 18-56 days and then crossed over to the alternative treatment.	9 patients: IVIg responsive patients with a confirmed or probable diagnosis of MMN	Equivalent dose of Ig given SubC (160mg/ml)m vs IVIg (50mg/ml)	ITT analysis performed. Paired student t-tests and Wilcoxon matched pairs signed ranks test were used, the level of significance being 0.05.	1ary: Strength of the affected muscles 2ary: QoL	Efficacy: Non sign. differences (p=0,86) in mean changes in the strength of the affected muscles: 3.6%; 95% CI: -3.6% to 10.9% with SCIg vs 4.3%; 95% CI: -1.3% to 10.0% with IVIg.	Low

Guillain-Barré syndrome

Author (year)	Country	study design	population, sample	Intervention/Comparator	statistical analysis	outcome	conclusion	risk of bias
Chaudury 2014	India	Open RCT	37 Patients with GBS	2 g/kg of IVIg over 5 days, vs plasmapheresis - consisting of removal of 200 -250mL/kg of plasma over 5-8 cycles, on daily basis. Most patients had 5 cycles.	Mean, standard deviation and Chi-squire test performed.	1ary: muscle strength (Medical Research Council sum score); Mean costs Complications/AEs	Efficacy: Muscle strength no sign.differences between IVIg and plasma exchange, neither at hospitalisation, nor at discharge. Safety: Complications not sign. different in the two groups.	High

							Costs Mean costs of plasmapheresis (US$2 585) sign. lower than IVIg (US$4 385).	
Maheshwari 2017	India	Open RCT	40 patients with a GBS disability score of grade 4-5	2 g/kg of IVIg over 5 days vs 5 cycles of plasmapheresis (200-250 mL/kg)	Mean, standard deviation comparisons	1ary: Disability scores Mean costs Complications/AEs	Efficacy: No sign. differences observed in disability scores over the treatment period. Safety: Frequencies of complications comparable and stat. insignificant in both treatment arms Costs: Costs lower with plasma exchange (US$2 041), vs IVIg (US$4 298).	Low
Idiopathic thrombocytopenic purpura - ITP								
Author (year)	**Country**	**study design**	**population, sample**	**Intervention/Comparator**	**statistical analysis**	**outcome**	**conclusion**	**risk of bias**
Koochakzadeh 2018	Iran	Double blind RCT	98 children with ITP randomised. Analysis performed in 96	1g/kg/day of IVIg for 8-12 hrs in 2 days, vs 75 g/kg of anti-D Ig	The effect of the drugs on the main outcome assessed with repeated measure analysis of variance. Paired t test and chi-square test used to evaluate the minimum time required for the for effect and the potency of the drugs to increase the platelet count N. of AEs evaluated with Fisher's test	1ary: platelet count and hemoglobin levels measured on days 1, 3, 7, 14, and 21. Complications/AEs	Efficacy: Platelet count increased in both groups (P < 0.001). No sign. differences seen between treatments (P > 0.05). Heamoglobin levels decreased sig. after treatment in both groups (P < 0.001), with a non-sign. difference between groups. Safety: No sign. differences between the two groups in terms of treatment-related AEs, included fever and chills (4.1% with anti-D group vs 10.4% with IVIG), severe haemolysis (4.5% with anti D group vs 0% with IVIG) and headache	Low

							(6.25% with anti-D group vs 4.1% with IVIg group)	
Heitink 2018	The Netherlands	Multicentre open RCT	200 children aged 3 months to 16 years newly diagnosed with ITP. Platelet count ≤20x109/L and mild to moderate bleeding randomised. Analysed n=200	1 injection of IVIg 0,8g/kg vs observation	Chi-square test to compare categorical variables. If expected cell count below 5, Fisher test used; Mann-Whitney U test for non parametric continuous variables. RR and 95%CI calculated for 1ary and 2ary outcomes. ITT analysis performed	1ary: Development of chronic ITP (platelet count <150x109/L after 6 months, and <100x109/L at 12 months) 2ary: Recovery rates, Bleeding scores, AEs and HRQoL	<u>Efficacy:</u> 18,6% IVIg patients developed chronic ITC (platelet count <150x109/L after 6 months), vs 28,9% in observation (RR: 0,64; 95%CI: 0,38-1,08) 10% of IVIg patients vs 12% in observation developed chronic ITP (platelet count <100x109/L at 12 months) (RR: 0,83; 95%CI: 0,38-1,84). Complete response sig higher for IVIg at 3 months. <u>Safety:</u> More grade 4-5 bleeding observed with observation (9% - 10 cases) vs IVIg (1% - 1 case) Treatment related AEs: 5 with IVIg vs none with observation Other AEs: 4 with IVIg vs 6 with observation.	Low
Elalfy 2017	Egypt	Open label RCT	72 patients aged 1- 18 years with newly diagnosed (<1 month) IT and platelet counts 5 - 20 x 109/L with no serious bleeding. 72 patients analysed	1g/kg IVIg from mini-pools of 20 plasma donations over 6-8 hours, vs standard IVIg (1g/kg at a single dose) and vs observation	Quantitative data expressed as mean (6 standard deviation) values. Frequency and percentages used for categorical variables. The Kolmogorov-Smirnov test used to examine the distribution of data. T test used to compare continuous parametric variables; Mann Whitney U test used for continuous nonparametric variables, and the chi-square test or Fisher exact test, used for categorical variables	Complete response, Time to response AEs	<u>Efficacy</u> Mini-pool IVIg has similar efficacy compared to standard IVIg and is sign. more effective than observation. <u>Safety:</u> Mini pool IVIg is well tolerated No unexpected AEs 8 AEs in each Ig group, vs 6 with observation More severe bleeding in the observation group	Unclear

Myasthenia Gravis								
Author (year)	Country	study design	population, sample	Intervention/Comparator	statistical analysis	outcome	conclusion	risk of bias
Zinman 2007	Canada	Single center, double blind RCT	51 patients; 18+ with confirmed diagnosis of myasthenia gravis (MG) and worsening weakness as judged by patient and clinician Patient with respiratory distress or possible aspiration were excluded no dropouts during study	IVIg: 2g/kg (n=24) infusion over 2 days Placebo: 5% dextrose in water (n=27) + diphenhydramine + paracetamol before infusion no change in immunomodualting therapy allowed (incl. corticosteroids)	Primary outcome was assessed with an analysis of covariance ANCOVA. P<0.05 Sample size needed of 22 per arm to detect change of 3.5 units on QMGS score (clinically significant) Subanalysis of patients with moderate to severe MG (>10.5 points in QMGS score)	1ary: Change in QMGS score from baseline to day 14 2ary: Change in QMGS score from day 1 to 28, changes in other elektrodiagnostic tests, clinical status scale, change in autoantibody levels, AEs	Efficacy: All patients: at day 14: Decrease in IVIg group 2.5units on QMGS compared to 0.89 units in placebo group (p=0.47) and maintained at 28 days 3.0 reduction in IVIg group (NS). Subanalysis in moderate to severe MG: at day 14: decrease in IVIg group of 4.1 units compared to 0.71 units in placebo (p=0.01) and treatment effect maintained at 28 days (p=0.015) Safety: (Reported in Zinman 2008): No serious AEs were observed, and headache was the most frequent side effect, occurring in 75% of patients in the IVIG group and in 19% of patients in the placebo group (P <0.001, chi-square test).	Low
Barth 2011	Canada	Single center, single blinded RCT	84 patients 18+ with a Quantitative Myasthenia Gravis Score (QMGS) >10.5, and worsening weakness requiring a change in treatment modality as judged by a neuromuscular expert 84 randomised, 80 completed	IVIg: Gamunex®, received 1 g/kg/day for 2 consecutive days + diphenhydramine + paracetamol before infusion (n=41) PLEX: 5 procedures in total (performed every second day) (n=43)	intention to treat (n=84) for primary outcome A repeated measures analysis of the change in QMGS from baseline - 28-day Kaplan-Meier survival analyses were used to analyze the duration of treatment effects. The effects of baseline covariates were analysed with ANCOVA	1ary: change in QMGS from baseline to day 14 2ary: change in QMGS from baseline to days 21 and 28, change in other muscle parameters QoL At day 60: clinical worsening of MG in need for any of the following: intensive care unit	Efficacy: At day 14: decrease in QMGS: 3.2+- 4.1 (95% confidence interval (2–4.5) IVIg group 4.7 +- 4.9 (95% CI 3.2–6.2) unit change for the PLEX group (p 0.13) At day 28: effect persisted no difference between treatments (p 0.26). Safety: IVIg were allergic reaction (2), nausea and vomiting (7),	Low

					Responders were defined as those who had a decrease in QMGS of 3.5, Sample size calculation: 29 patients per arm	(ICU) admission, positive pressure ventilation, hospitalization, nasogastric tube feeding, AEs	headache (8), chills (2), fever (3), hemolytic anemia (1), and hypertension(1) PE: citrate reaction (6), poor venous access delaying treatment (4), vasospasm (8), and vasovagal reaction (2) and myocardial infarct (1)	
Barnett 2013	Canada	RCT (follow-up study of Barth 2011)	62 adult patients with moderate to severe MG as defined by a QMGS of >10.5 units and worsening weakness	IVIg: Gamunex®, received 1 g/kg/day for 2 consecutive days (n=32) PLEX: 5 procedures in total (performed every second day) (n=30)	QMGS and QOL scores, and change at day 14 are expressed as mean ±SD and compared (Student t-tests and by Chi2) The relationship between the change in QMGS and change in QOL was assessed by Pearson's correlation and by responder analysis. Responders were defined as those who had a decrease in QMGS of 3.5 Linear regression analysis compared the changes in MG-QOL-60 with MG-QOL-15	1ary: change in MG-QoL-60 sore at baseline and 2 weeks after treatment change in MG-QoL-15score (derived from QoL-60) at baseline and 2 weeks after treatment	<u>Efficacy:</u> The scores in both QOL scales improved at day 14 in the IVIg and PLEX groups, without significant difference between groups (QOL-15: IVIg −5.7±8.5, PLEX: −7.0±7.6, p=0.52; QOL-60: IVIg −13.3±16.9, PLEX −18.5±22.0, p=0.41). The improvement in QOL showed a good correlation with the decrease in QMGS	High
Alipour-Faz 2017	Iran	Single center, RCT, not blinded	24 patients with MG in preoperative preparation before thymectomy	IVIG: 1kg/kg/day for 2 consecutive days (n=12) + diphenhydramine + paracetamol before infusion PLEX: 5 procedures 5% albumin replacement fluid (n=12)	Normality and homogeneity of variables was tested: independent sample T tests or MannWhitney U Chi² for categorical variable	1ary: postoperative outcomes duration of hospitalisation (days), ICU length of stay after surgery (hours), length of intubation period (hours) duration of surgery (hours) dose of	<u>Efficacy:</u> the post-operative intubation time was shorter for IVIg compared to PLEX (0 versus 13, p=0,01) the duration of surgery was shorter for IVIg compared to PLEX (3,46h versus 4,17, p=0,05) other outcomes did not significantly differ	High

						corticosteroid administered (Milligrams) no AE reported		
Gamez 2019	Spain	single centre, double blind RCT	47 well-controlled generalised MG before surgery (incl thymectomy) From 15 days before surgery till hospital discharge	IVIg: 0,4g/kg/day (Privigen®)for 5 consecutive days (n=25) placebo: saline solution for 5 consecutive days (n=22) At least 7 days before the surgery. Other treatment such as PE, rituximab, alemtuzumab, TNF-α blockers was not allowed	No dropouts or lost-to follow up normality of variables tested logistic regression to define variables associated with MC	1ary: myasthenia crisis (MC) 2ary: QMGS score, days of hospitalisation, MGQoL score, operation time, time in recovery, No AEs reported	<u>Efficacy:</u> 1ary: 1 patient in placebo group did a MC, compared to none in the IVIg. 2ary: No statistical difference in all other outcomes: Hospitalisation: mean days 3.2 (SD2.7) in IVIg vs. 4.2 (SD4.5) in placebo (p = 0.586) operation time: mean 122.9 (SD68.7) in IVIg vs. 118.2 (68.8) in placebo (p = 0.749). Time in recovery: mean 19.9 (SD28.9) in IVIG vs. 25.8 (SD54.1) in placebo (p = 0.733). but no details for QMG score (figure), MG-QoL score “preoperative IVIG to prevent crisis does not appear justified”	Low

Solid Organ Transplant

Author (year)	Country	study design	population, sample	Intervention/Comparator	statistical analysis	outcome	conclusion	risk of bias
Peraldi 1996	France	single center, non-blinded RCT	41 received a second kidney transplant of cadaveric origin	IVIg (0.4 g/kg/day) 4 consecutive days after transplantation + conventional quadruple-immunosuppressive therapy versus conventional quadruple-	Variables between groups were compared with a t test. Results are expressed as mean+/-SEM Kaplan-Meier Survival analysis (log rank analysis)	Delay of graft function CMV infection acute rejection episodes 5-year graft survival 5-year patient survival rate	Delay of graft function: 3.4+-1,0 days in the IVIg group compared with 9.9+-1,6 days in the group receiving no IVIg. NS CMV infection occurred with the same incidence: 54%(12/21) of the patients receiving IVIg and 60% (12/20) of the patients in the control group. NS acute rejection episodes: NS (2,1+-1,1 vs 2,0+-1,1)	Unclear

				immunosuppressive therapy			The 5-year graft survival rate: 68% in the IVIg, and only 50% in the control group. (P=0.0017 log rank) 5-year patient survival rate similar: 90% IVIg and 95% in the control group	
Casadei 2001	Argentina	Single center, non blinded RCT	30 recipients of primary kidney transplants experiencing steroid-resistant rejections	IVIg 500 mg/kg/day for 7 consecutive days or 5 mg/day (1 ampule) of OKT3 anti-CD3 monoclonal antibody for 14 consecutive days	Means and SD. Statistical comparison of groups was done using Fisher's exact test. Graft survival was analyzed using the Kaplan-Meier method per protocol analysis	Therapeutic response Graft rejection after 30 days Plasmacreatinine 2 year graft survival 2 year patient survival	A positive therapeutic response was observed in 11 of 15 patients treated with IVIg as compared with 13 of 15 treated with OKT3 (P=0.79). Graft rejection within a 30-day period after treatment: 5 (46%) of 11 patients in IVIg and 9 (75%) of 12 in OKT3 (P=0.4). Plasma creatinine 1 month after treatment (2.35+-0.78 vs. 2.51+-1.10, P=0.66) or 3 months after treatment (1.83+-0.58 vs. 2.30+-0.89, P=0.24) The patient and graft survival rates 2 years after treatment were comparable for the two groups: patient survival was 87% and 92%, respectively. Graft survival was identical 80% in both groups.	High
Jordan 2004	US	Multicenter, double blinded placebo RCT	HLA-Highly sensitised adult patients diagnosed as Panel Reactive Antibody (PRA) ≥50% awaiting kidney transplantation, regardless of any prior transplantation. (n=101) identified, randomised (n=98)	IVIg: Gamimune® 10% 2g/kg per month for 4 months (n=48) Placebo: 0,1% albumin per month for 4 months (n=50)	Intention-to treat and per protocol, survival statistics	PRA-level before transplantation: transplantation graft survival at 30 months mortality after 30 months AEs	<u>Efficacy:</u> PRA-level before transplantation: IVIg significant reductions although not < 40% (see figures in article) (p=0,033 for IgM and IgG) Transplantation: 27 patients in total 35% (17/48) IVIg vs. 20% (10/50) placebo (p=0.069)-intention to treat	Low

							35% (16/46) vs 17% (8/46), p=0.048 (per protocol) Time to transplantation: 4.8y for IVIg vs 10.3y for placebo (p=0.049) Graft survival at 30 months: 25% (4/16) IVIg vs. 38% (3/8) placebo Graft survival at 2y: 80% IVIG vs 75% placebo (p=0.57) Acute rejection episodes: 14/17 IVIg vs. 1/10 placebo (p=0.042) Mortality after 30 months: 4 in IVIg - 8 in placebo (p=0.22) <u>Safety:</u> AEs (monitor during and 1h after infusion): increase in headache after infusion. No serious AEs reported. Two IVIg patients experienced infusion reactions	
Moreso 2018	Spain	Multicenter, double blinded placebo RCT 1y follow-up	Renal transplants with biopsy-proven chronic Antibody mediated rejection (glomerulopathy+anti-HLA DSA), >18y n=25 randomisation 2 dropouts before administration: 1 in placebo and 1 in IVIG+RTX	IVIg: Privigen® 0,5g/kg every 3 weeks 4 times followed by a single dose RITUXIMAB 375mg/m² 1 week after the final IVIg dose (n=12) Placebo: isovolumetric saline solution same schedule (n=13)	Efficacy and safety analysis were performed in the population per protocol Study underpowered, sample size calculation based on a eGRF 10+-10ml/min per 1,73m² difference	1ary: mean difference eGFR at 1 year 2ary: change in daily proteinuria, serum creatinine, histological renal lesions, presence of anti-HLA DSA AEs	<u>Efficacy:</u> 1ary: mean difference eGFR at 1 year: NS -6,6+-12,0 for the placebo and -4,2+-14,4ml/min per1,73m² (p=0,457) The combination of IVIg and RTX does not stabilize renal function in patients with chronic ABMR with transplant glomerulopathy 2ary: proteinuria: +0.9+-2.1 vs. 0.9+-2.1g/day, p=0.378 <u>Safety:</u> AEs: number of AEs during the study period was not different in the placebo and treatment groups (28 vs. 26). There were no episodes of opportunistic infections. Serious AEs needing	Low

							hospitalisation was observed in four patients of the placebo group and five patients in the treatment group (urinary sepsis (n=1), fever (n=1), urinary tract infection (n=2), hyponatremia (n=1)).	

Fetomaternal trombocytopenia								
Author (year)	Country	study design	population, sample	Intervention/Comparator	statistical analysis	outcome	conclusion	risk of bias
Paridiaans 2015	Sweden, the Netherlands and Australia	Multicenter, open label RCT	23 Pregnant women with human platelet antigen (HPA) alloantibodies and an affected previous child without intracranial hemorrhage (ICH)	IVIg at 0.5/kg per week (n=12) OR IVIg 1 g/kg per week (n=11) From 26-28 week gestational age till birth	Intention-to-treat/ The trial was stopped early due to poor recruitment.	1ary: Fetal or neonatal ICH. 2ary: Platelet count at birth, maternal and neonatal IgG levels, neonatal treatment and bleeding other than ICH AEs: Maternal and fetal/neonatal	<u>Efficacy:</u> No ICH occurred. All other outcomes did not differ. However uncompleted trial lacked the power to conclusively prove the noninferiority of using the low dose <u>Safety</u> No AEs seen in both groups	Low (underpowered)

Immunobullous disease - Pemphigus (vulgaris, foliculae)								
Author (year)	Country	study design	population, sample	Intervention/Comparator	statistical analysis	outcome	conclusion	risk of bias
Amagai 2009	Japan (in 27 medical centers)	Multicenter RCT, double blind	61 patients with pemphigus vulgaris or pemphigus foliaceus who did not respond to prednisolone (20 mg/d).	IVIg: 200 mg/kg/d(n=20) vs. 400 mg/kg/d (n=21) administered in divided dose over 5 consecutive days. vs. placebo group: saline over 5 consecutive days (n=20)	intention-to-treat analysis dropout: placebo (n=5); 200 mg (n=3); and 400 mg (n=2) cumulative rate of TEP, via evaluation of dose-response relationship of TEP and via analysis using the Kaplan-Meier method, was compared among the treatment groups by log rank test	1ary: time to escape from the protocol (TEP) 2ary: change in clinical symptoms over time for skin lesion area, number of new blisters/d, and oral mucosal lesions, and their total scores (PAS score) ; and the titers of pemphigus autoantibodies over time AE (85 days)	<u>Efficacy:</u> TEP in the 400-mg group was significantly longer than that in the placebo group (P<0.001), whereas the difference between the 200-mg and placebo groups was not significant (P = .052). Log rank test of TEP for the 61 patients indicated a dose-response relationship (P<0.001). <u>Safety:</u> AE 28.6% (n = 6/21) in the 400-mg group, 35.0% (n = 7/20) in the 200-mg group, and 25.0% (n = 5/20) in the placebo group. One serious AE linked to treatment (dead due to aggravation of HepC) in the 200mg group	Low
Amagai 2017	Japan (53 medical centers)	Multicenter, RCT, double-blind	56 patients with steroid-resistant bullous pemphigoid (BP) no symptomatic improvement with prednisolone (0.4 mg/kg/day) Disease activity score (DAS) > 10	IVIg (400 mg/kg/day for 5 days) (n=29) + corticosteroids vs. placebo (saline for 5 consecutive days) + corticosteroids (n=27)	Efficacy analyses were carried out for the full-analysis set Dropout: 9 in IVIG and 6 in placebo Unpaired t-test for 1ary outcome post hoc analysis: of covariance using the DAS on day 1 as a covariate, which was conducted to increase the precision and statistical power	1ary: disease activity score on day15 (DAS15) 2ary: changes in the DAS over time, the anti-BP180 antibody titer, Time to treatment reduction, Oral steroid dosage/day. AEs (till 57 days)	<u>Efficacy</u> <u>DAS15:</u> IVIg group (mean 19.8 ± SD 22.2) was 12.5 points lower than in the placebo group (mean 32.3± SD 31.5), between group NS (p = 0.089). Posthoc analysis (covariance of DAS score on day 1): sign. Differ. Between IVIg and placebo (p=0.041) posthoc analysis: In the severe patient subgroup (DAS >40 on day 1, IVIg	Low

Immunobullous disease - Pemphigus (vulgaris, foliculae)								
Author (year)	Country	study design	population, sample	Intervention/Comparator	statistical analysis	outcome	conclusion	risk of bias
					cumulative rate of time to treatment reduction, which was estimated using the Kaplan-Meier method, was compared between the groups by a log-rank test.		treatment provided significantly lower values than the placebo group on days 8, 15, and 22 ($p<0.05$) DAS of erosions/blisters and new erythema: decreased in both IVIg and placebo group, although the significance in the difference was lost on day 29 and thereafter, indicating that the beneficial effects of IVIg are transient Safety: AEs: 37.9% (n = 11/29) in the IVIg group vs. 18.5% (n = 5/27) in placebo. No sign. differ (p = 0.143), no serious AEs reported	
Dermatomyostis and polymyositis								
Author (year)	**Country**	**study design**	**population, sample**	**Intervention/Comparator**	**statistical analysis**	**outcome**	**conclusion**	**risk of bias**
Dalakas 1993	US	Crossover Double blind RCT	15 adult patients with treatment resistant dermatomyositis (unresponsive to high dose of prednisolone or other immunosuppresant therapy)	IVIg (2g/kg over 2 days, per month) versus placebo (saline) Crossover: therapy during 3 months, with 1 month washout, before start of second period Patients were allowed to continue other therapy (no change in therapy was allowed during period)	Wilcoxon statistics analys of variance for outcome of the muscle biopsy	Response based on neuromuscular symptom scale ADL scale muscle strenght scale (MRC) photographs of rash muscle biobsy for a subset of patients	Efficacy: Statistically significant improvements in muscle strength from 76.6 ± 5,7 to 84.6 ± 4,6 in the IVIg group, versus no significant difference in the placebo group (78,6 ± 6,3 to 78,6 ± 8,2). Safety: In 2 patients, severe headache with each infusion	Low

Immunobullous disease - Pemphigus (vulgaris, foliculae)								
Author (year)	Country	study design	population, sample	Intervention/Comparator	statistical analysis	outcome	conclusion	risk of bias
							"high dose is safe and effective for refractory dermatomyositis"	
Miyasaka 2001	Japan (in 47 centers)	Crossover Double blind RCT, multicenter	Steroid resistant dermatomyositis (n=10) or polymyositis (n=16)	IVIg: 400mg/kg during 5 consecutive days (n= 12) or placebo (n=14) Crossover after 8 weeks, no washout	Intragroup comparison (change over time) intergroup comparison survival statistics (kaplan meier): days until improvement 1 dropout in IVIg group due to AEs (Last observation carried forward analysis)	1ary: MMT score: changes in muscle weakness ADL Creatinekinase in plasma AEs	Non sign. Difference between IVIg and placebo (in both groups the muscle strenght improved significantly): IVIg: mean change in MMT score was 11.8 ± 8.0,(paired t test p0.001) Placebo: 9.9 ± 8.3 (paired t test, p = 0.0007), <u>Safety:</u> 19 AE in 11 of 26 subjects (42.3%), of which 2 events (decreased muscle strength and increased serum creatine kinase) were assessed as serious absence of a clear intergroup difference between IVIG and placebo	Unclear

2.5 Systematic Reviews on 'other' indications

Author (year)	population	intervention	Types of studies	Number and ref of RCTs on IG included	Quality	Results	Conclusion of Authors
Multiple Sclerosis (8 SR found, of which 2 with low quality)							
Gray et al., 2010 (Cochrane)	Clinically or laboratory-supported definite MS (also relapsing remitting MS)	IVIg	RCTs	6 RCTs: Remitting multiple sclerosis: Fazekas 1997, Achiron 1998, Lewanska 2002, Fazekas 2008 secondary progressive cases: Hommes 2004, Poehlau 2007	AMSTAR: 8/11	Secondary progressive group: no positive effect on progression of disease assessed by the Expanded Disability Status Scale (EDSS): OR=0.96 [0.68, 1.36] (2 studies-515 patients) relapsing remitting group: reduction in relapse rate (WMD -0.72 95% CI -0.78 to -0.66)(4 studies 431 patients)	"Some evidence that immunoglobulins can reduce the rate of relapses in people who have relapsing remitting MS. There is no evidence that immunoglobulins can reduce the progression of MS."
Tramacere et al 2015 (Cochrane)	Adults with relapse remitting MS	all therapies	RCTs	4 RCTs: Fazekas 1997, Achiron 1998, Lewanska 2002, Fazekas 2008	AMSTAR 11/11	No significant impact. chance in relapse rate over 12 months: RR 0.78 (0.61 to 1.00) – (219 patients in 3 studies) – very low GRADE chance in relapse rate over 24 months: RR 0.74 (0.60 to 0.91)- (190 patients in2 studies) – moderate GRADE chance of disability getting worse over 24months:RR 0.70 (0.39 to 1.27)- (190 patients in 2 studies) – very low GRADE	Other treatment options appear to be more effective than IVIg in treating patients with relapsing-remitting multiple sclerosis, "The results of this review show that for preventing clinical relapses in the short term (24 months), alemtuzumab, natalizumab, and fingolimod are superior to several other treatments, on the basis of moderate to high quality evidence."
Olyaeemanesh et al 2016	Diagnosed MS (with Mcdonals criteria), also including relapsing-remitting MS	IVIg	RCTs	6 RCTs: Fazekas et al., 1997; Achiron et al., 1998; Strasser et al., 2000; Lewanska et al., 2002; Kocer et al., 2004; Fazekas et al., 2008	AMSTAR 5/11	beneficial effect on proportion relapse-free patients compared to placebo: OR: 1.69 (95% CI-1.21-2.38)(5 studies-608 patients) reduction in annual relapse rate: (Standerdised mean difference SMD=-0.218; 95% CI-0.412 to -0.024; p=0.028) (4studies, n=458) compared to placebo,	Beneficial effect on relapse rate, not on progression. "IVIg can be considered as an alternative therapeutic option, second-line therapy or adjuvant therapy, considering its beneficial

						However did not show significant differences between EDSS changes from baseline (SMD,-0.025; 95% CI,-0.211 to 0.161; p=0.860)(5studies)	effects for treating relapsing–remitting MS patients"
Filippini 2017 (Cochrane)	Adults with a **first clinical attack** suggestive of MS	all therapies	randomised and observational studies	1 RCT: Achiron 2004 (first attack)	AMSTAR 11/11	time to conversion to clinically diagnosed MS: Hazard ratio=0.36 95%CI [0.15, 0.86] (1study, n=91) Withdrawing from the study or discontinuing the drug for any reason over 12 months: OR=2.15 [0.37, 12.35]	"No sufficient data available for IVIg; Sufficient data were available from 22 studies disease modifying drugs: cladribine (Movectro), glatiramer acetate (Copaxone), interferon beta-1b (Betaferon), interferon beta-1a (Rebif; Avonex), and teriflunomide (Aubagio)."
INESSS 2017	All neurological conditions	IVIg	SR, and RCTs	SR: Gray et al., 2010, Tramacere et al., 2015, Olyaeemanesh et al., 2016 RCT: no additional found	AMSTAR 10/11	Descriptive analysis of the SRs: The results for disease progression measured with the EDSS score are heterogeneous across studies, and the clinical relevance of the statistically significant difference observed in 2 of the 4 RCTs appears to be low. The authors of the Cochrane review [Gray et al., 2010] did not consider the results for disease progression to be robust. Results regarding relapse rates and the proportion of patients without relapse from the Cochrane meta-analysis show a statistically significant effect in favour of IVIg, but significant heterogeneity was found on these parameters, with not all results being consistent across studies.	"weak recommendation for remitting MS"
CADTH rapid review 2018 (Neurology)	All ages- MS	IVIg and SCIg	HTAs, SR, meta-analyses, RCTs, nonrandomized studies	3 SRs : INESSS 2017, Olyaeemanesh et al, 2016, Vitaliti et al 2015	AMSTAR 7/11	descriptive analysis of the SRs	"for relapsing-remitting MS: alternative therapy, or second-line treatment option when compared with placebo but not for primary- or secondary-progressive multiple sclerosis (due to inadequate efficacy, a lack of pathophysiological justification or potentially harmful effect) when

							compared with placebo or no intervention."
Epilepsy (9 SR found of which 2 with a low quality)							
Walker et al, 2013	Adults (over 16 years) with **focal epilepsy** syndromes	corticosteroids and Immunosuppressants	RCTs	1 RCT: Van Rijckevorsel 1994	AMSTAR 9/11	At six months, intention-to-treat analysis showed no statistically significant improvement in favour of IVIG in the total refractory epilepsy group (risk ratio (RR) 1.76, 95%CI 0.79 to 3.93) (1study, n=61) or the sub-classified group with refractory partial epilepsy (RR 3.08, 95% CI 0.84 to 11.34) (1study, n=61).	"it is not possible to draw any conclusions about the role of immunomodulatory interventions in reducing seizure frequency or the safety of these agents in adults with epilepsy (1 RCT)"
Geng et al, 2017 (Cochrane)	All people with a diagnosis of epilepsy	IVIg	RCTs or quasi-randomized controlled trials	1 RCT (van Rijckevorsel-Harmant 1994)	AMSTAR 10/11	Satisfactory seizure control (reduction of ≥50% seizure frequency): RR 1.89 (0.85 to 4.21) (1 RCT n= 58, with low/unclear risk of bias). Global Assessment (integration of several clinical aspects including reduction in the number and severity of seizures, evolution of EEG, interictal status, patient perception), IVIG was better than placebo; RR=3.21 (95%CI 1.10 to 9.36, P = 0.033, 1 RCT, n= 60) Incidence of adverse or harmful effects: RR 3.29 (1.13 to 9.57) (1 study, n=60)	"no convincing evidence to support the use of IVIg as a treatment for epilepsy"
Zeiler et al 2017	18 years or older – **refractory status epilepticus**,	IVIg	All studies, prospective and retrospective	No RCTs	AMSTAR 8/11	No results based on RCTs only on retrospective case reports	"Routine use of IVIg in adult RSE cannot be recommended at this time"
Gadian 2017	Children: between 2 and 18 years with neurological conditions	IVIg	RCTs, uncontrolled trials, short reports and case series	No RCTs	AMSTAR 6/11	No results based on RCT, only some case series	"Insufficient evidence to support or refute the use of IVIg in **pediatric** patients with refractory epilepsy, febrile infection-related epilepsy syndrome, and Landau–Kleffner syndrome"
Gogou 2017	Children (not specified) with	IVIg	all prospective studies	No RCTs, 1 single blind prospective trial	AMSTAR 4/11	No results based on RCTs, results based on 9 prospective studies	"Most literature data show that IVIg can play an essential role in cases of

	neurological conditions			on Lennox-Gastaut Syndrome (Illum 1990)			resistant **pediatric epilepsy**. On het other hand, identified studies present heterogeneity in methodology, provide moderate to low level evidence"
CADTH rapid review 2018 (Neurology)	All ages-epilepsy	IVIg and SCIg	HTAs, SR, meta-analyses, RCTs, nonrandomized studies	4 SRs: Geng J et al 2017, Al Amrani 2017, Gogou et al 2017, Zeiler et al 2017	AMSTAR 7/11	IVIg was no better than placebo for> 50% reduction in seizure severity in patients with refractory epilepsy, risk ratio 1.76 (0.79 to 3.93, P = 0.17) and in patients with refractory partial epilepsy, risk ratio 3.08 (0.84 to 11.34, P = 0.091). In terms of Global Assessment (integration of several clinical aspects including reduction in the number and severity of seizures, evolution of EEG, interictal status, and perception of the participants and caregivers), IVIg was better than placebo; RR=3.21 (95%CI 1.10 to 9.36, P = 0.033, 1 RCT, n= 60) for refractory epilepsy.	"Conflicting results"
INESSS 2017	Opsoclonus myoclonus	IVIg	SR, and RCTs	SR: Feasby 2007: no RCT RCT: no new RCTs	AMSTAR 10/11	Only based on case series	"Feasby et al. recommended that IVIg be considered as an option for the treatment of patients with opsomyoclonic syndrome, given the severity of the disease"
Encephalitis (6 SR found of which 1 with a low quality)							
Iro 2017 (Cochrane)	**Children:** six weeks to 17 years with a clinical diagnosis of acute or subacute encephalitis (chronic encephalitis excluded)	IVIg	RCTs	3 RCTs : Chen 2006, Rayamajhi 2015, Wu 2014	AMSTAR 11/11	No significant difference between IVIG and placebo for disability at 6 months: RR=0.75 (95%CI 0.22-2.60) (➔ 1RCT -22patients)- very low GRADE ≥1 serious event: RR=1.00 (95%CI 0.07-14.05) (➔ 1 RCT -22patients)- very low GRADE length of hospital stay: 4.54 lower (95%CI 7.47-1.61) (➔ 2RCTs-116patients) – very low GRADE	"Risk of bias in the included studies and quality of the evidence make it impossible to reach any firm conclusions on the efficacy and safety of IVIg as add-on treatment for children with encephalitis. Furthermore, the included studies involved only

							children with viral encephalitis, therefore findings of this review cannot be generalised to all forms of encephalitis."
Gadian 2017	**Children:** between 2 and 18 years with neurological conditions	IVIg	RCTs, uncontrolled trials, short reports and case series	N-methyl-D-aspartate receptor antibody encephalitis: no RCTs, 1 large observational cohort (Titulaer MJ, 2013) Rasmussen syndrome: 1 RCT: Bien 2013	AMSTAR 6/11	No RCTs for N-methyl-D-aspartate receptor antibody encephalitis, 1 large observational cohort (n=462) on adults and children and found response to treatment with a combination of IVIG, steroids, and plasmapheresis in 52% (n=241 out of 462) at 4 weeks Rasmussen syndrome: An RCT (n=16) found that IVIG was as effective as tacrolimus in reducing seizures	It is possible that IVIgimproves recovery in N-methyl-D-aspartate receptor antibody encephalitis. For Rasmussen syndrome, It is likely that IVIg and tacrolimus are equally effective (level 2b, n=16).
Gogou 2017	Children (not specified) with neurological conditions	IVIg	all prospective studies	2 RCTs : Bien et al 2013 (rasmussen encephalitis), Rayamajhi et al 2015 (Japanese encephalitis)	AMSTAR 4/11	Based on 2 RCTs, no clear superiority of IVIG	The effect of IVIG on encephalitis course should be more systematically validated before IVIG administration can be incorporated into routine protocol for **children**
INESSS 2017	All ages with auto-immune encephalitis (15 subtypes)	IVIg	SR, and RCTs	NMDAR encephalitis: a SR (Zhang et al., 2017) of 83 case series), 12 case series and 1 large observational cohort RCT: Bien et al., 2013 (Rasmussen encephalitis-quasi experimental)	AMSTAR 10/11	NMDAR encephalitis: 12 case series and 1 large cohort (n= 577) on a combination of therapies incl. IVIG a SR on 83 case series (n=432): no sign. Difference between IVIG, corticosteroids and plasma exchanges or immune-adsorption (alone or in combination) Rasmussen encephalitis: 1 RCT with low quality (n=16) showed statistically significant difference in favour of IVIg or tacrolimus treatment (p = 0.038**) compared to no treatment (historical control group)	NMDAR encephalitis: the results of the 13 case series and those of the systematic review do not allow a judgment to be made regarding the efficacy of IVIg Rasmussen encephalitis: low quality evidence and not powered to detect difference between IVIG and tacrolimus
CADTH rapid review 2018 (Neurology)	All ages-encephalitis (including Bickerstaff encephaliti)	IVIg and SCIg	HTAs, SR, meta-analyses, RCTs, nonrandomized studies	Encephalitis 4 SRs : Iro MA et al 2017, Gogou et al 2017, Gadian et al 2017, INESSS 2017 Rasmussen	AMSTAR 7/11	Description of the findings of the SR:	For patients with encephalitis, one meta-analysis showed no difference between IVIG and placebo for disability outcomes or adverse events, and three other

				syndrome : Gadian et al 2017, INESSS 2017			SRs did not find sufficient evidence of an effect after treatment with IVIG to provide strong conclusions for Rasmussen Syndrome IVIG appears to be no more effective than their respective comparators
Paraprotein neuropathy (2 SR found)							
Lunn 2016 (Cochrane)	All age with a diagnosis of MGUS, demyelinating neuropathy and anti-MAG antibodies (Para proteins of IgM class)	Immunotherapy	RCTs or quasi-RCTs	IVIg vs placebo (Comi 2002; Dalakas 1996). IVIg vs interferon alfa-2a (Mariette 1997),	AMSTAR 10/11	Only short-term outcomes Comi 2002: Dalakas 1996: provide low-quality evidence for very short-term improvement: At two weeks, the mRS score showed a significant improvement with IVIg (-0.38, (SD) 0.58) over placebo (+0.19, SD 0.51) at two weeks (P = 0.008), a difference that may not be clinically significant and dissappears at 4 weeks Mariette 1997: participants in the IVIg group worsened by a mean of 2.3 (SD7.6) points on the NIS at six months, and those in the interferon alfa-2a group improved by 7.5 (11.1) points, a Mean difference of 9.80 (95%CI 1.46 to 18.14, n = 20) in favour of interferon alfa-2a	"Inadequate reliable evidence IVIg has a statistically but probably not clinically significant benefit in the short term"
INESSS 2017	All ages with IgM paraprotein neuropathy	IVIg	SR, and RCTs	SR: Lunn and Nobile-Orazio, 2003 RCTs: no additional RCTs found	AMSTAR 10/11	Description of the findings of the SR	The authors conclude that the evidence from immunotherapy trials – including IVIG – for the treatment of patients with IgM peripheral neuropathy with anti-MAG activity is insufficient to support recommendations.
Paraneoplastic neuropathy (2 SR found)							
Giometto et al., 2012 (Cochrane)	Definite paraneoplastic neurological syndrome	All therapies	RCTs and quasi-RCTs	No RCTs	AMSTAR 10/11	No RCTs, only 5 non-controlled, observational studies covering IVIg (with a total of 47 participants)	There is only evidence from case series, case reports or expert opinion of the effect of immunomodulation (IVIg, PE, steroid treatment or

	(according to Graus' criteria)						chemotherapy) on paraneoplastic neuropathy.
INESSS 2017	All ages-paraneoplastic neuropathy	IVIg	SR, and RCTs	SR: Giometto et al., 2012 RCT: no RCTs found	AMSTAR 10/11	No RCTs and no further description of the SR because nothing found	
Inclusion body myositis (3 SR found)							
Rose 2015 (Cochrane)	18+ y and a clinicopathologically defined diagnosis of IBM	All therapies	RCTs and quasi-RCTs	3 RCTs: (Dalakas 1997; Dalakas 2001; Walter 2000);	AMSTAR 10/11	None of the IVIg studies reported data in a form that could be combined at 3, 6, or 12 months. Dalakas 1997 (n=19) found NS difference in mean change in muscle strength MRC scale between IVIG and placebo at three months. Dalakas 2001 (n=36) found no significant difference in mean muscle strength MRC scores with IVIg compared with placebo at three months. Walter 2000 (n=20) found no significant changes in MRC scales at six months	"Unable to draw conclusions from trials of IVIg"
Jones 2016 (Cochrane)	All ages with long-term, progressive primary muscle disease (including Duchenne muscular dystrophy, myotonic dystrophy, oculopharyngeal muscular dystrophy , oculopharyngodistal myopathy, inclusion body myositis (IBM), metabolic myopathy, and congenital myopathy.	All therapies to treat dysphagia	RCTs and quasi-RCTs	1 low quality RCT with incomplete reporting of findings: crossover Dalakas 1997 on swallowing function in inclusion body myositis (IBM) one non RCT was also described (Dobloug 2012, n= 16 adults)	AMSTAR 10/11	The RCT did report reductions in the time taken to swallow, as measured using ultrasound (1 study, n=19, high risk of bias and uncertain confidence intervals for the review outcomes, which limited the overall quality of the evidence)	Insufficient and low-quality RCT evidence to determine the effect of interventions for dysphagia in long-term, progressive muscle disease. Clinically relevant effects of intravenous immunoglobulin for dysphagia in inclusion body myositis can neither be confirmed or excluded using the evidence presented

INESSS 2017	All ages- IBM	IVIg	SR, and RCTs	SR: Rose et al., 2015 RCTs: no new RCTs	AMSTAR 10/11	The efficacy of IVIG for the treatment of patients with IBM was evaluated in three RCTs that compared IVIG (2 g/kg dose over 2 to 5 days every month) to placebo over 3 or 6 months (Dalakas et al., 2001b; Walter et al., 2000; Dalakas et al., 1997). Two of these RCTs were of medium methodological quality and only one was of good quality	"The existence of a clinically relevant effect of IVIG on dysphagia in cases of inclusion body myositis could not be confirmed or reversed"
Stiff man syndrome (1 SR found)							
INESSS 2017	All ages-stiff man syndrome	IVIg	SR, and RCTs	SR: no SR found RCT: Dalakas et al., 2001	AMSTAR 10/11	Dalakas 2001 (n=14), showed a statistically significant improvement in mean scores for IVIG in terms of stiffness ($p = 0.01$) and spasm frequency ($p = 0.03$) compared to placebo. A persistent effect of IVIg was observed in patients who received this treatment first. Indeed, the observed improvement in stiffness with IVIg administration was maintained during the weaning period and then during the placebo phase ($p < 0.001$). the review found 2 small case series published in 2006 (n=3) and 2011 (n=1)	Although based on a small study authors conclude that IVIg could play a role in the treatment of stiffness syndrome, but GABAergic drugs remained the first-line treatment
Sydenham's Chorea (3 SR found of which 2 with a low quality)							
CADTH rapid Review (autoimmune-inflam)	Patients of all ages with sydenham's choea	IVIg and SCIg	HTAs, SR, meta-analyses, RCTs	1 SR: Mohammad et al 2015 in children with acute SC no new RCTs added	AMSTAR 8/11	Garvey 2005 (n=18) examined whether IVIg (n=4) or plasma exchange (n=8) are superior to prednisone (n=6) in decreasing the severity of SC (on a 6-point scale). IVIg group showed a quicker improvement in chorea, but NS difference was found in the change of severity scores between the groups at 1- or 12-month follow-up. Walker 2012 (n=20) examined 10 children with symptomatic management (haloperidol 0.025–0.05 mg/kg/day) to that of 10 children who received additional IVIg. In the IVIg group the improved clinical score at 1 month was greater than in the control group ($P< 0.05$); but not maintained at 3 and 6 months. For which shorter symptomatic treatment was necessary ($P < 0.05$)	"Off label use for Sydenham's chorea did not result in a significant improvement of symptoms"

Systemic Lupus Erythematosus (2 SR found of which 1 of low quality)							
CADTH rapid Review 2018 (auto-immune-inflam)	All ages SLE	IVIg and SCIg	HTAs, SR, meta-analyses, RCTs, nonrandomized studies	1 SR: Sakhiswary et al. 2014 included one RCT (Boletis 1999), 2 nonrandomized controlled studies, 6 prospective cohorts and 3 retrospective RCTs: no new studies found in this Rapid Review	AMSTAR 8/11	Description of RCT (Boletis, n=14 treatment resistant patients with nephritis did not show a sign. Difference in the 1ary outcome creatinine between IVIg and cyclophosphamide) MA performed by Sakthiswary et al: pooled analysis of disease activity scores from six studies (2 nonrandomised and 4 prospective cohorts), found that therapy with IVIg resulted in a significant reduction from baseline in disease activity (P = 0.002). Pooled complement level data from six studies showed a response rate of 30.9% (P = 0.001). A pooled analysis of three studies showed a mean decrease of 17.95 milligrams per day in the dose of corticosteroids with IVIg therapy	"Off-label IVIg use significantly increased response rate and significantly reduced the disease activity score and the daily dose of corticosteroids in patients with systemic lupus erythematosus compared with baseline". No evidence from controlled trials.
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) (4 SR found of which 2 of low quality)							
INESSS 2017	Children with PANDAS	IVIg	SR, and RCTs	SR: no SR found RCTs: Perlmutter et al., 1999, Williams et al., 2016	AMSTAR 10/11	Description of RCTs found: Perlmutter 1999 (n=29 children with OCD and tics after streptococ infection, randomised to IVIG, plasma exchange or placebo). A significant improvement was observed among patients treated with IVIg or plasma exchange compared to patients who received placebo for the following symptoms: OCD (p = 0.006), anxiety (p = 0.001), depression (p = 0.002), emotional lability (p = 0.001) and general functioning (p = 0.0009). After one year, the improvement in these symptoms had continued. Williams 2016 (n=35, low risk of bias) randomised to IVIG or placebo and after 6 weeks no significant difference between the 2 groups in OCD symptoms and on clinical improvement	Insufficient data to draw conclusions
CADTH rapid review 2018 (Neurology)	Children with PANDAS	IVIg and SCIg	HTAs, SR, meta-analyses, RCTs, nonrandomi	2 SR : Constantine MM et al 2007, INESSS 2017	AMSTAR 7/11	One SR reported that, based on one included RCT, more patients treated with plasma exchange than IVIg showed improvement in obsessive compulsive disorder scores, depression, anxiety, tics	One SR suggested that plasma exchange resulted in better outcomes than IVIg for children with PANDAS. More, higher

			zed studies			and global function; however, between-group statistical comparisons were not reported. Another SR concluded that there is insufficient data regarding the treatment of PANDAS when compared with placebo or no intervention.	quality evidence is required to determine the comparative effectiveness of IVIG versus plasma exchange for children with PANDAS
Postpolio Syndrome (4 SR found)							
Samuelsson 2014	Adults with late (> 1y) manifestations of polio following the initial complete recovery. Verified by a decrease in muscle strength or verified by typical EMG findings	IVIg	SR and RCTs Non-randomized controlled studies, Case series ≥ 10 patients	2 SR: Koopman et al., 2011, Patwa, 2012 3 RCTs: Gonzalez 2006;Farbu 2007; Bertolasi 2013	AMSTAR 8/11	Fatigue: 3 RCT (n=202), no MA, all 3 RCTs reported no sign. Diff between IVIG and placebo (moderate grade of evidence) Pain: 3 RCTs (n=202), no MA, all 3 RCTs reported no sign. Diff between IVIg and placebo (moderate grade of evidence) Physical capacity and walking ability: 2 RCTs (n=192),no MA, no sign. Differences between the IVIG-treated and the placebo-treated Muscle strength: no MA, The RCT with the largest sample size showed a sign. Increase in muscle strength in selected muscles, whereas the other two RCT did not find any differences in various muscle groups Quality of life: 2 RCTs, no sign. Diff between IVIg and placebo	"In controlled trials IVIg has not been shown to have any beneficial effects in patients with post-polio syndrome."
Huang et al 2015	Not specified	IVIg	RCTs and prospective studies	3 RCTs: Gonzalez 2006;Farbu 2007; Bertolasi 2013	AMSTAR 8/11	Meta-analysis of RCTs: Pain (3 RCTs, n=203): pooled mean difference was −1.02 (95% CI: −2.51 to 0.47), fatigue (2 RCTs, n=70) : NS (WMD = 0.28; 95% CI −0.56 to 1.12), Changes of muscle strength (2 RCTs, n=70): NS	"IVIg is unlikely to produce significant improvements in pain, fatigue, or muscle strength. Thus, routinely administering IVIg to patients with PPS is not recommended based on RCTs"
Koopman et al 2015 (Cochrane)	Participants with a diagnosis of PPS.	All therapies	RCTs	3 RCTs: Gonzalez 2006; Farbu 2007; Bertolasi 2013 ongoing study: NCT02176863 {published data only} NCT02176863. Study of the efficacy and safety of immune globulin	AMSTAR 10/11	Meta-analysis (2 RCTs, n=185) on activity limitations as measured with SF-36 PCS: NS between the IVIg group and the placebo group in either the short term (MD 2.35; 95% CI -0.06 to 4.76) or long term (MD-0.51; 95%CI -4.63 to 3.60) Meta-analysis (2 RCTs, n=70) right knee extensor muscle strength: NS between the IVIg group and the placebo group, either in the short term (MD -11.01;	"Moderate- and low-quality evidence that IVIg has no beneficial effect on activity limitations in the short term and long term; inconsistency in the evidence for effectiveness on muscle strength"

				intravenous (human) Flebogamma® 5% DIF in patients with post-polio syndrome		95%CI -53.86 to 31.84, with I2 = 60% indicating substantial heterogeneity) or in the long term (MD -10.29; 95%CI -55.37 to 34.78, with I2 = 73% indicating substantial heterogeneity) change of fatigue: NS in the short term (FSS: MD 0.08; 95% CI -0.71 to 0.87) and final fatigue scores in the long term (FSS: MD -0.50; 95% CI -1.15 to 0.15). Meta-analysis (n=3, n=203) in pain: NS between participants treated with IVIg and placebo in the short term (MD -9.27; 95% CI – 25.11 to 6.57, with I2 = 80%indicating substantial heterogeneity) or in the long term (MD -5.61; 95% CI -14.95 to 3.73)	
CADTH rapid review 2018 (Neurology)	All ages- post polio syndrome	IVIg and SCIg	HTAs, SR, meta-analyses, RCTs, nonrandomized studies	2 SR: Huang et al 2015, Koopman 2015	AMSTAR 7/11	description of the findings of the SR: IVIG was no better than placebo for improvement in activity limitations as measured by the Short Form-36 Health Survey Physical Component Summary (SF-36 PCS) for either short term (< 3 months) mean difference 2.35 (-0.06 to 4.76, P = 0.056); or long term (> 3 months) mean difference -0.51 (-4.63 to 3.60, P =0.81) Both SRs found that IVIG was no better than placebo for pain, fatigue and muscle strenght. insufficient reporting of adverse events in one SR	"Two SRs reported that IVIg was no better than placebo for post polio syndrome and reporting of adverse events associated with treatment was lacking."
Neuromyelitis optica/Devic's disease (3 SR found of which 1 with low quality)							
INESSS 2017	All ages- Neuromyelitis optica	IVIg (0,7 g/kg/day for 3 days, every 2 months/high doses of méthylprednisolone	SR, and RCTs	SR: no SR found RCTs: no RCTs found; 5 non comparative studies with a sample size ranging from 1 to 10 patients. 1 quasy experimental pre-post study (n=8)	AMSTAR 10/11	The (pre-post), quasy experimental study in 8 patients found a reduction in the mean annual relapse rate from 1.8 in the previous year to IVIg treatment to 0,006 after treatment with IVIg (p = 0,01). A sig. reduction in the mean score of EDSS scale from 3.3 at the beginning of the study to 2.6 at the end (p = 0,04) was also reported. However, given the limited patient numbers and the limitations in the methods used in this study, no clear conclusions could be drawn.	Very limited data of low quality (mainly case series) which does not allow to draw any conclusions on IVIg in neuromyelitis optica

CADTH rapid Review 2018	All ages-Neuromyelitis optica	IVIg and SCIG/ different therapies such as rituximab or mycofenolate mofetil or methylprednisolone or azathioprine, placebo or no treatment.	HTAs, SR, meta-analyses, RCTs, nonrandomized studies	2 SRs : INESSS 2017, Vitaliti 2015 RCT : Absoud M, et al 2017	AMSTAR 9/11	There is very limited evidence that immunosuppressant (rituximab, mycofenolate) may be better than IVIg for the treatment of children with neuromyelitis optica (based on very few, small case series (n < 5). Insufficient data exists to on the treatment of neuromyelitis optica with IVIg vs placebo or no intervention. The only RCT was ended due to low recruitment. No results were provided.	"The scientific data were considered insufficient to draw any conclusions on the clinical value of Ig in neuromyelitis optica."
Haemolytic disease in newborns (HD) (6 SR found)							
Dodd et al 2012 (antenatal therapy) (Cochrane)	Women with red-cell alloimmunisation undergoing intrauterine fetal blood transfusion for treatment of fetal haemolytic anaemia	All therapy	RCTs and quasi RCTs	1 RCT on IVIg as add on to intrauterine fetal blood transfusion vs. intrauterine fetal blood transfusion alone (Dooren 1994)	AMSTAR 10/11	1ary outcome: perinatal death (RR=3.00; 95% CI 0.37 to 24.17, 1 RCT, n=20) and neurodevelopmental delay at childhood follow up (RR 1.29; 95% CI 0.10 to 17.41 (one study 16 children)), non sign.difference 2ary outcomes: preterm birth less than 32 weeks; need for exchange transfusion; need for top-up transfusion; or fetal death: Non sign. difference	"Little available high quality information from RCTs to inform the optimal procedural technique when performing fetal intrauterine fetal blood transfusions for women with an anaemic fetus due to red cell allimmunisation"
Wong et al 2013 (antenatal therapy)	Women with red blood cell group antibodies and fetuses at risk of alloimmunisation	IVIg vs.no treatment or any other therapy	RCTs and quasi-RCTs, with parallel study design	No trials were found.	AMSTAR incomplete	No results from RCTs	"No information is available from RCTs to indicate whether the antenatal use of intravenous immunoglobulin is effective in the management of fetal red blood cell alloimmunisation. Several case series suggest a beneficial role in delaying the onset of fetal anaemia requiring invasive intrauterine transfusion"
Louis et al 2014 (neonatal therapy)	Term and preterm neonates with	IVIg vs. Placebo or no treatment	RCTs and quasi-RCTs,	12 included RCT focus on Rh isoimmunisation:	AMSTAR 9/11	Rh isoimmunisation: no overall MA because sign. Variations in risk of bias RCTs with high risk of bias showed that	"Efficacy of IVIg is not conclusive in Rh haemolytic disease of

	the diagnosis of isoimmune haemolytic disease secondary to Rh or ABO incompatibility			Dagoglu T 1995; Rubo J, et al 1992; Voto LS,1995;; Smits-Wintjens VE 2011; Santos MC 2013; Elalfy MS 2011; Garcia MG 2004; focus on ABO isoimmunisation: Pishva N, 2000; Huang WM 2006; Miqdad AM 2004; Alpay F, 1999; Nasseri F,2006		IVIg reduced the rate of exchange transfusion (RR 0.23, 95% CI 0.13 to 0.40, n=236), whereas studies with low risk of bias that also used prophylactic phototherapy did not show statistically significant difference (RR 0.82, 95% CI 0.53 to 1.26, n= 190). For ABO isoimmunisation, only studies with high risk of bias were available and meta-analysis revealed efficacy of IVIg in reducing ET (RR 0.31, 95% CI 0.18 to 0.55, n=350). No sign. effect on secondary outcomes	new-born with studies with low risk of bias indicating no benefit and studies with high risk of bias suggesting benefit. Role of IVIg in ABO disease is not clear as studies that showed a benefit had high risk of bias."
Cortey et al 2014 (neonatal therapy)	Neonates with jaundice caused by ABO incompatibility	IVIg + phototherapy (PT) vs phototherapy alone	RCTs	6 RCTs : Alpay F,1999; Atici A,1996; Huang WM,2006; Tanyer G,2001; Miqdad AM 2004; Nasseri F,2006	AMSTAR 5/11	MA of 6 RCTs: Requirement for exchange transfusions was lower in the IVIg + PT – RR= 0.27 (CI 95 % 0.17–0.42; P < 0.00001),n=516 2ary outcomes: The mean duration of PT was 4 days in the PT group and association of PT with IVIg significantly reduced the duration of PT treatment by 0.84 days. The tolerance of the IVIg and PT association was good	"IVIG associated with PT reduces the need for ET and the duration of PT in new-borns with hyperbilirubinemia due to ABO hemolytic disease. Their efficacy and good tolerance prompt consideration of IVIg as a therapeutic adjuvant to PT in severe hemolytic hyperbilirubinemia due to ABO incompatibility"
Zwiers et al 2018 (neonatal therapy)- cochrane	Neonates with alloimmune hemolytic disease due to either Rh (or other red cell antigens) or ABO incompatibility	IVIg + phototherapy (PT) vs phototherapy alone	RCTs and quasi-RCTs,	9 RCTs (Rübo 1992; Dagoglu 1995; Alpay 1999; Miqdad 2004; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). One study examined multiple doses (Nasseri 2006), and one study compared groups treated with a single dose or multiple doses with a control group (Tanyer 2001)	AMSTAR 10/11	The use of exchange transfusions decreased sig. in the IG group (RR 0.35, 95% CI 0.25 to 0.49; NNTB 5, 9RCTs n=658). The mean N. of ET per infant was also sig. lower in the IG treated group (MD -0.34, 95% CI -0.50 to -0.17). However SA showed the results not to be robust (some uncertainty remains).	Overall results in favour of Ig, but limited applicability of results due to a low – very low quality of the evidence

CADTH Rapid Review 2018 (hematology)	Neonates with alloimmune hemolytic disease due to either Rh (or other red cell antigens) or ABO incompatibility	IVIg vs. Placebo or no treatment	SR and RCTs Non-randomized controlled studies,	1 SR: Louis et al 2014 RCT on neonates with rhesus HDFN: Van Kink et al 2016 nonrandomised: Corvaquila 2012	AMSTAR 8/11	RCT Van Kink et al: IVIG (n= 41) vs. Placebo (n = 39), with a high lost to f/u = 18% (14/80). The 1ary outcome Incidence of neurodevelopmental impairment did not differ sign. 3% (1/34) vs. 3% (1/32); P = 1.00; 2ary outcomes such as median cognitive score, Incidence of allergies, infections did not differ sign.	RCT: We found no differences in long-term neurodevelopmental impairment in children with rhesus HDFN treated with IVIg compared to placebo".
Carditis (in acute rheumatic fever) (2 SR found)							
Cilliers et al 2015 (Cochrane)	Adults and children with acute rheumatic fever diagnosed according to Jones, or modified Jones, criteria	Anti-inflammatory drugs (amongst which Ig) vs. placebo or no treatment or other anti-inflammatories	RCTs	1 RCT (Voss 2001)l n=61	AMSTAR 10/11	The effect of IVIg vs placebo to prevent cardiac disease in patients with acute rheumatic fever was non sig. (RR 0.87, 95% CI 0.55 to 1.39). No reporting of AEs was provided.	No evidence supporting the benefit of using Ig to prevent or reduce cardiac disease in patients presenting with acute rheumatic fever. The only RCT found for IVIg presented considerable risk of bias.
CADTH rapid Review 2018 (auto-immune-inflam)	All ages Carditis	IVIg and SCIg	HTAs, SR, meta-analyses, RCTs	1SR: Cilliers et al 2015 no new RCTs	AMSTAR 8/11	See results Cilliers et al 2015	"Off-label use of IVIg in patients with carditis of acute rheumatic fever did not result in a significant improvement of symptoms"
Myocarditis (1SR found)							
Robinson 2015 (Cohrane)	Adults or children with acute myocarditis (duration of cardiac symptoms < than 6 months)	IVIg (at least 1 g/kg)/ No IVIg or placebo	RCTs and quasi RCTs	2 RCT (McNamara 2001 in adults, Bhatt 2012 in children)	AMSTAR 11/11	1 RCT with an unclear RoB (n=62) adults, showed death or requirement for cardiac transplant or placement of a LVA device was low in both groups (OR for event-free survival: 0.52, 95%CI: 0.12 – 2.30). Similar improvements in LVEF and in functional status seen at 12 months in both groups. Infusion related Aes were frequent but mild. 1 RCT with a high RoB (n=83 children), showed an OR for event-free survival of 7.39 (95% CI 0.91 to 59.86). LVEF was 49.5% with IVIg vs 35.9% with placebo (risk difference:	Until higher-quality studies have demonstrated benefit in a particular group of patients, IVIg for presumed viral myocarditis should not be provided as routine practice in any situation

						13.6%, 95% CI 5.1 to 22.1%; P value = 0.001).	
Wegnerer's granulomatosis (system vasculitis) (2 SR found)							
Fortin 2013 (cochrane) – update of a 2009 review	Adults with a confirmed diagnosis of Wegener's granulomatosis	IVIg as add on to systemic corticosteroids in combination with immunosuppressants, vs same therapies without the IVIg	RCTs, or quasi RCTs, or randomized cross-over trials	IVIG as add-on; 1 RCT (Jayne 2000), n=34.	AMSTAR 10/11	No sign. differences with adjuvant IVIg vs adjuvant placebo in mortality, serious Aes, time to relapse, open-label rescue therapy, and infection rates. Sig. increase in total Aes with adjuvant IVIg (RR: 3.50; 95% CI 1.44 to 8.48, P < 0.01).	Insufficient evidence that adjuvant IVIg provides a therapeutic advantage compared with steroids combined with immunosuppressants in patients with WG
CADTH Rapid Review 2018 (hematology)	All ages Wegener's granulomatosis	IVIg and SCIg	HTAs, SR, meta-analyses, RCTs, nonrandomized studies	SR: Fortin et al 2013 No RCTs found	AMSTAR 9/11	No additional RCTs found compared to Fortin et al 2013. For results see above	No additional 63avouri found. For conclusions of Fortin et al. 2013 see above.
Preventing infection (in nephrotic syndrome) (1 SR found)							
Wu et al 2012 (Cochrane)	All age with any type of nephrotic syndrome (1ary or 2ary) regardless of pathologic changes	All therapies	RCTs and quasi-RCT	4 RCTs on IVIg (Dang 1999; Dou 2000; Tong 1998; Wu 2009). No studies conducted in adults. All chinese	AMSTAR 11/11	4 RCTs (n=248) showed a sig. better effect of IVIg at preventing infections in children with nephrotic syndrome (RR: 0.47, 95% CI 0.31 to 0.73).	IVIg may have positive effects on prevention of nosocomial or unspecified infections with no serious AEs in children with nephrotic syndrome. However the quality of all studies was low, the sample sizes small and all studies were from China
Preventing infection in preterm/low birthweight (1 SR found)							
Ohlsson et al 2013 (Cochrane)	Preterm (< 37 weeks' gestational age (GA) at birth) or low birth	IVIg/ placebo or no intervention	19 RCTs (n=5000)	19 included RCTs: Haque 1986; Bussel 1990a; Atici 1996, Christensen 1989, Ratrisawadi 1991, Weisman 1994a; Stabile 1988; Baker	AMSTAR 9/11	Sign. reduction in sepsis with IVIg (RR: 0.85, 95%CI: 0.74 to 0.98); NNT: 33. Sig. reduction of one or more episodes was found for any serious infection (RR: 0.82, 95% CI 0.74 to 0.92; NNT 25. Non sig. differences in mortality from all causes	IVIg offers a 3% reduction in sepsis and a 4% reduction in one or more episodes of any serious infection but is not associated with reductions in other clinically

	weight (< 2500 g)			1992; Chirico 1987; Clapp 1989, Fanaroff 1994, Tanzer 1997, Van Overmeire 1993, Conway 1990, Didato 1988; Magny 1991b; Spady 1994; Sandberg 2000; Chou 1998.		(RR: 0.89, 95% CI 0.75 to 1.05). No sig. difference in mortality from infection	important outcomes, including mortality. Prophylactic use of IVIg is not associated with any short-term serious Aes.
Preventing Hepatitis A (1 SR found)							
Liu et al 2009 (Cochrane)	Any age or ethnic origin, who were at the stage of preexposure or post-exposure of hepatitis A (infectious hepatitis).	Pre- or post-exposure prophylaxis with Ig	13 RCTs (n= 567,476). Excluded quasi-randomised trials and historically controlled studies	13 RCTs (Mosley 1968; Conrad 1972; Ignatieva 1972;Gorbunov 1981a;Gorbunov 1981b; Iurkuvenas 1982;Kark 1982a; Kark 1983; Gorbunov 1984; Green 1993; Lerman 1993; Shouval 1993a; Victor 2007).	AMSTAR 10/11	MA of 6 RCTs showed that Ig sig. reduced the number of adult patients with hepatitis A at 6 to 12 months (RR: 0.53; 95% CI 0.40 to 0.70); vs no intervention or inactive control. MA of 4 RCTs showed sig. reductions also in children (RR: 0.45; 95% CI: 0.34 to 0.59). Higher dosage was more effective than lower dosage. No sign. systemic AEs were reported.	Ig seem to be effective for pre-exposure and post-exposure prophylaxis of hepatitis A. However, caution is warranted for the positive findings due to the limited number of trials, year of conductance, and RoB
Infection-sepsis-septic shock (neonate) (3 SR found)							
Alejandria et al 2013 (Cochrane)	Any age with sepsis or septic shock caused by bacteria. Specific analysis for neonates	IVIg (standard or IgM-enriched) vs placebo or no intervention	RCTs	8studies (Brocklehurst 2011; Chen 1996; Mancilla-Ramirez 1992; Shenoi 1999; Weisman 1992), 3 IVIGAM (Erdem 1993; Haque 1988; Samatha 1997).	AMSTAR 10/11	IVIg in neonates, offer no sig. reduction in mortality (standard IVIg – RR: 1.00; 95% CI 0.92 to 1.08; 5 trials, n =3667; IgM-enriched IVIg – RR: 0.57; 95% CI 0.31 to 1.04; 3 trials, n = 164). MA of trials with low RoB showed no reduction in mortality with standard IVIg in neonates (RR: 1.01; 95% CI 0.93 to 1.09; 3 trials, n = 3561).	Among neonates with sepsis, there is sufficient evidence that standard polyclonal IVIg, as adjunctive therapy, does not reduce mortality. Ig-M enriched IVIg, evidence remains insufficient to support a robust conclusion of benefit.
Ohlsson et al 2015 (Cochrane)	Newborn (< 28 days of age) infants with suspected or proven serious infection.	IVIg vs placebo or no intervention	RCTs and quasi-RCT	8 studies (Ahmed 2006; Christensen 1991; Erdem 1993; Haque 1988; INIS 2011; Samatha 1997; Shenoi 1999; Sidiropoulos 1981)	AMSTAR 10/11	Non sig. differences with IVIg or w/o in: mortality during hospital stay in patients with suspected infection (RR: 0.95, 95% CI: 0.80 -1.13, 9 studies, n=2527); death or major disability at 2 yrs in suspected infection (RR: 0.98, 95% CI 0.88 -1.09, 1 study, n= 1985); mortality during hospital in patients with proven infections (RR: 0.95, 95% CI 0.74 – 1.21; 1 study, n=1446); death or major disability at 2	Routine administration of IVIg or IgM-enriched IVIg to prevent mortality in infants with suspected or proven neonatal infection is not recommended.

						years in infants with proven infection (RR: 1.03, 95% CI 0.91 – 1.18, 1 study, n= 1393); LoS at hospital for infants with suspected or proven infection (MD: 0.00 days, 95% CI -0.61- 0.61; based on 1 study, n = 3493); No sig. difference in mortality during hospital stay with IgM-enriched IVIG for suspected infection RR: 0.68, 95% CI 0.39 to 1.20, 4 studies, n= 266). Data on AEs was not reported in all studies and no pooling of results could be done	
Pammi et al 2011 (Cochrane)	Neonates with neutropenia and confirmed or suspected sepsis, on antibiotics, born at any gestational age or birth weight	Granulocyte transfusion – (IVIg comparator)	RCTs and quasi-RCT	1 RCT comparing granulocyte transfusion to intravenous immunoglobulin was identified (Cairo 1992). No info on randomisation in this study	AMSTAR 9/11	Granulocyte transfusion compared with IVIg reduced 'all-cause mortality' (borderline statistical sig.) RR: 0.06, 95% CI: 0.00 to 1.04; NNT 2.7, 95% CI 1.6 to 9.1). Based on 1 RCT, n=35 infants with sepsis and neutropenia	Inconclusive evidence from randomised controlled trials (RCTs) to support or refute the routine use of granulocyte transfusions in neutropenic, septic neonates
Sepsis-septic shock (adults) (3 SR found for which one an update was included Soares et al 2014)							
Alejandria et al 2013 (Cochrane)	Any age with sepsis or septic shock caused by bacteria. Specific analysis for adults	IVIg (standard or IgM-enriched) vs placebo or no intervention	RCTs	10 RCTs on standard polyclonal versus placebo: Burns 1991; Darenberg 2003; De Simone 1988; Dominioni 1991; Grundmann 1988; Just 1986; Lindquist 1981; Masaoka 2000; Werdan 2007; Yakut 1998 6 RCTs on Ig M enriched IVIG: Behre 1995; Hentrich 2006; Karatzas 2002; Rodriguez 2005; Tugrul 2002; Wesoly 1990)	AMSTAR 10/11	Sig. reduction in mortality in adults with IVIg for treating sepsis, severe sepsis and septic shock (RR: 0.81; 95% CI: 0.70 to 0.93; 10 studies, n=1430 for standard IVIg; and RR: 0.66; 95% CI 0.51 to 0.85, 7 studies, n=528 for IgM-enriched IVIG).MA of trials with low RoB showed no reduction in mortality with standard IVIG in adults (RR: 0.97; 95% CI 0.81 to 1.15; 5 trials, n = 94).	Standard (polyclonal) IVIG reduced mortality in adults with sepsis but this benefit was not seen in trials with low RoB.
Busani et al 2016	Adult with sepis or septic shock	IVIg (standard or IgM-	RCTs	9 RCTs on polyclonal IVIG:Burns 1991; Darenberg 2003; De	AMSTAR 6/11	The pooled analysis for standard polyclonal IVIG compared to placebo or no treatment is a significant decrease in	The available evidence is not clearly sufficient to support the widespread

		enriched) vs placebo or no intervention		Simone 1988; Dominioni 1991; Grundmann 1988; Lindquist 1981; Masaoka 2000; Werdan 2007; Yakut 1998 9 RCTs on IgM enriched IVIG: Schedel 1991, Spannbrucker 1897, Behre 1995; Hentrich 2006; Karatzas 2002; Rodriguez 2005; Tugrul 2002; Wesoly 1990) including the more recent Toth, 2013 (n=33 , IgM enriched IVIG compared to placebo)		all-cause mortality (OR=0,45 ,95%CI 0,24-0,87 - n=1736, 9R CTs). The pooled analysis for IgM enriched IVIG compared to placebo or no treatment also showed a significant decrease in all-cause mortality: OR=0,55 (95%CI 0,38-0,81) (n=597, 9RCTs). A sensitivity analysis showed that high quality studies (Jadad score ≥3) also reported a significant decrease but with a high level of heterogeneity (OR=0.51, 95%CI 0,31-0,84, 11 RCTs, n=2025, heterogenicity I^2=58.43). No AE were reported	use of Ig in the treatment of sepsis: reduced mortality but the treatment effect generally tended to be smaller or less consistent if considering only those studies that were deemed adequate on each indicator.
Necrotising soft tissue infections (1 SR found)							
Hua et al 2018 (Cochrane)	18+y hospitalised with a diagnosis of necrotizing soft tissue infections (NSTI) characterised by rapidly spreading inflammation and subsequent necrosis of the muscle, fascia, or subcutaneous tissue	All therapies (including adjuvant IVIg 25g/day for 3 days, vs placebo	RCTs in hospital setting	1 trial of 100 randomised participants assessed IVIG as an adjuvant (Madsen 2017).	AMSTAR 11/11	Non sign. difference between IVIG and placebo in of mortality at 30 days (RR: 1.17, 95% CI 0.42 to 3.23); no serious AEs experienced in ICU (RR: 0.73 CI: 95% 0.32 to 1.65); Serious Aes included acute kidney injury, allergic reactions, aseptic meningitis syndrome, haemolytic anaemia, thrombi, and transmissible agents.	Little evidence on the effects of medical and surgical treatments for NSTI. Cannot draw conclusions regarding the relative effects of any of the interventions on 30-day mortality or serious AEs due to the very low quality of the evidence.
Dengue Shock Syndrome (1 SR found)							
Alejandria et al 2015	Children with dengue	All therapies	RCTs and SR of RCTs	1 RCT (Dimaano EM et al 2007); n=31	AMSTAR 4/11	1 RCT (n=31) comparing standard IV fluids + high dose IVIG vs standard IV	The limited published evidence of low quality

	haemorrhagic fever and dengue shock syndrome		–at least 20 patients (10 per arm)	Filipino children with secondary dengue infection		fluids alone in children with secondary dengue infection). Mortality was not studied. The additiona of IVIg offered non significantly different reductions in mean duration of severe thrombocytopenia (3,1 days with IVIg and 2,1 w/o IVIg, p=0,11), or increases in platelet counts (x10^3/microlitres): 54.9 with Ig vs 48.0 w/o IVIG . No data on AEs. The evidnce was rated as low quality	does not offer any information on the possible clinical impact that IVIg added to standard trearment may have on the risks of shock, pleural effusion, or mortality in children qith 2ary dengue infection
Severe or recurrent clostridium difficile colitis (1 SR found of low quality O Horo et al 2009)							
Atopic dermatitis							
Roekevish et al 2014	Patients with moderate-to-severe AD or non-adequately controlled AD	All therapies	RCTs or open-label extensions of RCTs	3 RCTs (Bemanian et al 2005; Jee Sj et al 2011; Paul D et al 2002)	AMSTAR 6/11	IVIg less efficacious than placebo and cyclosporin A. The weekly rate of any Aes ranged between 0.6% and 2.8%	No clear conclusions could be dradted for mycophenolate, montelukast, IVIG, and systemic glucocorticosteroids because of limited evidence
CADTH rapid review 2017 (dermatology)	All ages-atopic dermatitis	IVIg and SCIg	HTAs, SR, meta-analyses, RCTs, nonrandomized studies	No SR 1 RCT (n=40): Jee (2011):Moderate to severe childhood atopic dermatitis	AMSTAR 4/11	IVIg sig. reduces the disease severity index at 3 months (P<0.05), although results were not sustainable beyond 6 months.	This study suggests that IVIg therapy may clinically improve AD in patients after 3 months of therapy, but the improvement may decline by 6 months after therapy.
Toxic epidermal necrosis/Stevens Johnson Syndrome (10 SR found, of which 4 with low quality)							
Roujeau et al 2011	SJS or TEN in search terms	All therapies	All published series of SJS/TEN that included at least 10 patients, and use the SCORTEN tool to analyse outcome	No RCTs (case series: 439 cases of patients)	AMSTAR 4/11	IVIg was used in 162 patients. Pooled mortality ratio: 0.82 (95%CI: 0.58- 1.12, p=0.23).	The authors concluded that IVIg do not provide any important reduction in the mortality from SJS and TEN

Huang et al 2012	SJS or TEN in search terms	IVIg	RCTs In the absence of RCTs, we included observational studies (controlled and noncontrolled) with at least eight patients	No RCTs (17 studies of which 6 observational studies with control group)	AMSTAR 4/11	For mortality, IVIg vs supportive care or high-dose IVIg vs supportive care shwed no sig. different rates. Adults treated with high-dose IVIg had a sig. lower mortality than those treated with low-dose IVIg (18,9% vs. 50%, respectively; P = 0,022); but multivariate logistic regression model adjustment showd that IVIg dose does not correlate with mortality.	High-dose IVIg showed a trend towards improving mortality but the limited evidence does not support a clinical benefit of IVIg. Randomized controlled trials are necessary
Barron et al 2015;	Adults (or children) whose diagnosis met the established criteria for SJS or TEN as determined by a physician;	IVIg	Studies which include a minimum of five patients.	No RCTs (13 studies, 8 studies included a control group of patients)	AMSTAR 4/11	No sig. standardised mortality rates found: 0.322, 95% CI: 0.766 -0.122; P = 0.155). Sas showed that removal of the 2 studies using the lowest dosages of IVIG produced results suggesting that IVIG has a beneficial impact on the SMR. A large, randomized, placebo- controlled trial with and without the concomitant use of corticosteroids is required to resolve this issue definitively	Although non sig. results were found, a SA excluding the 2 studies with the lowest IVIg dose showed that of the two studies using the lowest doses resulted in IVIg showing a beneficial impact on SMR. A large, RCT with and without the concomitant use of corticosteroids is needed
Ye et al 2016	SJS and TEN	IVIg + corticosteroid	Case-control studies	No RCTs (26 articles studies)	AMSTAR 4/11	IVIg + corticosteroid sig. reduced recovery time (by 1.63 days, 95% CI: 0.83±2.43, P < 0.001), compared to corticosteroids only. Results were more marked in the case of Asian patients, TEN (2.56, 95% CI: 0.35±4.77, P = 0.023) and high-dose IVIG (1.78, 95% CI: 0.42±3.14, P = 0.010). Length of hospital stay reduced by 3.19 days (95% CI: 0.08±6.30, P = 0.045)	IVIg + corticosteroid could reduce recovery time for SJS and TEN. This effect is > in Asian patients. No sig. impact on mortality rates was found
Zimmerman et al 2017	Diagnostic accuracy of SJS/TEN	Systemic Immunomodulating Therapies	All studies with at least 5 participants per study.	No RCTs	AMSTAR 9/11	A MA of 9 studies (non RCTs) comparing IVIG vs supportive care showed no sig. differences in mortality OR: 0.99; 95% CI: 0.64-1.54. Publication bias cannot be ruled out.	Among different proposals, glucocorticosteroids and cyclosporine are the most promising SITs in the treatment of SJS/TEN. Prospective studies of high quality are needed to be able to reduce the

							uncertainty on these findings.
CADTH rapid review 2017 (dermatology)	All ages – SJS and TEN	IVIg and SCIg	HTAs, SR, meta-analyses, RCTs, nonrandomized studies	SR : Zimmermann et al 2017, Huang et al 2016, Ye et al 2016, Barron et al 2015, Huang et al 2012, Del Pozzo-Magana 2011, Roujeau et al 2011 RCTs : no RCTs found	AMSTAR 4/11	Only the SRs already picked in our search were 69avourin and reported on. T see details on their results see above the 69avouring69 SRs	Uncler results found.
Mycoplasma pneumoniae-associated mucocutaneous disease (1 SR found with a low quality Canavan et al 2015)							
Connective tissue diseases (1 SR found with a low quality Dourmishev et al 2018)							
Chronic Urticaria (3 SR found of which 2 with low quality Morgan et al 2008 and Holm et al 2018)							
CADTH rapid review 2017 (dermatology)	All ages-urticaria	IVIg and SCIg	HTAs, SR, meta-analyses, RCTs, nonrandomized studies	No SR and RCTs found	AMSTAR 4/11	No relevant results found	NA
Recurrent miscarriage (9 SR found of which 1 with a low quality Mikinian 2016)							
Ata et al 2011	Women with unexplained primary (without a prior live birth) or secondary (subsequent to a live birth) recurrent miscarriage.	IVIg	RCTs	6 RCTs (n=272): Coulam 1995, German RSA/IVIG 1994, Jablonowska 1999, Perino 1997, Stephenson 1998, Stephenson 2010	AMSTAR 5/11	No sign. clinical benefit when using IVIg. OR for live birth: 0.92, (95% CI: 0.55–1.54), indicating a lack of a treatment effect with IVIG. Subgroup analyses on women with 1ary or those with 2ary RM did not find any sig clinical benefit for IVIg either. Live birth rates did not sig. differ either neither when IVIG was started before (OR, 1.21; 95% CI, 0.58– 2.51), or after conception (OR, 0.71; 95% CI, 0.34–1.47).	No clinical benefits of IVIg in treating RM was found. IVIg administration for treatment of RM is not justified outside the context of properly designed RCTs.
Lia et al 2013	Women undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)	IVIg	All types of studies	3 RCT: Sher et al 1998; Stephenson MD,2000; De Placido 1994 (but 10 studies included in meta-analysis; n=8207)	AMSTAR 6/11	IVIg (vs placebo) offers a sig. higher implantation rate RR: 2.708 (95%CI: 1.302–5.629, based on 4 studies); a sig. higher pregnancy rate RR: 1.475 (95%CI: 1.191–1.825 based on 7 studies); a sig. higher live birth rate RR:1.616 (95%CI: 1.243–2.101 based on 6 studies) and a sig. lower miscarriage rate RR:0.352, (95%CI: 0.168–0.738; based on 6 studies). No separate analysis was	

						carried out for RCTs vs observational or for high quality vs low quality studies.	
Polanski et al 2014	Assisted reproduction techniques in women with elevated NK cell numbers or activity	All therapies	RCTs and uasi or pseudo-randomized trials and observationa l studies	No RCTs on IVIG 2 non randomised observational studies on IVIG use n=129): Winger et al 2011, Moraru et al 2012	AMSTAR 9/11	RR for clinical pregnancy rates: 3.41 (95%CI 1.90–6.11) in favour of IVIg. Live birth rate RR: 3.94 (95% CI 2.01– 7.69) 70avouring IVIg intervention. Heterogeneity was high (I^2 =66%)	Well designed, RCTs using the same Nkcell testing methodology are required to ascertain the actual benefit of using adjuvant therapy treatment for elevated NK cell levels or activity in the context of pregnancy outcome following IVF
Wong 2014	Women with recurrent miscarriages + ≥3 prior miscarriages and/or; no more than one prior live birth and/or; negative evaluations for non-immunologic causes	Immunother apy	RCTs (quasi and crossover excluded)	7 RCTs: Christiansen 1995, Coulam 1995, German RSA/IVIG 1994, Stephenson 1998, Perino 1997, Jablonowska 1999, Christiansen 2002 1 extra trial Cauchi 1991 included in meta-analysis (only 2 patients	AMSTAR 10/11	IVIg did not result in increased odds of live birth as compared to placebo, (Peto OR 0.98, 95% CI 0.61 to 1.58; 8 RCTs; n= 303). The use of ITT did not show sig. differences between IVIg and control groups for subsequent live births: IVIg; OR: 1.18, (95% CI 0.72 to 1.93; 4RCTs, n=279). The possibility of publication bias was considered low.	IVIg do not improve the live birth rate in women with unexplained recurrent miscarriage. They ae expensive and have potential serious AEs
Egerup 2015	Women with recurrent miscarriages	IVIg versus placebo, no intervention, or treatment as usual	RCTs For assessment s of harms: quasi-RCTs and observationa l studies that we identified during our search for randomised clinical trials were included.	11 RCTs overall found (published between 1994-2014): Christiansen 2002 ; Coulam 1995; Christiansen 1995; The German RSA/IVIG Group 1994; Perino 1997; Stephenson, 1998; Jablonowska 1999; Stephenson 2010; Christiansen 2014; Triolo 2003; Mahmoud 2004	AMSTAR 10/11	Non sign. difference in the frequency of no live birth found with IVIg vs placebo or standard treatment RR: 0.92, (95% CI 0.75–1.12, p = 0.42; 11 RCTs, n=531). Subgroup analysis showed that women with 2ary RM may be more likely to obtain a clinical benefit from IVIg RR for no live birth: 0.77, (95%CI 0.58–1.02, p = 0.06; 6 RCTs; n=221). IVIg increases the risk of Aes vs placebo.	The authors conclude that there is insufficient evidence to recommend or refute IVIg for women with RM.
Wang 2016	Women with Primary Recurrent	IVIg	RCTs	11 RCTs: (Christiansen, 2014; Christiansen et al.,	AMSTAR 8/11	Non sig. differences found between IVIg and placebo RR; 1.25, (95% CI 1.00 to 1.56, P = 0.05; 11 RCTs, n=582).	The limited available evidence does not support the use of IVIg on an

	spontaneous abortion ≥2 or more spontaneous abortions, without a history of live birth. Secondary RSA ≥3 spontaneous abortions subsequent to a live birth or stillbirth.			1995, 2002; Coulam et al., 1995; Group, 1994; Jablonowska et al., 1999; Lin and Li, 2015; Liu and Chen, 2010; Perino et al., 1997; Stephenson et al., 1998).		Subgroup analysis showed the live birth rate in 1ary and 2ary RSA patients not to differ sig. between IVIg and placebo (RR: 0.88, 95% CI 0.71 to 1.07 for 1ary, and RR: 1.26, 95% CI 0.99 to 1.61for 2ary). Live birth rate was sig. different when IVIg was administered before conception (RR = 1.67, 95% CI 1.30 to 2.14, P < 0.0001) but not after implantation (RR = 1.10, 95% CI 0.93 to 1.29).	unexplained RSA. Further high quality studies are needed to draw clearer conclusions
Rasmark Roepke 2018	Women with idiopathic RPL, defined as at least three consecutive miscarriages.	All therapies(including comparisons of IVIg vs placebo)	RCTs	Six RCTs : Christiansen OB, 2015;Jablonowska B,1999; Perino A,1997;Stephenson MD 2010;The German RSA/IVIG Group,1994; Nazari Z,2015;	AMSTAR 7/11	IVIg showed no sig. differences on live birth rates compared to placebo or other treatments (i.e.albumin, saline, LMWH+ASA) RR: 1.07, (95% CI 0.91–1.26; 5 RCTs n=273). No detailed reporting or comparison on AEs was offered due to the heterogeneous reporting of these. The evidence was rated as being of low quality by the authors of this SR	Evidence is insufficient to recommend IVIg for idiopathic RPL starting after conception. They suggest that any other treatment for RPL should be used within the context of an RCT.
CADTH Rapid reviews (Recurrent spontaneous abortion)	Patients any age with recurrent spontaneous abortion	IVIg vs placebo , no treatment or standard care	HTAs, SR, meta-analyses, RCTs, nonrandomized studies	2 SR: Wang et al 2016 and Egerup et al 2015 RCTs: Meng, 2016, Christiansen, 2015, Nazari, 2015	AMSTAR 7/11	Contradicting results found: 5 studies (1 SR, 3 RCTs and 1 non randomised study) reported non sig. differences in live birth rates with IVIg versus the controls. 4 studies (1 SR, 1 RCT and 2 non randomised studies) found sig. differences in rates of live births favouring IVIg treatment. No serious AEs were reported (based on 5 studies that reported these data). Some minor AEs were reported when using IVIg vs controls (based on 4 studies)	The authors concluded that the clinical effectiveness of IVIg for RSA remains unclear and that further evidence from high quality studies — particularly those that focus on subgroups of RSA patients — remains necessary to reduce uncertainty.
Alzheimer's Disease							
INESSS 2017	All ages – Alzheimer	IVIG	SR, and RCTs	SR: no SR found RCTs: ClinicalTrials.Gov, 2009, Kile et al., 2017	AMSTAR 10/11	All RCTs (and additional ones) captured in the CADTH. No sig differences found between IVIg and placebo in any of the 2 studies identified (1 RCT of high quality,	IVIg appear not to be effective in the treatment of Alzheimer (based on 1 study of moderate to low quality)

						n=383; and 1RCT of moderate quality, n=50)	
CADTH rapid review 2018 (Neurology)	All ages – Alzheimer	IVIg vs placebo	HTAs, SR, meta-analyses, RCTs, nonrandomized studies	1 SR: INESS 2017 3 RCTs: Dodel R et al 2013, Kile S et al 2017, Relkin NR et al 2017	AMSTAR 7/11	IVIg was not sig. more effective than placebo for any of the outcomes studied for effectiveness (e.g.annualised % change in ventricular volume (APCV); change in cognitive performance measured in different recognised scales; change in activities of daily living). Aes (both serious and mild) were less frequent with IVIg.	The authors concluded that the use of IVIg in Alzheimer's disease, appears to be no more effective than placebo.

3 QUALITY ASSESSMENT

3.1 Systematic Reviews

Each systematic review was classified per indication for which the AMSTAR quality assessment was done. Some systematic reviews cover more than 1 indication, e.g. neurological diseases, and are categorised under the different indications.

The table below is in three parts. The first part is on the SR for the in Belgium reimbursed indications, the second part is on the indications commonly recognised or reimbursed in at least ¾ of the investigated countries (France, England, Canada, Australia) and the third part is on other indications for which SR were published.

SYSTEMATIC REVIEW	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated	SCORE on 11
SR found on Safety												
Amman 2016	NA	Y	Y	Y	Y	Y	Y	Y	Y	N	N	8
Yang et al 2016	Y	Y	Y	N	N	N	Y	N	Y	Y	N	6
Primary immunodeficiency disease (PID)												
Wood 2007 (former KCE report)	N	Y	Y	N	N	N	Y	Y	N	N	N	4
Orange 2010	N	Y	Y	Y	Y	Y	N	NA	Y	N	N	6
Orange 2012	N	N	N	N	N	Y	N	NA	Y	N	N	2
Abolhassani 2012	N	Y	Y	Y	N	Y	Y	N	N	N	N	5
Lingman-Framme 2013	Y	Y	Y	Y	N	Y	Y	Y	NA	N	Y	8
Song 2015	N	Y	Y	Y	N	Y	Y	Y	Y	N	N	7
Shabaninejad 2016	Y	N	Y	Y	N	Y	Y	N	N	N	N	5
Jones 2018	N	N	Y	N	N	Y	N	N	NA	N	N	2
Lymphoproliferative disorders (Multiple Myeloom (MM) & chronic lymphocytic leukemia (CLL) and (Allogenic) stem cell transplantation/ hematopoietic stem cell transplantation												
Raanani 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Shah et al 2016 (virus infections)	Not further analysed because no RCTs found											
Chronisch inflammatoire demyeliniserende polyneuropathie (CIPD)												
Etimov et al 2009(former KCE report)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Gaebel et al 2010	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	9

SYSTEMATIC REVIEW	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated	SCORE on 11
Etimov et al 2013 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Bright et al 2014	N	N	N	N	N	Y	Y	Y	N	N	N	3
Oaklander et al 2017	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	9
Racosta et al 2017 (IVIG-SCIG)	N	N	Y	N	N	Y	Y	N	N	Y	N	4
Sala et al 2018 (SCIG)	Y	Y	Y	N	N	Y	Y	Y	N	N	N	6
Streptokokken toxisch shock syndroom												
Alejandra 2008 (former KCE report)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	9
Alejandra 2013 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Soares 2014 (including cost-effectiveness)	Y	Y	Y	N	Y	Y	Y	N	Y	Y	N	8
Busani et al 2016	N	N	N	N	N	Y	Y	Y	Y	Y	Y	6
Parks et al 2018	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	7
Kawasaki Syndrome												
Oates-Whiteheat 2003 (former KCE report)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	9
Chan 2019	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Patel 2015	N	N	N	N	N	N	N	N	N	N	N	0
Yang 2015	Y	N	Y	N	N	Y	Y	Y	Y	N	N	6
Chen 2012	Y	Y	N	N	N	Y	Y	Y	Y	N	N	6
Multifocal Motor Neuropathy												
van Schaik et al. 2005 (update 2007) (former KCE report)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Umapathi et al 2015 (cochrane)	Not further analysed as IVIG not main intervention											
Racosta et al 2017	N	N	Y	N	N	Y	Y	N	Y	Y	N	4
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Sala et al 2018 (SCIG)	Y	Y	Y	N	N	Y	Y	Y	N	N	N	6
Idiopathic thrombocytopenic purpura												

SYSTEMATIC REVIEW	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated	SCORE on 11
Chen 2008 (former KCE report)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	9
Qin 2010	Y	NA	N	N	N	Y	Y	Y	Y	Y	N	6
Lioger 2018	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	9
Marti-Carvajal et al 2009 (cochrane pregnancy)	not further analysed as not the focus on IVIG, and no studies were found											
Sruamsiri 2015 (HTA)	not further analysed as this was an HTA											
Guillain-Barre Syndrome												
Hughes 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	9
Vitaliti 2015 narrative review	N	Y	N	N	Y	N	N	N	N	N	N	3
Ortiz-Salas et al 2016	N	Y	Y	N	N	Y	Y	Y	Y	Y	N	7
Gadian 2017	N	Y	N	N	N	Y	Y	Y	Y	Y	N	6
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10

SYSTEMATIC REVIEW	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated	SCORE on 11
Myasthenia gravis (including Lambert-Eaton myasthenic syndrome												
Gajdos 2008 (former KCE report)	Y	Y	Y	N	N	Y	Y	N	Y	N	N	6
Gajdos et al 2012 (cochrane)	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	8
Keogh et al 2011 (cochrane) (lambert eaton)	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	7
Ortiz-Salas et al 2016	N	Y	Y	N	N	Y	Y	Y	Y	Y	N	7
CADTH (neurological conditions)	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	7
Gogou et al 2017	N	N	N	N	N	Y	Y	Y	N	N	N	3
Dermatomyositis and Polymyositis												
Choy et al., 2005.(Cochrane)												
Wang 2012	N	Y	N	N	N	Y	Y	N	N	N	N	3
Gordon 2012 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	9
Vermaak et al. 2015	N	N	Y	N	Y	Y	Y	N	Y	N	N	5
Ahn-Tu Hoa 2017	N	N	Y	N	N	Y	N	N	N	N	N	2
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
CADTH Rapid Review 2018 (dermatology)	Y	N	Y	Y	N	Y	N	N	N	N	N	4
CADTH Rapid Review 2018 (auto-immune-inflammatory)	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	8
Solid organ transplant												
Hodson et al 2008(Cochrane) former KCE report	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	9
Wan et al 2018 (kidney)	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	9
CADTH (solid organ transplant)	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	8
Fetomaternal alloimmune thrombocytopenia (FMAIT)												
Rayment et al 2011 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Winkelhorst et al 2017	N	Y	Y	N	N	Y	Y	N	Y	N	N	5
CADTH Rapid Review 2018 (hematology)	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	8
Pemphigus / Pemphigus vulgaris, pemphigus foliculae												
Frew et al 2011 (narrative review mainly based on cochrane Martin et al 2009)	N	N	N	N	N	N	N	N	N	N	N	0
Joly et al 2011 (french)	N	N	Y	N	N	Y	N	N	N	N	N	2

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Zhao 2015	N	N	Y	N	N	Y	Y	N	N	N	N	3
Cholera 2016	N	N	Y	N	N	Y	N	N	N	N	N	2
Atzmony 2015	N	N	Y	Y	N	Y	N	N	Y	N	N	4
CADTH Rapid Review 2018 (dermatology)	Y	N	Y	Y	N	Y	N	N	N	N	N	4
CADTH rapid Review 2018 (autoimmune inflam)	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	8
Erythroblastopenia = Pure red cell aplasia												
no SR found												
post transfusion purpura (trombocytopenia)												
no SR found												

SYSTEMATIC REVIEW	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated	SCORE on 11
Hemolytic disease in newborns (Rh or ABO incompatibility)												
Dodd et al 2012 (antenatal therapy)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Wong et al 2013 (antenatal therapy)	Y	Y	Y	Y	no included studies	NA	NA	NA	not pooled	N	N	
Louis et al 2014	Y	Y	Y	N	NA	Y	Y	Y	Y	Y	Y	9
Cortey et al 2014	NA	N	Y	N	N	Y	NA	NA	Y	Y	Y	5
Zwiers et al 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
CADTH Rapid Review 2018 (hematology)	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	8
Von Willebrand disease												
no SR found												
Multiple Sclerosis												
Gray et al., 2010 (Cochrane)	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	8
Zare-Shahabadi et al 2015	N	N	N	N	N	Y	N	N	N	N	N	1
Tramacere et al 2015 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Olyaeemanesh et al 2016	Y	N	Y	Y	N	Y	N	N	Y	N	N	5
Filippini 2017 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Rosa et al 2018 (postnatal)	not further assessed as there are no RCTs found and a low quality (not really systematic)											
Vitaliti 2015 narrative review	N	Y	N	N	Y	N	N	N	N	N	N	3
CADTH rapid Review 2018 (neurology)	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	7
Epilepsy												
Walker et al, 2013	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	9
Geng et al, 2017 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Zeiler et al 2017	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	8
Gadian 2017	N	Y	N	N	N	Y	Y	Y	Y	Y	N	6
Al Amrani 2017 (narrative review)	N	N	N	N	N	N	N	N	N	N	N	0
Gogou 2017	N	Y	N	N	N	Y	Y	Y	N	N	N	4
CADTH rapid Review 2018 (neurological)	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	7

SYSTEMATIC REVIEW	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated	SCORE on 11
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Encephalitis												
Radja and Cavanna 2013	N	N	N	N	N	Y	N	N	N	N	N	1
Iro 2017 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Gadian 2017	N	Y	N	N	N	Y	Y	Y	Y	Y	N	6
Gogou 2017	N	Y	N	N	N	Y	Y	Y	N	N	N	4
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
CADTH rapid Review 2018(neurological)	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	7
Paraprotein neuropathy												
Storck et al 2015 (IgG and IgA) (cochrane)	not further assessed as there are no RCTs found											
Lunn 2016 (IgM) (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Paraneoplastic neuropathy												
Giometto et al., 2012 (Cochrane)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	10
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
inclusion body myositis												
Rose 2015 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Jones 2016 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Anh-Tu Hoa 2017	N	N	Y	N	N	Y	N	N	N	N	N	2
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
stiff man syndrome												
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Sydenham's Chorea												
Mohammad et al 2015	N	N	Y	N	N	Y	N	N	N	N	N	2
Vitali et al 2015 (narative review)	N	Y	N	N	Y	N	N	N	N	N	N	3
CADTH rapid Review 2018 (autoimmune inflam)	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	8
Systemic Lupus Erythematosus												
Sakhiswary et al. 2014	N	N	Y	N	N	Y	N	N	Y	N	N	3
CADTH rapid Review 2018 (autoimmune inflam)	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	8
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)												

SYSTEMATIC REVIEW	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated	SCORE on 11
Vitali et al 2015 (narative review)	N	Y	N	N	Y	N	N	N	N	N	N	3
Farhood 2016	N	Y	Y	N	N	N	N	N	N	N	N	2
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
CADTH rapid Review 2018 (neurological)	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	7
Postpolio Syndrome												
Samuelsson 2014 (HTA)	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	8
Huang et al 2015	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	8
Koopman et al 2015 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
CADTH rapid Review 2018 (neurological)	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	7
Neuromyelitis optica/Devic's disease												
Vitali et al 2015 (narative review)	N	Y	N	N	Y	N	N	N	N	N	N	3
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
CADTH rapid Review 2018 (neurological)	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	7
carditis (in acute rheumatic fever)												
Cilliers et al 2015 (cochrane)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	10
CADTH rapid Review 2018 (autoimmune inflam)	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	8
myocarditis												
Robinson 2015 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Wegnerer's granulomatosis(autoimmune vasculitis)												
Fortin 2013 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
CADTH rapid Review 2018 (Hematology)												9
Preventing infection (in nephrotic syndrome)												
Wu et al 2012 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Preventing infection in preterm/low birthweight												
Ohlsson et al 2013 (cochrane)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	9
preventing Hepatitis A												
Liu et al 2009 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
infection-sepsis-septic shock (neonate)												
Alomran 2013	Y	N	Y	N	N	N	N	N	N	N	N	2
Alejandria et al 2013 (Cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10

SYSTEMATIC REVIEW	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated	SCORE on 11
Ohlsson et al 2015 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Pammi et al 2011 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	9
Necrotising soft tissue infections												
Hua et al 2018 (Cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Dengue Shock Syndrome												
Alejandria et al 2015	N	N	Y	N	N	Y	Y	Y	N	N	N	4
Severe or recurrent clostridium difficile colitis												
O Horo et al 2009	N	N	N	N	N	Y	N	N	N	N	N	1
atopic dermatitis												
Roekevish et al 2014	N	Y	Y	N	N	Y	Y	Y	Y	N	N	6
CADTH Rapid Review 2017(dermatological)	Y	N	Y	Y	N	Y	N	N	N	N	N	4
Toxic epiderman necrolyse, Stevens Johnson Syndrome												
Roujeau et al 2011	N	Y	N	N	N	Y	N	N	Y	Y	N	4
Del Pozzo Magana 2011 (pediatric)	N	N	Y	N	N	N	N	N	Y	N	N	2
Huang et al 2012	N	Y	Y	N	N	Y	N	N	Y	N	N	4
Barron et al 2015;	N	N	N	N	Y	Y	N	N	Y	Y	N	4
Huang et al 2016	N	Y	N	N	N	Y	N	N	Y	N	N	3
Ye et al 2016	N	Y	N	N	N	Y	N	N	Y	Y	N	4
Schneider et al 2017 - Narrative review	N	N	N	N	N	N	N	N	N	N	N	0
Zimmerman et al 2017 (only online) https://jamanetwork.com/journals/jamadermatology/fullarticle/2612108	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	9
CADTH Rapid Review 2017(dermatological)	Y	N	Y	Y	N	Y	N	N	N	N	N	4
Mycoplasma pneumoniae-associated mucocutaneous disease												
Canavan et al 2015	N	N	Y	N	N	N	N	N	N	N	N	1
Connective tissue diseases												
Dourmishev et al 2018	N	N	N	N	N	N	N	N	N	N	N	0
Chronic urticaria												
Morgan et al 2008,	N	N	N	N	N	N	N	N	N	N	N	0

SYSTEMATIC REVIEW	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated	SCORE on 11
Holm et al 2018	N	N	N	N	N	Y	N	Y	N	N	N	2
CADTH rapid review 2017 (dermatological)	Y	N	Y	Y	N	Y	N	N	N	N	N	4
Recurrent miscarriage												
Ata et al 2011	N	Y	Y	Y	N	Y	N	N	Y	N	N	5
Li et al 2013	Y	Y	Y	N	N	Y	N	N	Y	Y	N	6
Polanski et al 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	9
Wong 2014 (cochrane)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
Egerup 2015	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10
Mekinian 2016	N	N	N	N	N	N	N	N	N	N	N	0
Wang 2016	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	8
Rasmark Roepke 2018	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	7
CADTH Rapid reviews	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	7
Alzheimer's disease												
INESSS 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
CADTH rapid review 2018 (Neurological)	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	7

3.2 Risk of Bias of the RCTs

Risk of Bias – 1ary studies on PID

Bias	Authors' judgement	Support for judgement
Roifman 1987 IVIG 0.2g/kg per month- 0.6g/kg per month		
Random sequence generation (selection bias)	• Unclear risk of bias	Randomized crossover: no further information
Allocation concealment (selection bias)	• Unclear risk of bias	No information.
Blinding of participants and personnel (performance bias)	• Low risk of bias	Double blind, but no further information
Blinding of outcome assessment (detection bias)	• Low risk of bias	Spirometry and radiologist were blinded for the protocol
Incomplete outcome data (attrition bias)	• Low risk of bias	No dropouts.
Selective reporting (reporting bias)	• High risk of bias	For all outcomes a result was given. Hower no statistics
Other bias	• Unclear risk of bias	No washout period between administration of different concentrations, but probably no effect.
Chapel 2000 IVIG-SCIG (crossover)		
Random sequence generation (selection bias)	• Unclear risk of bias	Randomized crossover: no further information
Allocation concealment (selection bias)	• Unclear risk of bias	No info
Blinding of participants and personnel (performance bias)	• Unclear risk of bias	Non blinded
Blinding of outcome assessment (detection bias)	• High risk of bias	No impact on serious infection and through level, but on the preference of treatment this has an impact
Incomplete outcome data (attrition bias)	• Unclear risk of bias	4 dropouts during the SCIg arm, 2 in the IVIg. Only patients completing both arms were in the analysis (22/30)
Selective reporting (reporting bias)	• Low risk of bias	
Other bias	• Unclear risk of bias	No washout period between administration of different concentrations, but probably no effect because for infections were only counted after 30 days after start of treatment
Desai 2009 IVIG-SCIG (crossover, pilot study)		
Random sequence generation (selection bias)	• Unclear risk of bias	Randomized crossover: no further information

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	• Unclear risk of bias	No further info
Blinding of participants and personnel (performance bias)	• Unclear risk of bias	Non blinded
Blinding of outcome assessment (detection bias)	• High risk of bias	No impact on serious infection and through level, but on the preference of treatment this has an impact
Incomplete outcome data (attrition bias)	• Low risk of bias	1 dropout due to pregnancy.
Selective reporting (reporting bias)	• High risk of bias	
Other bias	• Unclear risk of bias	No washout period between administration of different concentrations, but probably no effect because for IgG through level they only calculated the last 3 months of the 6 month period. No information on dosages used 'only stated that the same doses were used'
Wasserman 2017		
Random sequence generation (selection bias)	• Unclear risk of bias	Randomized (1:1) crossover design for the adults (no randomisation for the childeren)
Allocation concealment (selection bias)	• Unclear risk of bias	No information.
Blinding of participants and personnel (performance bias)	• High risk of bias	Open label study, 2 concentrations of the same product with different administration times.
Blinding of outcome assessment (detection bias)	• Unclear risk of bias	Open label study. Although outcomes were based on objective blood values and parameters. The study was sponsored and carried out by the sponsor for whom a higher concentrated product could mean economic profit
Incomplete outcome data (attrition bias)	• Low risk of bias	Bioequivalence analysis: 1 adult dropout of the randomized trial 1 child dropout, For outcomes such as AEs or through levels, intention to treat analysis was used. However they started to include only those patients that received ≥1 infusion (1 dropout during first infusion was not included). Well documented
Selective reporting (reporting bias)	• Low risk of bias	All outcomes stated in method section were reported in results section. 90%CI instead of 95%

Bias	Authors' judgement	Support for judgement
Other bias	• Unclear risk of bias	No washout period between administrations of different concentrations. Only referral to a 21-day or a 28-day infustion schedule. But unclear whether this has an impact.
Bienvenu 2018		
Random sequence generation (selection bias)	• Unclear risk of bias	Randomized (1:1) to pump and then Rapid push or reverse sequence. Crossover. Patients were free to switch from pump to RP withouth being dropped out
Allocation concealment (selection bias)	• Unclear risk of bias	No information.
Blinding of participants and personnel (performance bias)	• High risk of bias	Open label study, because the nurse must educate the patient before administration the patient as well as nurse knows in which group
Blinding of outcome assessment (detection bias)	• High risk of bias	Open label study, primary outcome: impact of administration on QoL. Self-reported by patients
Incomplete outcome data (attrition bias)	• High risk of bias	2 dropouts due to AE in the rapid push arm (after being first treated with pump): for which no information can be given. Excluded from intention-to-treat
Selective reporting (reporting bias)	• Low risk of bias	All outcomes stated in method section were reported in results section
Other bias	• High risk of bias	Patients were free to premedicate with Pain killers, non-steroid anti-inflammatory drugs, or corticosteroids before infusion. This was recorded and reported by patients themselves;

Risk of Bias – 1ary studies on SID

Hematological cancers

Bias	Authors' judgement	Support for judgement
Vacca 2018		
Random sequence generation (selection bias)	• Unclear risk of bias	Random assignment stratified per MM isotype and previous therapy at enrollment, but no information on how the randomisation occured
Allocation concealment (selection bias)	• Unclear risk of bias	No info
Blinding of participants and personnel (performance bias)	• High risk of bias	Not blinded study: IVIg vs no treatment
Blinding of outcome assessment (detection bias)	• High risk of bias	Not blinded study: the primary endpoint infection must be defined by at least 2 criteria. Self-reported fever is one of them
Incomplete outcome data (attrition bias)	• High risk of bias	Not sure whether all outcomes are based on all patients and which study period was taken into consideration. Because after 6 months 3/24 patients in the IVIg arm dropped out based on AEs
Selective reporting (reporting bias)	• Unclear risk of bias	All outcomes stated in method section were reported in results section. However sometimes only p-values
Other bias	• Unclear risk of bias	

hematopoetic stem cell transplantation

Bias	Authors' judgement	Support for judgement
Azik 2016		
Random sequence generation (selection bias)	• Unclear risk of bias	No extra info, except “randomised”
Allocation concealment (selection bias)	• Unclear risk of bias	No info
Blinding of participants and personnel (performance bias)	• Unclear risk of bias	No info
Blinding of outcome assessment (detection bias)	• Low risk of bias	All classifications of infections and other outcomes such as AE were performed in a blinded fashion
Incomplete outcome data (attrition bias)	• Low risk of bias	Primary and other outcomes were reported for all randomized patients. No dropouts
Selective reporting (reporting bias)	• Low risk of bias	All outcomes stated in method section were reported in results section
Other bias	• Unclear risk of bias	

Solid organ transplantation

Bias	Authors' judgement	Support for judgement
Lederer et al 2014 (lung transplant) cross-over		
Random sequence generation (selection bias)	• Unclear risk of bias	Randomly assigned, but no further info
Allocation concealment (selection bias)	• Low risk of bias	The Research Pharmacy at Columbia University randomly assigned the treatment order.
Blinding of participants and personnel (performance bias)	• Low risk of bias	Study drug was prepared by an unblinded research pharmacist and delivered IVIg and placebo infusion bags had identical color and appearance
Blinding of outcome assessment (detection bias)	• Low risk of bias	all infectious events were determined with blinding to the treatment period
Incomplete outcome data (attrition bias)	• Low risk of bias	Eleven subjects were eligible and randomized, and 10 completed all study assessments. One subject discontinued the interventions because of inability to comply with the schedule of study visits. All analyses were done intent-to-treat
Selective reporting (reporting bias)	• Low risk of bias	All outcomes stated in method section were reported in results section, however adverse events not specified,
Other bias	• Low risk of bias	Sample size was calculated: 10 subjects.

Risk of Bias – 1ary studies on CIPD

Bias	Authors' judgement	Support for judgement
Markvardsen 2013		
Random sequence generation (selection bias)	• Low risk of bias	Randomized in blocks of 4 by the hospital pharmacy (30 randomised)
Allocation concealment (selection bias)	• Unclear risk of bias	No information, randomization done in hospital pharmacy
Blinding of participants and personnel (performance bias)	• Low risk of bias	Blinded- uniformly labeled containers of saline (placebo) or SCIG
Blinding of outcome assessment (detection bias)	• Low risk of bias	Neurophysiologists and evaluating physicians were blinded
Incomplete outcome data (attrition bias)	• Low risk of bias	Analysis done on all participants who received a treatment (no drop out during treatment). 1 dropout after randomization but before administration. Analysis done on n=29

Bias	Authors' judgement	Support for judgement
Selective reporting (reporting bias)	• Low risk of bias	All outcomes stated in method section were reported in results section
Other bias	• Unclear risk of bias	
Markvardsen 2017		
Random sequence generation (selection bias)	• Low risk of bias	Randomized 1:1 in blocks of 4 via website
Allocation concealment (selection bias)	• Unclear risk of bias	No info, crossover study
Blinding of participants and personnel (performance bias)	• High risk of bias	Single blinded: patients are aware of the treatment as it are 2 different administration forms including different duration. However they are treatment naïve patient and cannot predict the result.
Blinding of outcome assessment (detection bias)	• Low risk of bias	Evaluator was blinded to the treatment arm
Incomplete outcome data (attrition bias)	• High risk of bias	20 patients randomized but 6 dropouts during period. ITT + per protocol analysis 17 patients being analyzed for SCIG 15 patients for IVIG Patients who underwent accelerated switch or who did not response to IVIG and SCIG were excluded from study analysis
Selective reporting (reporting bias)	• Low risk of bias	All outcomes stated in method section were reported in results section
Other bias	• Unclear risk of bias	Half-life of IG is 3 weeks, hangover effect is possible. Washout period was 5 weeks. SCIG administered at home, IVIG in controlled hospital setting
Van Schaik 2017		
Random sequence generation (selection bias)	• Low risk of bias	Randomized 1:1:1 in blocks of 6, stratified per region (Japan or non-Japan). first a IgG dependency test and select only IgG dependent patients for randomisation
Allocation concealment (selection bias)	• Low risk of bias	Interactive voice and web response system (parexel);
Blinding of participants and personnel (performance bias)	• Low risk of bias	Double blind
Blinding of outcome assessment (detection bias)	• Low risk of bias	2 physician approach: treating physician for contact, AE, patient questions and an assessing physician for efficacy

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias)	• Low risk of bias	Relapse together with Withdrawal from studyprotocol was 1ary endpoint. Therefore dropouts were included in analysis. Analysis are shown separately.
Selective reporting (reporting bias)	• Low risk of bias	All outcomes stated in method section were reported in results section.
Other bias	• Unclear risk of bias	

Risk of Bias – 1ary studies on MULTIFOCAL MOTOR NEUROPATHY

Bias	Authors' judgement	Support for judgement
Hahn et al. 2013		
Random sequence generation (selection bias)	• Low risk of bias	The authors only specify that patients were randomised 1:1
Allocation concealment (selection bias)	• Unclear risk of bias	No clear information provided
Blinding of participants and personnel (performance bias)	• Low risk of bias	Participants were blinded
Blinding of outcome assessment (detection bias)	• Low risk of bias	Outcome assessors were blinded
Incomplete outcome data (attrition bias)	• Low risk of bias	No missing outcome data. All reported
Selective reporting (reporting bias)	• Low risk of bias	All outcomes appear to be reported in the pre-specified way (ITT and PP analyses performed)
Other bias	• Low risk of bias	Other bias unlikely
Harbo et al. 2008		
Random sequence generation (selection bias)	• Low risk of bias	Used block randomization with a block size of four
Allocation concealment (selection bias)	• Low risk of bias	Central (hospital pharmacy) allocation
Blinding of participants and personnel (performance bias)	• Unclear risk of bias	Participants could not be blinded. Main outcome was combined dynamometric strength score expressed relative to normal strength in five to six affected muscle groups at three joints and at hand grip.
Blinding of outcome assessment (detection bias)	• Low risk of bias	Outcome assesors blinded

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias)	• Low risk of bias	No missing outcome data. All reported
Selective reporting (reporting bias)	• Low risk of bias	All outcomes appear to be reported in the pre-specified way (ITT analyses performed)
Other bias	• Low risk of bias	Other bias unlikely
Léger et al. 2018		
Random sequence generation (selection bias)	• Low risk of bias	Participants were randomised 1:1 to two sequence groups, via a centralised interactive web response system. There was no predefined randomisation list.
Allocation concealment (selection bias)	• Low risk of bias	Assignment was done dynamically using the minimisation method of Pocock and Simon to reduce the risk of imbalanced treatment sequence assignment in sites and study. It was de centrally
Blinding of participants and personnel (performance bias)	• Low risk of bias	Participants and staff blinded (masking methods for infusions used).
Blinding of outcome assessment (detection bias)	• Low risk of bias	Assesors blinded
Incomplete outcome data (attrition bias)	• Low risk of bias	One participant withdrew his consent 4 months after treatment initiation, due to dissatisfaction with study treatment. This participant was not excluded from any of the populations for analysis (ITT)
Selective reporting (reporting bias)	• Low risk of bias	All outcomes reported in tabular form
Other bias	• Low risk of bias	Other bias unlikely
Al-Zuhairy et al. 2019		
Random sequence generation (selection bias)	• Low risk of bias	Block randomisation
Allocation concealment (selection bias)	• Low risk of bias	Sequence generated from randomization.com and study nurses at allocated therapy according to the generated list.
Blinding of participants and personnel (performance bias)	• High risk of bias • Unclear risk of bias	For HRQoL – (not blinded) For primary outcome - isometric strength (dynamometer).
Blinding of outcome assessment (detection bias)	• Low risk of bias	Assessors were blinded
Incomplete outcome data (attrition bias)	• Low risk of bias	ITT analysis performed (including 2 patients who left prematurely one of the arms (the tested intervention)

Bias	Authors' judgement	Support for judgement
Selective reporting (reporting bias)	• Low risk of bias	All outcomes (primary and secondary reported in tabular form.
Other bias	• Low risk of bias	Other bias unlikely

Risk of Bias – 1ary studies on STSS

Bias	Authors' judgement	Support for judgement
Darenberg 2003		
Random sequence generation (selection bias)	• Unclear risk of bias	Randomly assigned 1:1
Allocation concealment (selection bias)	• Unclear risk of bias	No info
Blinding of participants and personnel (performance bias)	• Low risk of bias	Double blind, but not details
Blinding of outcome assessment (detection bias)	• Low risk of bias	Double blind, but not details
Incomplete outcome data (attrition bias)	• Low risk of bias	Justification
Selective reporting (reporting bias)	• Low risk of bias	Justification
Other bias	• High risk of bias	Stopped early due to low recruitment

Risk of Bias – 1ary studies on Guillain Barre Syndrome

Bias	Authors' judgement	Support for judgement
Chaudhury et al. 2014		
Random sequence generation (selection bias)	• Low risk of bias	All patients were selected randomly to receive either IVIG or plasmapheresis in 1:1 ratio
Allocation concealment (selection bias)	• Unclear	No information on allocation given
Blinding of participants and personnel (performance bias)	• High risk of bias	Open label study
Blinding of outcome assessment (detection bias)	• High risk of bias	Open label study
Incomplete outcome data (attrition bias)	• Low risk of bias	3 patients died and were excluded from the analysis. 2 in one group 1 in the other. Unlikely to unbalance the groups or have an important weight in the results.

Bias	Authors' judgement	Support for judgement
Selective reporting (reporting bias)	• High risk of bias	For the Hughes grade, the authors mention “No sig. difference in outcome at discharge or at follow up at 30, 60, 180 days and 1 year between both groups”, but the table showing the results does not present the actual results at discharge. Although the main outcome was mentioned to be measured at discharge, reporting was done for 37 patients at 30 days, for 33 patients at 60 days and 180 days and for 29 patients at 1 yr. No specific explanation of lost to follow up mentioned during these different time periods.
Other bias	• Unclear risk of bias	Mean LoS sig different in both groups at baseline. Significantly higher number of days in the plasmapheresis group. However the authors explain that “this difference could be attributed to the hospital working system”.
Maheshwari et al. 2018		
Random sequence generation (selection bias)	• Low risk of bias	Randomised using computer-based graph pad software.gThe treatment plan was decided by computer generated slip showing TPE or IVIG.
Allocation concealment (selection bias)	• Low risk of bias	Result from the computer generated slip was sealed in an opaque envelope and numbered from 1 to 40.
Blinding of participants and personnel (performance bias)	• Unclear risk of bias	Blinding not mentioned but probably not possible due to the nature of the two therapies here analysed. Unclear how much weight the unblinded nature of the study could have on the study outcomes, since both are active tretments
Blinding of outcome assessment (detection bias)	• High risk of bias	No blinding mentioned.
Incomplete outcome data (attrition bias)	• Low risk of bias	All patients analysed throught the study
Selective reporting (reporting bias)	• Low risk of bias	All outcomes analysed as pre-specified
Other bias	• Low risk of bias	Unlikely

Risk of Bias – 1ary studies on ITP

Bias	Authors' judgement	Support for judgement
Koochakzadeh et al. 2018		
Random sequence generation (selection bias)	• Low risk of bias	The balanced-block randomization method in size of 4 was used. The research analysis and statistics (RAS) software was used to produce the random blocks
Allocation concealment (selection bias)	• Low risk of bias	Blocks generated by the computer and vials labelled A and B to impede the administrating nurses to know which one was which
Blinding of participants and personnel (performance bias)	• Low risk of bias	Administrating nurses and patients blinded to the intervention
Blinding of outcome assessment (detection bias)	• Low risk of bias	Double blind RCT
Incomplete outcome data (attrition bias)	• Low risk of bias	1 patient in each group dropped out and the reasons were explained. The groups remained balanced and the drop outs are unlikely to have had a weight in the overall results
Selective reporting (reporting bias)	• Low risk of bias	All outcomes reported as pre specified
Other bias	• Low risk of bias	No other bias identified
Heitink-Pollé et al. 2018		
Random sequence generation (selection bias)	• Low risk of bias	Web-based randomization performed using a computer generated randomization list ensuring concealment and stratified by platelet count at diagnosis.
Allocation concealment (selection bias)	• Low risk of bias	Centralised via website
Blinding of participants and personnel (performance bias)	• Low risk of bias • High risk of bias	For primary outcome (platelet count) – no blinding For one of the 2ary outcomes (HRQoL) – no blinding
Blinding of outcome assessment (detection bias)	• Low risk of bias	No blinding mentioned but primary outcome was platelet count
Incomplete outcome data (attrition bias)	• Low risk of bias	All patients analysed throught the study. No missing information for all randomized ITT analysis performed
Selective reporting (reporting bias)	• Low risk of bias	All outcomes analysed as pre-specified
Other bias	• Low risk of bias	Unlikely
Elalfy et al. 2017		
Random sequence generation (selection bias)	• Unclear risk of bias	No explanation given on the specific randomization method used

Allocation concealment (selection bias)	• Unclear risk of bias	No explanation given on allocation concealment
Blinding of participants and personnel (performance bias)	• Low risk of bias	Open label study but primary outcomes based on specific platelet counts
Blinding of outcome assessment (detection bias)	• Low risk of bias	Open label study but primary outcomes based on specific platelet counts
Incomplete outcome data (attrition bias)	• Low risk of bias	All patients analysed throught the study. No missing information for all randomized, ITT analysis performed
Selective reporting (reporting bias)	• Low risk of bias	All outcomes analysed as pre-specified
Other bias	• Low risk of bias	Unlikely

Risk of Bias – 1ary studies on Myasthenia gravis

Bias	Authors' judgement	Support for judgement
Barth 2011		
Random sequence generation (selection bias)	• Low risk of bias	Randomized in block of 4
Allocation concealment (selection bias)	• High risk of bias	A hematologist (D.B.) conducted the randomization, administered IVIg and PLEX treatments, and provided care for complications of treatments
Blinding of participants and personnel (performance bias)	• low risk of bias	Single blinded study, patients as well as the one who randomized the patients and administerd the treatment was not blinded. Propably no effect on outcome
Blinding of outcome assessment (detection bias)	• Low risk of bias	The evaluater (neurologist) was blinded to the treatment allocation.
Incomplete outcome data (attrition bias)	• Low risk of bias	Intention to treat analysis for primary outcome: n=84 (at day 14) Lost to follow up at day 14 (1 in IVIG and 2 in PLEX); lost to follow up after day 14 (9 in IVIg, and 6 in PLEX)
Selective reporting (reporting bias)	• High risk of bias	Not all outcomes were shown: Secondary outcome: clinical worsening and need for intubation, hospitalization was only reported at day 14 instead of the planned day 60… “Hospitalization or intubation were not required by any of the patients in the study by day 14.”

Bias	Authors' judgement	Support for judgement
		No information on QoL (see follow-up study)
Other bias	• Unclear risk of bias	Funded by a clinician-initiated research grant by Grifols (formerly Talecris Biotherapeutics). However, this specific paper on secondary analyses received no specific funding.
Barnett 2013 (a subset of study population of Barth 2011)		
Random sequence generation (selection bias)	• Low risk of bias	Details of this trial have been published previously➔ randomisation in blocks of 4
Allocation concealment (selection bias)	• High risk of bias	
Blinding of participants and personnel (performance bias)	• High risk of bias	Single blinded study, patients as well as the one who randomized the patients and administerd the treatment was not blinded.
Blinding of outcome assessment (detection bias)	• High risk of bias	A 60-item Self-reported QoL questionnaire
Incomplete outcome data (attrition bias)	• Low risk of bias	No mentioning lost of follow-up. A subset of 62 patients
Selective reporting (reporting bias)	• Low risk of bias	Table 2 Changes in MG-QOL in patients receiving IVIG and PLEX, correlation between QoL items and clinical symptoms was seen in 3 items
Other bias	• Unclear risk of bias	Original study funded by a clinician-initiated research grant by Grifols (formerly Talecris Biotherapeutics). However, this specific paper on secondary analyses received no specific funding.
Alipour-Faz 2017		
Random sequence generation (selection bias)	• Low risk of bias	Randomisation allocation developed with a simple method
Allocation concealment (selection bias)	• Unclear risk of bias	No info
Blinding of participants and personnel (performance bias)	• High risk of bias	All the patients and investigators were aware of the identity of the treatment groups
Blinding of outcome assessment (detection bias)	• High risk of bias	Not blinded, the outcomes reported were not on clinical paramters, but more intermediate outcomes
Incomplete outcome data (attrition bias)	• Low risk of bias	No dropouts were mentioned, all outcomes were reported
Selective reporting (reporting bias)	• Unclear risk of bias	All outcomes stated in method section were reported in results section
Other bias	• High risk of bias	The intervention was not similar in both groups. The patients in the IVIg group also received an antihistaminic and painkiller.

Bias	Authors' judgement	Support for judgement
Gamez 2019		
Random sequence generation (selection bias)	• Low risk of bias	A computer generated list of random numbers was used to allocate the patients to the treatment or placebo group
Allocation concealment (selection bias)	• Low risk of bias	Medications provided by pharmacy in photoportective bags and opaque tubes
Blinding of participants and personnel (performance bias)	• Low risk of bias	Double blind
Blinding of outcome assessment (detection bias)	• Low risk of bias	Double blind
Incomplete outcome data (attrition bias)	• Low risk of bias	No lost-to follow up
Selective reporting (reporting bias)	• Low risk of bias	All outcomes stated in method section were reported in results section
Other bias	• Unclear	Concurrent treatment with immunosuppressants, PE, not allowed
Liu 2010		
Random sequence generation (selection bias)	• High risk of bias	No information on randomisation: “the patients were divided divided into the plasmapheresis group (PP group) and the IVIg group” but the PP group was furter devided in 2 groups
Allocation concealment (selection bias)	• Unclear risk of bias	No information
Blinding of participants and personnel (performance bias)	• High risk of bias	Patients and administers of therapy are aware of the group because 3 different treatments
Blinding of outcome assessment (detection bias)	• Unclear risk of bias	Blinded examiners for the QMG score before and after the entire course of treatment. But not stated for the other outcomes
Incomplete outcome data (attrition bias)	• Unclear risk of bias	No info on dropouts. Presumingly all data of all patients was obtained
Selective reporting (reporting bias)	• Unclear risk of bias	No clear listing of outcomes in methods section. In results more outcomes reported
Other bias	• Unclear risk of bias	Conflict of interest and funding not stated
Zinman 2007		
Random sequence generation (selection bias)	• Low risk of bias	Blocks of four

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	• Unclear risk of bias	Eligible patients screened by neurologist (who remained msked). Hospital pharmacist prepared solutions in opaque bottles
Blinding of participants and personnel (performance bias)	• Low risk of bias	Double blind
Blinding of outcome assessment (detection bias)	• Low risk of bias	Masked neurologist, however AE were recorded via an unmasked neurologist
Incomplete outcome data (attrition bias)	• Low risk of bias	No dropouts during study. 1 dropout before randomisation
Selective reporting (reporting bias)	• Unclear	Protocol not available but the report include all expected outcomes
Other bias	• Unclear	

Risk of Bias – 1ary studies on FNAIT

Bias	Authors' judgement	Support for judgement
Berkowitz 2006 (standard risk pregnancy no sibling with ICH)n=39		
Random sequence generation (selection bias)	• Low risk of bias	Adequate. Sequence generation was undertaken by computer generated random number list balanced by computed blocks. Randomisation was performed at the coordinating centre and communicated to the participating institutions by telephone
Allocation concealment (selection bias)	• Low risk of bias	Treatment assignment was undertaken by study biostatisticians away from the individual centres
Blinding of participants and personnel (performance bias)	• High risk of bias	Clinicians, patients and outcome assessors were not blinded to treatment allocation
Blinding of outcome assessment (detection bias)	• High risk of bias	Clinicians, patients and outcome assessors were not blinded to treatment allocation
Incomplete outcome data (attrition bias)	• Unclear risk of bias	39 women were randomised in this trial (IVIG n=19; prednisolone n=20) The paper reports that there were 19 (of 19) evaluable women in the IVIg arm and 19 (of 20) evaluable women in the IVIg alone arm. No details are provided as to whether the 1 woman not evaluable was lost due to attrition or exclusion from the trial, the final outcome for this 1 women or at what stage she left the trial. It is also unclear whether any of her outcome data was reported in the paper.

Bias	Authors' judgement	Support for judgement
Selective reporting (reporting bias)	• High risk of bias	All outcomes in methods reported in results There were two ICHs in this group, but the trial did not report the treatment arm in which the two ICHs occurred
Other bias	• Unclear	Source of funding: not stated. Two authors (RB,MW) receive Clincial Research Support from IgG America Inc, Linthicum, Maryland, USA
Paridaans et al 2015		
Random sequence generation (selection bias)	• Low risk of bias	Web based - Stratification for center and HPA1
Allocation concealment (selection bias)	• Low risk of bias	Web based randomization service provided by karolinska institute
Blinding of participants and personnel (performance bias)	• High risk of bias	Open label
Blinding of outcome assessment (detection bias)	• Low risk of bias	Open label, outcomes cannot be influenced. Intracranial hemorrhage and mortality and clinical labo (platelet count)
Incomplete outcome data (attrition bias)	• Low risk of bias	Intention to treat (low dose n= 12, standard dose n=11), 1 patient switched from low dose to high dose
Selective reporting (reporting bias)	• Low risk of bias	All outcomes were reported
Other bias	• Unclear risk of bias	Underpowered. Sample size: 212 patients to show non-inferiority of low dose➔ risk of bias for interpretation of outcomes

Risk of Bias – 1ary studies on DERMATOMYOSITIS AND POLYMYOSITIS

Bias	Authors' judgement	Support for judgement
Dalakas 1993		
Random sequence generation (selection bias)	• Low risk of bias	Block randomization with groups balanced for disease severity (based on MRC score)
Allocation concealment (selection bias)	• Low risk of bias	Randomisation was done at the hospital pharmacy and bottle of drug was wrapped in alluminium foil before it went to the patients room. Intraveneus set was covered with opaque bag
Blinding of participants and personnel (performance bias)	• Low risk of bias	Double blind
Blinding of outcome assessment (detection bias)	• Low risk of bias	Double blind
Incomplete outcome data (attrition bias)	• Low risk of bias	No dropouts; only 4/8 patients of the IVIG crossover after 3 months to placebo and 4/7 patients on placebo crossover to IVIG after 3 months
Selective reporting (reporting bias)	• Low risk of bias	Justification
Other bias	• Unclear risk of bias	Other treatments were allowed and differed between the groups. Though no change in the drug therapy during the 3 months. Funded by a grant from governement
Miyasaka 2001		
Random sequence generation (selection bias)	• Unclear risk of bias	No info on which kind of randomisation
Allocation concealment (selection bias)	• Unclear risk of bias	No info
Blinding of participants and personnel (performance bias)	• Low risk of bias	Double blind- Indistinguisable placebo
Blinding of outcome assessment (detection bias)	• Low risk of bias	Double blind
Incomplete outcome data (attrition bias)	• Low risk of bias	1 dropout in IVIG group due to AE in the 6th week ((Last observation carried forward analysis)
Selective reporting (reporting bias)	• Low risk of bias	All outcomes as stated in methods were reported
Other bias	• Unclear risk of bias	Funded by a grant from pharma

Risk of Bias – 1ary studies on IMMUNOBULLOUS DISEASE (PEMPHIGUS)

Bias	Authors' judgement	Support for judgement
Amagai 2017		
Random sequence generation (selection bias)	• Low risk of bias	Randomization code was computer-generated by independent staff members and was not revealed until completion of the study
Allocation concealment (selection bias)	• Low risk of bias	central enrollment system controlled by a dynamic allocation scheme
Blinding of participants and personnel (performance bias)	• Low risk of bias	The bottles of investigational drugs prepared by the independent staff member in charge of preparation were masked and were provided to the staff member in charge of administration
Blinding of outcome assessment (detection bias)	• Unclear risk of bias	Double blind, no specific info who recorded the primary endpoints which is based on the summation of blisters and new erythema on different body parts
Incomplete outcome data (attrition bias)	• Unclear risk of bias	All treated patients in both groups were included in the analyses according to the requirements stated in the protocol? Four patients (placebo, 1; IVIG, 3) were withdrawn before day 15 and 11patients (placebo, 5; IVIG, 6) were withdrawn after day 15
Selective reporting (reporting bias)	• Low risk of bias	All outcomes descibed in methods are reported
Other bias	• Unclear risk of bias	Funding by Nihon Pharmaceutical Co Authors receive consulting and lecture fees from Nihon Pharmaceutical Co.
Amagai 2009		
Random sequence generation (selection bias)	• Unclear risk of bias	No info on randomisation code
Allocation concealment (selection bias)	• Low risk of bias	Central enrollment system to the treatment groups according to a dynamic allocation scheme
Blinding of participants and personnel (performance bias)	• Low risk of bias	Independent staff at each study institution separately prepared and administered the dosing solution,
Blinding of outcome assessment (detection bias)	• Low risk of bias	Double blind, and evaluated efficacy and safety in each patient to maintain blinding
Incomplete outcome data (attrition bias)	• Low risk of bias	Intention to treat: All the enrolled patients including 10 patients (placebo, 5; 200 mg, 3; and 400 mg, 2) who were withdrawn from the

Bias	Authors' judgement	Support for judgement
		study according to the requirements in the protocol were included in the analyses
Selective reporting (reporting bias)	• Low risk of bias	All outcomes descibed in methods are reported. But not for all outcomes analysis between groups was done. Most of the time chenge over time (e.g.gChanges of pemphigus activity score (PAS)
Other bias	• Unclear risk of bias	Funding by Nihon Pharmaceutical Co Authors receive consulting and lecture fees from Nihon Pharmaceutical Co.

Risk of Bias – 1ary studies on SOLID ORGAN TRANSPLANTATION

Bias	Authors' judgement	Support for judgement
Peraldi et al 1996 (renal re-transplant) brief communication		
Random sequence generation (selection bias)	• Unclear risk of bias	Randomized – no further info
Allocation concealment (selection bias)	• Unclear risk of bias	No info
Blinding of participants and personnel (performance bias)	• High risk of bias	Not blinded
Blinding of outcome assessment (detection bias)	• Low risk of bias	Not blinded, outcomes were , objective parameters (microbiology, clinical biology)
Incomplete outcome data (attrition bias)	• Low risk of bias	No details on loss to follow-up. were given additional therapy)
Selective reporting (reporting bias)	• Unclear risk of bias	Studied parameters
Other bias	• Unclear risk of bias	
Casadei et al 2001 (renal transplant)		
Random sequence generation (selection bias)	• Unclear risk of bias	Randomized – no further info
Allocation concealment (selection bias)	• Unclear risk of bias	No info
Blinding of participants and personnel (performance bias)	• High risk of bias	Not blinded
Blinding of outcome assessment (detection bias)	• High risk of bias	Not blinded, outcomes were, tolerability both subjective and objectively measured…

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias)	• High risk of bias	No details. However the outcome graft rejection was analyzed on a total of 11 patients in the IVIG group instead of the 15 randomized (4 patients did not respond and were given additional therapy)
Selective reporting (reporting bias)	• High risk of bias	Outcomes were not predefined listed in methods section: in terms of safety no info on how it was measured: IVIg treatment was tolerated better than OKT3 treatment both subjectively and objectively
Other bias	• Unclear risk of bias	
Jordan et al 2004 (renal transplant)		
Random sequence generation (selection bias)	• Low risk of bias	Randomized 1:1 (98 randomised). The statistical center prepared a center-blocked randomisation plan
Allocation concealment (selection bias)	• Low risk of bias	Called the statistical center who then instructed the pharmacy
Blinding of participants and personnel (performance bias)	• Low risk of bias	The pharmacy prepared blinded material and shipped it per patient
Blinding of outcome assessment (detection bias)	• Unclear risk of bias	Clinical laboratory tests done retrospectively, but for outcome transplantation and graft survivial no info
Incomplete outcome data (attrition bias)	• Low risk of bias	Intention to treat data for mortality, PRA levels and transplantation rate, also per protocol analysis for graft survival, transplantation rate and allograft rejection
Selective reporting (reporting bias)	• Unclear risk of bias	Outcomes were not listed in methods section:
Other bias	• Unclear risk of bias	
Moreso et al 2018 (renal transplant)		
Random sequence generation (selection bias)	• Low risk of bias	Randomized 1:1 central blocked computerised random-generator
Allocation concealment (selection bias)	• Low risk of bias	Computerised random-generator by the hospital pharmacy of 1 hospital
Blinding of participants and personnel (performance bias)	• Low risk of bias	Drugs and placebo were wrapped to assure double blind procedure
Blinding of outcome assessment (detection bias)	• Unclear risk of bias	Outcomes based on serum analysis were centrally determined, other outcomes were not specified
Incomplete outcome data (attrition bias)	• Low risk of bias	25 patients randomized, but 1 dropout in IVIG+RTX + 1 dropout in placebo. All analyses were done per protocol
Selective reporting (reporting bias)	• Low risk of bias	All outcomes stated in method section were reported in results section, however adverse events not specified,

Bias	Authors' judgement	Support for judgement
Other bias	• High risk of bias	Study was stopped before reaching sample size (n=50) due to budget restrictions: underpowered

4 EXPERT CONSULTATION

Experts were consulted for ensuring no important studies had been missed and no important indications had been omitted.

Experts were identified via their publication record or their participation in Belgian or European disease networks. In total 32 experts were contacted and asked to fill in the online survey, of which five filled in the survey, and one other replied via email.

4.1 Online survey

Question 1.

Are there any important indications missing from our selection (see below), for which evidence is available on the effectiveness or safety of Immunoglobulins?

Yes/No. If yes, which indications and once your write the indication add a word field on add references

REIMBURSED IN BELGIUM	***REIMBURSED IN OTHER COUNTRIES*** *in which recent reviews have been completed (i.e. Australia, Canada, England and France)*
Primary Immunodeficiency Disease (PID)	Myasthenia Gravis (MG)
Secondary hypogammaglobulinemia (SID)	Dermatomyositis and Polymyositis
Post-haemopoietic stem cell transplantation (HSCT)	Solid organ transplant
Chronic Inflammatory demyelinating polyradiculoneuropathy (CIDP)	Fetomaternal Thrombocytopenia
Sepsis-Toxic shock-invasive streptococcal group A infection (streptococcal toxic shock syndrome)	Pure red cell aplasia
Kawasaki disease (KD)	Post transfusion purpura/Thrombocytopenia
Multifocal Motor Neuropathy	Pemphigus Vulgaris, Foliculae
Idiopathic thrombocytopenic purpura (ITP)	
Guillain-Barre Syndrome (GB)	

Question 2.

Are there **important studies** (Systematic reviews or RCTs) **missing** for our list of selected indications (see below)?

Yes/no (if yes, for which indication? (click on a list) and then a field asking add references)

REIMBURSED IN BELGIUM	***REIMBURSED IN OTHER COUNTRIES*** *in which recent reviews have been completed (i.e. Australia, Canada, England and France)*
Primary Immunodeficiency Disease (PID) **Systematic reviews**: (*Wood 2007; Orange 2010; Lingmann 2013; Shabaninejad 2016; Jones 2018*) **More recent RCTs:** (*Wasserman 2017; Bienvenue 2018)*	**Myasthenia Gravis (MG)** **Systematic reviews**: *(Gajdos 2012; Keogh 2011; Ortiz-Salas 2016; Cadth 2018)* **More recent RCTs:** *(Gamez 2019; Grifols 2019; Barnett 2013)*
econdary hypogammaglobulinemia (SID) **Systematic reviews**: (*Raanani 2008)* **More recent RCTs:** (*Vacca 2018)*	**Dermatomyositis and Polymyositis** **Systematic reviews**: *(Vermaak 2015)* **More recent RCTs:** (*No recent RCTs identified)*
Post-haemopoietic stem cell transplantation (HSCT) **Systematic reviews**: *(Raanani 2008)* **More recent RCTs:** (*Azik 2016)*	**Solid organ transplant** **Systematic reviews**: *(Hodson 2017; Wan 2018; CADTH 2018)* **More recent RCTs:** (*No recent RCTs identified)*
Chronic Inflammatory demyelinating polyradiculoneuropathy (CIDPN) **Systematic reviews**: *(Etimov 2013; Oaklander 2017)* **More recent RCTs:** *(Markvardsen 2013 & 2017; Van Schaik 2018)*	**Fetomaternal Thrombocytopenia** **Systematic reviews**: (*Rayment 2011; Winkelhorst 2017)* **More recent RCTs:** (*No recent RCTs identified)*

Sepsis-Toxic shock-invasive streptococcal group A infection (streptococcal toxic shock syndrome) **Systematic reviews**: (*Alejandria 2013; Busani 2014; Parks 2018)* **More recent RCTs:** (*No recent RCTs identified)*	**Pure red cell aplasia** **Systematic reviews**: (*No SR found)* **More recent RCTs:** (*No recent RCTs identified)*
Kawasaki disease (KD) **Systematic reviews**: (*Oates-Whitehead 2003; Chen 2012; Chan 2019; yang 2015)* **More recent RCTs:** (*No recent RCTs identified)*	**Post transfusion purpura//Thrombocytopenia** **Systematic reviews**: (*No SR found)* **More recent RCTs:** (*no RCTs identified)*
Multifocal Motor Neuropathy **Systematic reviews**: (*Van Schaik 2005)* **More recent RCTs:** (*Harbo 2009; Hahn 2012; Leger 2018; Al-zhuhairy 2019)*	**Pemphigus Vulgaris, Foliculae** **Systematic reviews**: (*Atzmony 2015; CADTH 2018)* **More recent RCTs:** (*Search ongoing)*
Idiopathic thrombocytopenic purpura (ITP) **Systematic reviews**: (*Lioger 2018; Qin 2010)* **More recent RCTs:** (*Koochakzadeh 2018; Heitink 2018; Elalfy 2017)*	
Guillain-Barre Syndrome (GB) **Systematic reviews**: (*Hughes 2014)* **More recent RCTs:** (*Chaudhuri 2014; Maheshwari 2018)*	

Question 3.

Are there any **indications for which very limited evidence** exists but that remain in your view interesting for Ig use?

Offer first a Yes/No answer. Then if yes add word field that asks, "which indications" and then for each of them ask based on what? And add a list of possible answers such as: limited cases/case series, but all/most positive (give option to add some references); expert consensus; no other therapeutic option for patients and very rare disease, other…

Question 4.

Are there any **ongoing RCTs or large/important observational studies** in any indication looking at Immunoglobulins that you are aware of?

Yes/No. If yes, word field "please give references".

5 ECONOMIC EVALUATION

5.1 Template table for data extraction – Economic evaluations

Table 1 – Data Extraction Template for Economic Evaluations

1	Title
2	Reference (including all authors)
3	Conflict of interest and/or study funding
4	Country
5	Study question – clear and complete including statement of problem
6	Need for modelling – justified
7	Type of analysis (analytic technique)
8	Specific model design –complete description
9	Population – full description
10	Intervention
11	Comparator
12	Time horizon – appropriate and justified
13	Discount rate – inclusion and justification of rates used
14	Perspective
15	Costs
	• Cost items included
	• Measurement of resource use
	• Valuation of resource use
	• Data sources and references
	• Currency and cost year
16	Outcomes

	• Endpoints taken into account and/or health states
	• Valuation of health states
	• Treatment effect and Extrapolation
	• Utility assessment (Quality of Life)
	• Data sources for outcomes and references –values used in base case scenario and justification
17	Uncertainty
	• Scenario analysis
	• Sensitivity analysis – univariate and or multidimensional – ranges of values used and justification
18	Assumptions and discussion regarding their impact on the results
19	Results
	• Cost-effectiveness and/or cost-utility (base case)
	• Scenario analysis
	• Sensitivity analysis
20	Conclusions and applicability
21	Remarks – ongoing research which could affect results

5.2 Data extraction tables – Economic evaluations

Table 2 – Data Extraction for Economic Evaluations

1	***Title: Economic evaluation of immunoglobulin replacement in patients with primary antibody deficiencies***
2	***Ref: Beauté, J. Levy, P. Millet, V et al. 2010 Clinical and Experimental Immunology 160: 240–245***
3	COI: No COI, Financed by the French MoH
4	Country: France
5	Question: To determine whether SCIG is cost-effective compared with IVIG from a French social insurance perspective
6	Need for modelling: Simple theoretical model looking at costs.
7	Type of analysis: Cost minimisation analysis
8	Modelling technique: Theoretical model, in which costs are first, calculated through a simulation testing different hypothesis on costs drivers. Then costs were estimated on the basis of field data collected by a questionnaire completed by a population of patients suffering PID
9	Population: Patients with congenital agammaglobulinaemia (Bruton's disease or autosomal recessive agammaglobulinaemia) or hyper-IgM syndrome. All patients having an IgG level below 2 g/l at the time of diagnosis. No age limit.
10	Intervention: IVIg
11	Comparator: SCIg
12	Time horizon: Ig replacement is assumed to be constant over time with a continuous effect, so time frame limited to one year
13	Discount rate: No discount rate used given the limited time horizon
14	Perspective: French Social Insurance
15	Costs
	Costs included: Out-patient treatment, hospitalisation, transportation; nursing costs and costs of supplies (eg pumps)
	• Micro costing based on literature and recommended doses. Field data used in the second part to see the differences with the theoretical model
	• Reimbursement costs for medication and services, national statistics for productivity costs and surveys
	• 2008€
16	Outcomes: literature review showing equivalence in efficacy, so focus purely on costs
	• Endpoints taken into account and/or health states: NA
	• Valuation of health states: NA
	• Treatment effect and Extrapolation: NA
	• Utility assessment (Quality of Life); NA

	• Data sources for outcomes and references –values used in base case scenario and justification: Clinical trials referenced showing no sig. differences between IVIg and SCIg
17	Uncertainty
	• Scenario analysis: NA
	• Sensitivity analysis – univariate and or multidimensional – ranges of values used and justification: univariate, checking the weight of material, transportation, period and nurse care. Results are highly sensitive to the N. of pumps required for SCIg
18	The N. of pumps had an important weight on results. Similarly, the field results were different with higher doses (and therefore costs) for IVIg
19	Results
	• Annual costs: €19 484 (home IVIg); €25 583 (hospital IVIg); €24 952 (home SCIg). Estimations from field data differed, with sig. higher costs for IVIg due to higher IVIg doses prescribed
	• Scenario analysis: NA
	Conclusions: While the theoretical model showed very little difference between SCIG and hospital-based IVIG costs, SCIG appears to be 25% less expensive with field data because of lower doses used in SCIG patients. The reality of the dose difference between both routes of administration needs to be confirmed by further and more specific studies.
20	Remarks – NA
1	***Title: Cost-utility of Intravenous Immunoglobulin (IVIG) compared with corticosteroids for the treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in Canada***
2	***Ref: Blackhouse, G. Gaebel, K. Xie, F. et al. Cost Effectiveness and Resource Allocation 2010, 8:14***
3	COI: One author received some funding from industry. The study was funded by the CADTH
4	Country: Canada
5	Question: to evaluate, from a Canadian perspective, the cost-effectiveness of IVIG compared to corticosteroid treatment of CIDP
6	Need for modelling: Markov model to estimate incremental costs and QALYs over 5 years.
7	Type of analysis: Cost utility analysis
8	Model: Markov model looking at 5 years in the life of CIDP patients. Model with 10 health states and cycles of 12 weeks.
9	Population: Patients with CIDP assumed to be 54 years of age and weighing 75 kg
10	Intervention: IVIg
11	Comparator: Corticosteroids
12	Time horizon: 5 years
13	Discount rate: 5% for both costs and outcomes as recommended in Canadian guidelines

14	Perspective: Canadian public health care system
15	Costs
	Costs included: Costs of IVIg infusion, costs of cortocosteroids, AEs
	• Micro costing based on literature and recommended doses and reimbursement charges and official costs/tariffs.
	• Sources: Canadian Blood Services, formularies and reimbursement rates. Nursing costs from national salary stats
	• 2008 CAN$
16	Outcomes: literature review
	• Endpoints taken into account and/or health states: IVIg responders and IVIG non repondents. The non respondents move to corticosteroids and there there are patients on corticosteroids with no AEs and patients on corticosteoirds with AEs (diabetes, glaucoma, cataract, infection or fracture), with the last helth state being death.
	• Valuation of health states: via the literature
	Extapolation: Treatment effect and Extrapolation: cumulative relapse rate from the 25 week ICE study was extrapolated in the model by applying a constant relapse rate of 6.5% to patients in the IVIG responder health state in each cycle throughout the model time horizon.
	Utility assessment (Quality of Life); ut. Derived from IVIg treatment versus corticosteroids assumed to be 0.12, based on findings from McCrone *et al.* Other utilities from published CE models
	• Effectiveness from published lit.
17	Uncertainty
	• Scenario analysis: NA
	• Sensitivity analysis – Probabilistic SA , expressed as CEACs, based upon Monte Carlo simulations
18	< 1% for IVIg at WTP of CAN$50,000. Results sensitive to frequency and dosing of maintenance IVIG.
19	Results
	• $687,287/QALY
	• Scenario analysis: NA
	Conclusions: Based on commonly quoted WTP thresholds, IVIg for CIDP is unlikely to be considered CE. Results varied according to the frequency and dose of IVIg administration
20	Remarks – NA
1	***Title: Canadian cost-utility analysis of intravenous immunoglobulin for acute childhood idiopathic thrombocytopenia Purpura***
2	Ref: Blackhouse, G. Xie, F. Levine M et al. 2012; Popul Ther Clin Pharmacol Vol 19(2):e166-e178;
3	COI: None. Study by the Canadian CADTH

4	Country: Canada
5	Question: to evaluate, from a Canadian perspective, the cost-effectiveness of intravenous immunoglobulin (IVIG) compared to alternative inpatient treatments for acute childhood idiopathic thrombocytopenic purpura (ITP).
6	Need for modelling: Markov model to estimate incremental costs and QALYs over a life time.
7	Type of analysis: Cost utility analysis
8	Model: Markov model with a lifelong time horizon with 6 health states and 1-yr cycles
9	Population: hospitalized children with ITP and a platelet count <20,000/µL. The model cohort was assumed to be 6 year olds weighing 20kg.
10	Intervention: 1) observation (no treatment); 2) IVIG (single dose 0.8 g/kg); 3) Anti-D (single dose 75 mcg/kg); 4) prednisone (4 mg/kg per day for 4 days); and 5) IV methylprednisolone (30 mg/kg for 3 days).
11	Comparator: NA
12	Time horizon: lifelong
13	Discount rate: 5% for both costs and outcomes as recommended in Canadian guidelines
14	Perspective: Canadian public health care system
15	Costs
	Costs included: Drug costs; hospitalisation costs for ITP; hospitalisation and management costs for intracraneal hemorrague (ICH)
	• Micro costing based on literature and recommended doses and Canadian public costing sources
	• Sources: Canadian Formularies, Ontario Case Costing Project and other Canadian public sources
	• 2008-2009 CAN$
16	Outcomes: literature review, ICH but no references reported on that as such. Instead a surrogate endpoint (low platelet counts was used and the risk for ICH increased every day a paitent spent with low platelet counts. Outcome data mainly from 1 SR: Chen et al. 2008
	• Endpoints taken into account and/or health states: Hospitalised with ITP, ICH or no ICH, immediate death after ICH or alive and death.
	• Valuation of health states: via the literature
	Extapolation: Outcomes from Chet et al. 2008. Not on ICH but on an intermediate outcome (low platelet counts) used in al the RCTs. Extrapolation methods unclear.
	Utility assessment (Quality of Life); Age specific utility values used in the long-term phase of the model were based on a study that estimated utility values in the U.K. general population.29 The post-ICH utility weight was based on the mean utility for major stroke reported in a study by Shin et al.
	• Effectiveness from published lit. (SR: Chen et al. 2008)
17	Uncertainty

	• Scenario analysis: NA
	• Sensitivity analysis – Probabilistic SA , and one way SA
18	Highest prob. of being CE: Prednisone at WTP<CAN $112,000/QALY; IVIG at WTP>Can$112,000. Results sensitive to patient's weight. If patient weight <10kg, IVIG dominates; if weight =30kg, ICER of IVIG=$163,708.
19	Results
	• $53,846/QALY
	• Scenario analysis: NA
	Conclusions: IVIG is cost-effective for the treatment of children with ITP
20	Remarks – NA
1	***Title: Kiovig for primary immunodeficiency: Reduced infusion and decreased costs per infusion***
2	Ref: Connolly, M. Simoens, S. 2011; International Immunopharmacology 11:1358–1361
3	COI: Authors report no COI. Financial support received from Baxter Healthcare.
4	Country: Belgium
5	Question: to conduct an economic evaluation which compares the intravenous immunoglobulin (IVIg) preparations Kiovig, Multigam, and Sandoglobulin from the Belgian societal perspective
6	Need for modelling: Decision-analytic model constructed to compare the cost per infusion of the three brands
7	Type of analysis: Cost minimisation analysis
8	Model: Decision analytic model. The costs of a single infusion calculated in the economic model with the ability to extrapolate findings to multiple infusion cycles.
9	Population: Based on the population of a Dutch study composed of adult patients who received in-hospital replacement therapy with a 6% IV Ig lyophilized solution for min 6 months and were switched to 10% Kiovig. Patients had a median age of 53.5 years (range: 23–80 years). 12 diagnosed with common variable immunodeficiency, 1 patient with X-linked agammaglobulinemia and 1 with dysgammaglobulinemia. Our analysis assumed that the patient population treated in the Dutch study was similar to patients treated in Belgium.
10	Intervention: Kiovig
11	Comparator: The two leading 5% intravenous Ig products in Belgium at the time of the study: Multigam and Sandoglobulin
12	Time horizon: The authors justify the short time frame (one infusion) by reporting that there are no difference in outcomes or costs over time of repeated infusions; and that therefore, it was considered appropriate to focus on the costs of one IV Ig infusion.
13	Discount rate: NA given the short time frame of the study
14	Perspective: Societal
15	Costs

	Costs included: IG costs, pharmacy administration, nursing costs, hospital infusion costs, costs of AEs, and productivity costs
	• Micro costing based on recommended doses in Belgium and Belgian public costing sources
	• Sources: Belgian public sources and administration costs
	2009€
16	Outcomes: Three clinical studies have observed no differences in the outcome measures of incidence of infections and antimicrobial use between the three different brands. The focus was on infusion times and maximum infusion rates, as well as rate and duration of AEs. Data was extracted from the Dutch study in a stable population of PID patients
	• Endpoints taken into account and/or health states: NA
	• Valuation of health states: NA
	Extapolation: No extrapolation performed.Analysis only for one single infusion.
	Utility assessment (Quality of Life): NA
	• Effectiveness from published lit. (from 3 clinical studies)
17	Uncertainty
	• Scenario analysis: NA
	• Sensitivity analysis – Probabilistic SA
18	Results dependent on the time of infusion, which was taken from a very small Dutch study (n=14).
19	Results
	Incremental costs: with Multigam: €56 and with Sandoglobulin: €101 (vs Kiovig)
	• Scenario analysis: NA
	Conclusions: Mean cost/ infusion cycle lower with Kiovig vs other IVIg brands
20	Remarks – NA
1	***Title: COST-MINIMIZATION ANALYSIS COMPARING INTRAVENOUS IMMUNOGLOBULIN WITH PLASMA EXCHANGE IN THE MANAGEMENT OF PATIENTS WITH MYASTHENIA GRAVIS***
2	Ref: FURLAN, J C. BARTH, D. BARNETT, C. BRIL, V. 2016; Muscle Nerve 53: 872–876.
3	COI: No info on CoI provided.
4	Country: Canada
5	Question: To compare IVIg with PLEX for treatment of patients with MG exacerbation.
6	Need for modelling: No modelling performed

7	Type of analysis: Cost-minimization analysis
8	Analysis: Limited to cost -comparison (CMA). Mann–Whitney U-tests and Fisher exact tests used for comparisons between the 2 groups
9	Population: Adults with moderate to severe MG, requiring a change in treatment
10	Intervention: IVIg
11	Comparator: Plasma Exchange
12	Time horizon: Unclear - probably whole treatment period
13	Discount rate: NA
14	Perspective: Public healthcare payer and tertiary university hospital perspectives
15	Costs
	Costs included: Hospital costs, physician fees and cost of blood products
	• Expenses and data from small RCT (n= 81). Physician fees from the Ontario Health Insurance and official prices
	• Sources: Hospital expenses/patient (from RCT). Physician fees from the Ontario Health Insurance and official prices
	Costing year and currency: 2014 CAN$
16	Outcomes: Equivalent effectiveness based on results from RCT (Barth et al.2011)
	• Endpoints taken into account and/or health states: NA
	• Valuation of health states: NA
	Extrapolation: No extrapolation performed. Analysis for treatment period based on RCT data.
	Utility assessment (Quality of Life): NA
	• Effectiveness (equivalence) from RCT (Barth et al.2011)
17	Uncertainty
	• Scenario analysis: NA
	Sensitivity analysis – SA comparing costs for both treatment groups based on BMIs for individuals of similar height to those in this cohort
18	Limitations/ sensitivity of results: Equivalence in AEs unclear. Specific characteristics of patients may affect the generalisability. Cost for 11 patients missing. Costs of IVIg dependant on dose.
19	Results
	Incremental costs: CAN$2039
	• Scenario analysis: NA
	Conclusions: The CMA favoured PE as a short-term cheaper alternative compared with IVIg from a public payer perspective.

20	Remarks – NA
1	***Title: Plasma Exchange vs. Intravenous Immunoglobulin for Myasthenia Gravis Crisis: An Acute Hospital Cost Comparison Study***
2	Ref: Heatwole, Ch. Johnson, N. Holloway, R. and Noyes, K. 2011; Clin Neuromuscul Dis. 2011 December ; 13(2): 85–94
3	COI: No CoI mentioned. Funding mentioned in the acknowledgments and none from the industry
4	Country: Netherlands
5	Question: To compare the short term financial costs of treating a patient in myasthenia gravis crisis (MGC) with IVIG versus PLEX.
6	Need for modelling: Decision tree
7	Type of analysis: Cost-minimization analysis
8	Analysis: Itemised comparative decision tree looking at short time costs and consequences of IVIg vs PE.
9	Population: myasthenia gravis crisis population
10	Intervention: IVIg
11	Comparator: Plasma Exchange
12	Time horizon: Short term
13	Discount rate: NA
14	Perspective: Healthcare system
15	Costs
	Costs included: Cost of therapy; hospitalization; AEs. Ambulance costs, standard initial chest X-rays and lab tests not included
	Costing methods: Prevalence and cost data were assigned to each outcome arm based on best available literature
	• Sources: Local cost, accounting data and a literature review
	Costing year and currency: USA$. Costing year not mentioned.
16	Outcomes: Literature showing non sig differences and lit also reporting AEs from each therapeutic alternative.
	• Endpoints taken into account and/or health states: Consequences of each therapy considered
	• Valuation of health states: NA
	Extrapolation: No extrapolation performed.
	Utility assessment (Quality of Life): NA
	• Effectiveness (equivalence) from literature
17	Uncertainty

	• Scenario analysis: NA
	Sensitivity analysis – Deterministic SA performed to assess different values for cost items for which evidence was uncertain
18	Limitations/ sensitivity of results: Based on historical data. Standard of care may vary from one clinician to another. Costs of come AEs (eg stroke) uncertain. Assumption: patients would suffer from one AEs or none.
19	Results
	Incremental costs: $22,326 PE vs IVIg
	• Scenario analysis: NA
	Conclusions: IVIG for MGC may be a short term cost minimising therapy compared to PLEX. Additional prospective studies are required to confirm these results
20	Remarks – NA
1	***Title: Subcutaneous vs intravenous administration of immunoglobulin in chronic inflammatory demyelinating polyneuropathy: an Italian cost-minimization analysis***
2	Ref: Lazzaro, C. Lopiano, L. Cocito, D. 2014; Neurol Sci (2014) 35:1023–1034
3	COI: Authors state no COIs but the study was funded by CSL Behring
4	Country: Italy
5	Question: To compare costs of SCIG vs IVIG for CIDP patients in Italy.
6	Need for modelling: Model to calculate costs over 1 year.
7	Type of analysis: Cost-minimization analysis
8	Analysis: 1-year model based CMA. A stat. distribution given to each parameter and a reasonable coefficient of variation applied to the base case
9	Population: Patients with CIDP
10	Intervention: IVIg
11	Comparator: SCIg
12	Time horizon: 1-year
13	Discount rate: NA
14	Perspective: Societal
15	Costs
	Costs included: IG, drugs and management of AEs, staff time, pump, disposables. Transport, losses of working and leisure time (patients and caregivers)
	Costing methods: Micro costing methods by which health care and non-health care resources were identified and quantified based on neurologists' opinion and research hypotheses

	• Sources: Public sources and expert opinion
	Costing year and currency: 2013€
16	Outcomes: Literature showing non sig differences for IV and SCIg
	• Endpoints NA
	• Valuation of health states: NA
	Extrapolation: No extrapolation performed.
	Utility assessment (Quality of Life): NA
	• Effectiveness (equivalence) from literature. Two sources from the same author, (one of the authors of this article) mentioned for the equivalence of IV and SC Ig: Cocito 2011 & 2012
17	Uncertainty
	Scenario analysis: Scenario analysis performed to assess the impact of shifting the costs of self- infusion pump and disposables for SCIG from pharmaceuticals to hospital or patient and their family budget
	Sensitivity analysis – One way SA carried out and results expressed in a tornado diagram.
18	Limitations/ sensitivity of results: Model based mainly on experts' opinion. Experts consulted, worked all at the same department. Generalisability? Results highly sensitive to the cost of Ig (per gr)
19	Results
	Incremental costs: €1361 IVIg vs SCIg
	Scenario analysis: the overall saving in favour of SCIG would not change event if costs for self-infusion pump and disposables were borne by hospital or patient and their family instead of pharmaceuticals producing SCIG.
	Conclusions: Home based SCIg appears to offer savings compared to IVIg, mainly driven by the lower need for informal care and the reduced time loses for SC Ig administration
20	Remarks – NA
1	***Title: Subcutaneous gammaglobulin in common variable immunodeficiency. First experience in Spain***
2	Ref: Maroto Hernando, M. Soler Palacın, P. Martın Nalda, A. et al. 2009; An Pediatr (Barc).;70(2):111–119
3	COI: No declaration of conflicts of interest or funding reported
4	Country: Spain
5	Question: To investigate the efficacy, safety, related quality of life and cost effectiveness of SCIg in our area
6	Need for modelling: NA

7	Type of analysis: Cost-consequences analysis
8	Analysis: Comparison of annual cost during the last year on IVIg and the 1st and following years with SCIg. Comparison of infection rates and proportion of systemic and local AEs linked to the treatment via the non-parametric t test of Wilcoxon.
9	Population: Children diagnosed with common variable immunodeficiency (n=11)
10	Intervention: SCIg
11	Comparator: IVIg
12	Time horizon: 1-year
13	Discount rate: NA
14	Perspective: Societal
15	Costs
	Costs included: Medication, pumps, infusion kit, other medical costs, training and infusion times/visits (patients and family carers), transportation
	Costing methods: Costing and outcomes captured during the study
	• Sources: Data captured for every patient during the study
	Costing year and currency: 2006-2008€
16	Outcomes: Capture per individual during the study (retrospective observational). All AES and infections registered per patients.
	• Endpoints Number, type and severity of infections; AEs
	• Valuation of health states: NA
	Extrapolation: No extrapolation performed.
	Utility assessment (Quality of Life): 2 interviews performed to assess acceptability and impact on QoL
	• Effectiveness (equivalence) from study.
17	Uncertainty
	Scenario analysis: NA
	Sensitivity analysis – NA
18	Limitations/ sensitivity of results: Study based on few patients (only 11). Exploratory nature. Larger studies would be needed before generalisation is advised
19	Results
	Incremental costs: €1921 (1st year); €4030 (following years) IV vs SCIg; Incremental outcomes: IV: 21 infectious episodes (7/11 patients at 2,74 infections/patient/yr); SCIg: 17 episodes (8/11 paitents at 2,22/infections/patient/yr)
	Scenario analysis: NA

	Conclusions: SCIg is a safe and cost-effective alternative to IVIg for replacement therapy of 1ary antibody deficiencies
20	Remarks – NA
1	***Title: Economic benefits of subcutaneous rapid push versus intravenous immunoglobulin infusion therapy in adult patients with primary immune deficiency***
2	Ref: A. Martin, A. Lavoie, L. Goetghebeur, M. and Schellenberg1, R.
3	COI: Authors state no COIs, but the study received funding from CSL Behring
4	Country: Canada
5	Question: To evaluate the economic benefits of Ig replacement therapy achieved subcutaneously (SCIG) by the rapid push method compared to IV infusion therapy (IVIG) in PID patients from the healthcare system perspective
6	Need for modelling: Treatment pathway model looking at costing differences over 3 years
7	Type of analysis: Cost-minimisation analysis
8	Analysis: CMA over a 3-year period comparing mean costs
9	Population: Adult patients with PID
10	Intervention: SCIg by rapid push
11	Comparator: IVIg
12	Time horizon: 3-years
13	Discount rate: Not mentioned
14	Perspective: Healthcare system
15	Costs
	Costs included: Supplies and personnel costs. Ig costs were not considered since thought to be equivalent for IVIg and SCIg
	Costing methods: Treatment pathway for the base case models comparing rapid push SCIG and IVIG treatment in primary immune deficiency (PID) based on current practice at the adult SCIG home infusion program, St Paul's Hospital, Vancouver
	• Sources: Hospital's SCIg home infusion program
	Costing year and currency: 2011 CAN$
16	Outcomes: Equivalent effectiveness reported, based primarily on Chapel et al. 2000
	• Endpoints: NA
	• Valuation of health states: NA
	Extrapolation: No extrapolation performed.

	Utility assessment (Quality of Life): NA
	• Effectiveness: No effectiveness considered since assumed to be equivalent for SCIg and IVIg (Chapel et al. 2000 quoted as the main source)
17	Uncertainty
	Scenario analysis: NA
	Sensitivity analysis – One way SA performed
18	Limitations/ sensitivity of results: Only valid for rapid push (pump not required). The study did not consider costs borne by patients. The study did not consider 2ary immune deficiencies. Results sensitive to the N. of visits during IVIg treatment. Results also sensitive to the duration of IVIg infusion during each visit.
19	Results
	Incremental costs: CAN$5736 IVIg vs SCIg
	Scenario analysis: NA
	Conclusions: From a health systems's perspective, rapid push home-based SCIg is less costly than hospital-based IVIg in adult PID patients
20	Remarks – NA
1	***Title: Cost-utility analysis of intravenous immunoglobulin and prednisolone for chronic inflammatory demyelinating polyradiculoneuropathy***
2	Ref: McCrone P, Chisholm D, Knapp M, et al. Cost-utility analysis of intravenous immunoglobulin and prednisolone for chronic inflammatory demyelinating polyradiculoneuropathy. European Journal of Neurology 2003; 10(6): 687-694
3	COI: Funded by Novartis and the GBS Support Group
4	Country: 9 EU countries incl. BE
5	Question: To compare two 6-week treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): prednisolone (PRE) and IVIg.
6	Need for modelling: NA. RCT
7	Type of analysis: Cost-utility analysis
8	Analysis: Prospective, double-blind, crossover, RCT carried out in nine European centres (the UK, Belgium, Italy, Spain, the Netherlands, Greece and the Czech Republic). The first treatment period lasted 6 weeks, followed by a 4-week washout period, after which the second 6-week treatment period with the other intervention began. For the cost utility evaluation only data from the baseline and first treatment periods were used.
9	Population: adult patients with a clinical diagnosis of CIDP; progressive or relapsing motor and sensory dysfunction of more than one limb over more than 2 months caused by neuropathy; reduced or absent tendon reflexes; less than 10 white cells/microL in the cerebrospinal fluid; fulfilment of neurophysiological criteria for CIDP; significant physical disability in upper or lower limb function; and a stable or worsening clinical condition.
10	Intervention: IVIg
11	Comparator: Prednisolone
12	Time horizon: 6 weeks
13	Discount rate: NA

14	Perspective: Healthcare system (presented as societal but no productivity or indirect costs considered
15	Costs
	Costs included: Inpatient stay (including intensive care, acute and rehabilitation wards), outpatient visits (neurology and others), attendance at day hospitals, drugs, other workers, and informal care (provided by family and friends).
	Costing methods: Micro costing based on resource use from the sample of patients included in the effectiveness study
	Sources: derived from a UK source (the Personal Social Service Research Unit). The cost of informal care was based on the unit cost of a home care worker
	Costing year and currency: 2000/2001€
16	Outcomes: QALYs. These were obtained from the QoL obtained in the clinical trial.
	Endpoints: Changes in disability scores and QoL. Disability scores were assessed using an 11-point scale. QoL was examined using the EuroQol EQ-5D instrument. Only those patients who completed the treatment were considered (n=25)
	Valuation of health states: NA.
	Extrapolation: NA. Short term horizon of 6 weeks.
	Utility assessment (Quality of Life): No published studies found for the ut. of patients with relapsed or refractory ITP; A value of 0.76 was used, based on the mean of the ut. for thrombocytopenia without major bleeding or haemorrhagic stroke.
	• Effectiveness: Measured as QALYs from study
17	Uncertainty
	Scenario analysis: NA
	Sensitivity analysis – SA carried out to examine the uncertainty due to variability in the data. Price per gr of IVIg and unit costs used in the cost calculations were varied.
18	Limitations/ sensitivity of results: Short term study based on a very small sample size. Long term AEs and QoL could have an impact on the overall results. Nevertheless SA results showed that highly unlikely variations in the baseline factors were required for IVIg to be more likely to be more cost-effective than PRE.
19	Results
	ICER: €268 000/QALY. Prob for IVIg to be cost effective: 50% at WTP>€250 000/QALY
	Scenario analysis: NA
	Conclusions: IVIg shown to be more expensive than treatment with prednisolone for patients with CIDP.
20	Remarks – NA
1	***Title: Treatment of Guillain-Barre syndrome: a cost-effectiveness analysis***
2	Ref: Nagpal S, Benstead T, Shumak K et al. 1999; Treatment of Guillain-Barre syndrome: a cost-effectiveness analysis. Journal of Clinical Apheresis; 14(3): 107-113
3	COI: No information provided

4	Country: Canada
5	Question: To compare plasma exchange and IVIgG in the treatment of acute Guillain-Barre syndrome
6	Need for modelling: Decision tree model over 48 weeks.
7	Type of analysis: Cost-minimisation analysis
8	Analysis: Decision model used to estimate the costs of the treatments (effectiveness assumed equivalent)
9	Population: patients diagnosed with acute Guillain-Barre, unable to walk without assistance and who presented within two weeks of the onset of symptoms.
10	Intervention: IVIg
11	Comparator: PE
12	Time horizon: 48 weeks
13	Discount rate: NA
14	Perspective: Healthcare system
15	Costs
	Costs included: Supplies and therapy costs, staff costs, overhead costs and hotel costs
	Costing methods: Micro costing based on literature and provincial costing
	Sources: Pharmacy and supply costs, hospital costs, insurance charges and provincial salaries derived from Queen Elizabeth II Health Science Centre, Halifax, in Nova Scotia, Canada.
	Costing year and currency: 1997US$
16	Outcomes: NA. From the literature (2 RCTs)
	Endpoints: Improvement in disability grade of patients. Assumed to be equivalent based on results from 2 RCTs (with different results). Only 1 RCT used for populating th model.
	Valuation of health states: 7 health states. NA
	Extrapolation: No details offered.
	Utility assessment (Quality of Life): NA
	Effectiveness: Equivalence based on 2 RCTs
17	Uncertainty
	Scenario analysis: NA
	Sensitivity analysis – One-way SA were performed for the cost of replacement fluid in plasma exchange, nurses' time for administering treatments, rent, discounting rate of equipment and the cost of IV IgG.

18	Limitations/ sensitivity of results: Based on just 1 of the 2 RCTs found during the SR. QoL not considered (PE and IVIg's HRQoL outcomes may differ). Costs of managing AEs not analysed.
19	Results
	Incremental costs: $3961 for IVIg versus PE
	Scenario analysis: NA
	Conclusions: PE and IVIg are equaly effective in GB syndrome but PE is cheaper
20	Remarks – NA
1	***Title: A Cost-Utility Analysis of Treatment for Acute Childhood ITP***
2	Ref: O'Brien, S. Kim Ritchey, A. and Smith, K J. 2007; Pediatr Blood Cancer;48:173–180
3	COI: No info provided
4	Country: USA
5	Question: To evaluate the cost-utility of four commonly used treatment Strategies in acute paediatric ITP
6	Need for modelling: Decision analytic model
7	Type of analysis: Cost-utility analysis
8	Analysis: Decision analytic model over an unclear time horizon (most likely to cover just the treatment period).
9	Population: Acute Childhood ITP
10	Intervention: IVIg
11	Comparator: Anti-D; methylpred/prednisone
12	Time horizon: Unclear, but most likely to cover the treatment period
13	Discount rate: Unclear time frame but likely to be a short time frame, which would explain the lack of discounting.
14	Perspective: Societal
15	Costs
	Costs included: Medication, infusion, AEs, Intracraneal hemorrhage, lost wages (parents)
	Costing methods: Micro costing based on hospital sources, published data, tariffs and reimbursement rates
	• Sources: Cost data and QoL measures from hospital sources and published data, tariffs and reimbursement rates
	Costing year and currency: 2004 US$
16	Outcomes: QALYs. From the literature

	Endpoints: Response rates, AEs liked to each therapy, incidence of ICH, death and utilites.
	Valuation of health states: 7 health states. Values derived from the literature (RCTs)
	Extrapolation: No details offered.
	Utility assessment (Quality of Life): Used health state values derived from the Health and Activity Limitation Index. Based on assumptions since no literature found.
	• Effectiveness: Measured as QALYs
17	Uncertainty
	Scenario analysis: NA
	Sensitivity analysis – One way SA performed
18	Limitations/ sensitivity of results: Strong assumptions: all patients admitted to hospital; all patients respond to initial therapy; incidence of intracranial haemorrhage assumed to be 0.1%, for all. Results for anti-D sensitive to: patient weight, time to platelet count >20,000 for both prednisone and anti-D, cost of anti-D, and daily cost of hospitalization
19	Results
	ICER: IVIg dominated by anti-D
	Scenario analysis: NA
	Conclusions: A short course of high-dose prednisone is a cheap and effective treatment for acute ITP
20	Remarks – NA
1	***Title: Switching Patients to Home-Based Subcutaneous Ig: an Economic Evaluation of an Interprofessional Drug Therapy Management Program***
2	Ref: Perraudin, C. Bourdin, A. Spertini, F. et al. J Clin Immunol (2016) 36:502–510
3	COI: Authors declare no COIs but funding provided from CSL Behring
4	Country: Switzerland
5	Question: To evaluate if switching patients to home-based SCIg including an interprofessional drug therapy management program (physician, community pharmacist and nurse) would be cost-effective within the Swiss healthcare system
6	Need for modelling: Treatment decisions modelled over 3 years
7	Type of analysis: Cost-minimisation analysis
8	Analysis: Decision tree simulation model over a 3-year time period
9	Population: Any PID patients
10	Intervention: SCIg weekly
11	Comparator: IVIg monthly

12	Time horizon: 3-years
13	Discount rate: Not mentioned
14	Perspective: Societal
15	Costs
	Costs included: Ig, staff time, infusion pump, disposables; Non-medical costs: transport and productivity costs.
	Costing methods: Micro costing based on current practices and characteristics of patients treated at the PMU
	• Sources: Medical costs from administrative data. Non-medical costs from experts
	Costing year and currency: 2015€
16	Outcomes: Equivalent effectiveness reported, based on two published studies (Chapel et al.2000 and Ducruet et al. 2013)
	• Endpoints: NA
	• Valuation of health states: NA
	Extrapolation: No extrapolation performed.
	Utility assessment (Quality of Life): NA
	• Effectiveness: No effectiveness considered since assumed to be equivalent for SCIg and IVIg – equivalence from literature (Chapel et al.2000 and Ducruet et al. 2013)
17	Uncertainty
	Scenario analysis: NA
	Sensitivity analysis – One way SA performed, by which the monthly dose varied according to patient's regimen, and the annual number of infusions varied for IVIg from 9 (i.e. one infusion every 6 weeks) to 17 (i.e. one infusion every 3 weeks) and for SCIg from 26 (i.e. one infusion every 2 weeks) to 104 (i.e. two infusions weekly) according to the patient's tolerance of the drug but with the same annual dose. Prices and costs were also varied.
18	Limitations/ sensitivity of results: Only costs considered. Many assumptions made. Results sensitive to the cost per gram of IgG in both strategies and the annual N. of SCIg and IVIg infusions
19	Results
	Incremental costs: €8897 IVIg vs SCIg
	Scenario analysis: NA
	Conclusions: Home based SCIg+ interprofessional management program may offer an efficient alternative to IVIg. Results sensitive to the cost of IgG, equipment and the annual N. of infusions
20	Remarks – NA

1	***Title: An evaluation of the feasibility, cost and value of information of a multicentre RCT of IVIg for sepsis (severe sepsis and septic shock): incorporating a SR, MA and value of information analysis***
2	Ref: Soares, MO. Welton, NJ. Harrison, DA
3	COI: None. Study by the NIHR
4	Country: UK
5	Question: to develop a decision-analytic model structure and identify key parameter inputs consistent with the decision problem and relevant to an NHS setting; and to populate the decision model and determine the cost effectiveness of IVIG and to estimate the value of additional primary research.
6	Need for modelling: Treatment decision-modelling over a lifetime
7	Type of analysis: Cost-utility analysis
8	Analysis: Markov model. Transition probabilities derived from clinical and cost effectiveness SRs.
9	Population: Patients with severe sepsis
10	Intervention: IVIg + standard care
11	Comparator: standard care
12	Time horizon: Lifelong
13	Discount rate: 3,5% for costs and outcomes. Based on UK guidelines
14	Perspective: National healthcare system
15	Costs
	Costs included: Costs of IVIG and LoS in hospital (critical-care unit and other wards). Cost of managing survivors after the initial hospitalisation
	Costing methods: Costing based on literature and national costings
	• Sources: National Schedule of Reference Costs 2007/08, formularies and literature
	Costing year and currency: 2009 GBP
16	Outcomes: QALYs. Lit. on IVIg and severe sepsis. Case-mix and outcome data on critical care. Survey on admissions with severe sepsis.
	Endpoints: response rates, survival and QoL.
	Valuation of health states: Derived from the studies identified in a systematic literature review (RCTs and MAs);
	Extrapolation: The time point at which patients were assumed to revert from the predicted survival distributions from the long-term cohort data to survival estimates from the general population was varied.
	Utility assessment (Quality of Life): Ut. from Drabinski et al (study on ut. after severe sepsis)
	• Effectiveness: Measured as QALYs

17	Uncertainty
	Scenario analysis: Time horizons varied to check the weight that extrapolations methods would have (less with shorter time horizons that were used in clinical studies)
	Sensitivity analysis – One way and probab. SAs performed
18	Limitations/ sensitivity of results: Methodological quality of the available evidence considered to be low. ICERs sensitive to the clinical effectiveness model used to estimate relative effectiveness
19	Results
	ICER: GBP20850/QALY. Probability of being cost effective: 50,5% at WTP=GBP20000; 78,9% at WTP=GBP30000
	Scenario analysis: NA
	Conclusions: Uncertainties over the mechanism of action of IVIg and the heterogeneous nature of severe sepsis make it difficult to define the plausibility of the scenarios presented and the CE of IVIg
20	Remarks – NA
1	***Title: Cost–utility analysis comparing hospital-based IV Ig with home-based subcutaneous Ig in patients with secondary immunodeficiency***
2	Ref: Windegger,1 T M. Nghiem, S. Nguyen, K H. et al. 2019 Vox Sanguinis, 114, 237–246
3	COI: Study partly funded by CSL Behring Australia
4	Country: Australia
5	Question: To assess whether SCIg provides a good value-for-money treatment option in patients with secondary immunodeficiency disease (SID).
6	Need for modelling: Markov to calculate cost effectiveness over 10 years.
7	Type of analysis: Cost-utility analysis
8	Analysis: Markov model: weekly cycles - 6 health states (SID no infection, SID with infection, SID with bronchiectasis no infection, SID with bronchiectasis with infection, SID with bronchiectasis and chronic Pseudomonas aeruginosa infection, and death), over a 10 year period.
9	Population: Adult patients with SID specifically acquired hypogammaglobulinaemia secondary to malignancy or associated treatment. The cohort included eight females and five males, with a mean age of 62_5 years (39–76)
10	Intervention: SCIg
11	Comparator: IVIg/SCIg
12	Time horizon: 10 years
13	Discount rate: 5% for costs and outcomes. Based on Australian guidelines
14	Perspective: Healthcare system
15	Costs

	Costs included: IG; consumables; pumps; training; haematology fee; pathology tests; costs of bronchiectasis; infection costs
	Costing methods: Micro costing based on literature and accounting data
	• Sources: Accounting data from hospital and health services
	Costing year and currency: 2018 AUS$
16	Outcomes: QALYs
	Endpoints: Incidence of infection at home or hospital, development of bronchiectasis (with and without infection), bronchiectasis with chronic Pseudomonas aeruginosa infection and mortality (from patient files (n=13)
	Valuation of health states: 6 health states. Infection data from our cohort were used in the model with the exception of transition probabilities for Pseudomonas aeruginosa infection and death. As neither were observed in the cohort over the 52 weeks period, data from the literature were used
	Extrapolation: No details offered. The authors appear to have assumed constant probabilities at every cycle.
	Utility assessment (Quality of Life): quality of life estimate using the Assessment of Quality of Life–6 Dimensions (AoQL-6D) instrument. Overall 192 responses to the survey were received (some patients filled it more than once)
	• Effectiveness: Measured as QALYs
17	Uncertainty
	Scenario analysis: NA
	Sensitivity analysis – Deterministic and probabil. SAs
18	Limitations/ sensitivity of results: Clinical data based on 13 patients only. Results most sensitive to product and Ig replacement treatment costs, followed by costs of bronchiectasis
19	Results
	ICER: SCIg dominant. Probability of SCIg being cost effective: 88,3% at a WTP AUS$50 000/QALY
	Scenario analysis: NA
	Conclusions: SCIg is a safe and CE alternative to IVIg for replacement therapy of primary antibody deficiencies
20	Remarks – NA
1	***Title: Cost-minimization analysis of the direct costs of TPE and IVIg in the treatment of Guillain-Barré syndrome***
2	Ref: Winters, J L. Brown, D. Hazard, E.
3	COI: Study sponsored by CaridianBCT
4	Country: USA
5	Question: Due to increases in the price of IVIg compared to human serum albumin (HSA), used as a replacement fluid in TPE, we examined direct hospital-level expenditures for TPE and IVIg for meaningful cost-differences between these treatments.

6	Need for modelling: NA
7	Type of analysis: Cost-minimisation analysis
8	Analysis: Cost comparison in excel using a micro costing approach over a sho time horizon (5 infusions)
9	Population: GBS patients
10	Intervention: IVIg
11	Comparator: Supplies; nursing costs, central venous catheter; hospital costs, TPE equipment and infusion costs
12	Time horizon: Short term (5 infusions)
13	Discount rate: NA
14	Perspective: Hospital
15	Costs
	Costs included: Supplies; nursing costs, central venous catheter; hospital costs, TPE equipment and infusion costs
	Costing methods: Micro costing based on hospital accounting/financial data and reimbursement rates
	• Sources: Hospital accounting/financial data and reimbursement rates
	Costing year and currency: 20010-2011 USA$
16	Outcomes: Equivalence in efficacy derived from SR by Hugues et al. 2007
	Endpoints: NA – Cost minimisation analysis. Focus purely on costs.
	Valuation of health states: NA
	Extrapolation: NA
	Utility assessment (Quality of Life): NA
	• Effectiveness: Equivalence assumed based on SR by Hughes et al. 2007
17	Uncertainty
	Scenario analysis: NA
	Sensitivity analysis – No SA performed
18	Limitations/ sensitivity of results: Differences in AEs despite similar frequencies (differences in costs cannot be excluded). Shorter courses of PE or IVIg were not considered. Study limited to direct hospital costs
19	Results
	Incremental costs: $5692 (IVIg vs PE)
	Scenario analysis: NA

	Conclusions: In GBS patients, direct costs of IVIg are over 2x those of PE. Given the equivalent efficacy and similar severity and frequencies of AEs, PE appears to be a less expensive 1st-line therapy
20	Remarks – NA
1	***Title: Results of a Model Analysis to Estimate Cost Utility and Value of Information for Intravenous Immunoglobulin in Canadian Adults With Chronic Immune Thrombocytopenic Purpura***
2	Ref: Xie, F. Blackhouse, G. Assasi, N. et al. 2009; Clinical Therapeutics/Volume 31, Number 5.
3	COI: No conflict of interest. Study funded by the Canadian Agency for Drugs and Technologies in Health
4	Country: Canada
5	Question: To estimate the cost-effectiveness of IVIg, compared with oral prednisone as a treatment for Canadian adults with persistent chronic ITP.
6	Need for modelling: Treatment decisions modelled over a lifetime so modelling was necessary
7	Type of analysis: Cost-utility analysis
8	Analysis: Markov model. Transition probabilities derived from a SR. Cycle length was 1 yr.
9	Population: Adults with persistent, chronic ITP
10	Intervention: IVIg
11	Comparator: Oral prednisolone
12	Time horizon: Lifelong
13	Discount rate: 5% for costs and outcomes. Based on Canadian guidelines
14	Perspective: Healthcare system
15	Costs
	Costs included: IVIg costs, prednisone costs, and splenectomy costs. No costs of administration or distribution included
	Costing methods: Micro costing based on literature and national costing
	• Sources: Formularies national costing and literature
	Costing year and currency: 2007 CAN$
16	Outcomes: QALYs. From the literature (authors carried out a SR
	Endpoints: response rates, splenectomy to those not responding. Post splenectomy response or refractory and death. Clinical data from SR of the lit. (Chen 2008) and expert opinion. Ut. Assumed since no data available in the lit.
	Valuation of health states: 7 health states. Transition probabilities (ie, point estimates and 95% CIs) were estimated from the studies identified in a systematic literature review using a random-effect meta-analysis; point estimates were weighted-mean values from the meta-analysis.
	Extrapolation: No details offered.

	Utility assessment (Quality of Life): No published studies found for the ut. of patients with relapsed or refractory ITP; A value of 0.76 was used, based on the mean of the ut. for thrombocytopenia without major bleeding or haemorrhagic stroke.
	• Effectiveness: Measured as QALYs
17	Uncertainty
	Scenario analysis: NA
	Sensitivity analysis – One way and probab. SAs performed
18	Limitations/ sensitivity of results: AEs of IVIg, prednisone, and splenectomy and their impact on costs and ut. not included in the model. Results sensitive to time horizons, ut. weights and discounts. Prob for IVI got be cost effective: 20%, at WTP =CAN$100,000
19	Results
	ICER: CAN $1.13 million/ QALY
	Scenario analysis: NA
	Conclusions: Based on the available published evidence, IVIg may not be a cost-effective option for adults with persistent chronic ITP in Canada
20	Remarks – NA

6 INTERNATIONAL COMPARISON

6.1 BELGIUM

6.1.1 Off-label indications in Belgium

The Special Solidarity Fund can allow reimbursement for off-label indications. In the table below there is an overview of requests that were made to the Fund between Nov 2017- April 2019 for immunoglobulins. The information for which indications the commission of the Fund has decided to grant reimbursement is confidential.

Requested indication	Number of requests
juvenile dermatomyositis	1
dermato-polymyositis	1
auto-immune necrotizing myopathy	2
auto-immune myositis	2
sarcoidosis	1
desensitisation before 2ary renal transplant	2
desensitisation before 3th renal transplant	1
rejection/failure of heart transplant	1
rejection/failure of liver transplant	1
multivisceral transplantation	1
auto-immune encephalitis	2
inflammatory myeloradiculitis dysimmunitair	1
bilateral optic neuropathy	1
small fiber neuropathy	1
Susac's syndrome(=retinocochleocerebral vasculopathy)	2
secondary hypogammaglobulinemia with a non-Hodgkin lymphoma	1
post transplantation refractory viral infection	1
respiratory insufficiency due to a viral infection in a chronic sick patient (liver transplant, terminal renal insufficiency)	1
toxic shock syndrome (multi-organ failure)	1
neonatal thrombopenia transitoir	2
autoimmune thrombocytopenia	2

6.2 AUSTRALIA

6.2.1 – The IG CRITERIA (as published on the website since January 2019)

Indication with an established therapeutic role	Level of Evidence	justification
Acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT)	Evidence of probable benefit – more research needed (Category 2a)	Cochrane meta-analysis 2009
Chronic inflammatory demyelinating polyneuropathy (CIDP), (including IgG and IgA paraproteinaemic demyelinating neuropathies)	Clear evidence of benefit (Category 1)	Cochrane review (update in 2013)
Fetal and neonatal alloimmune thrombocytopenia (FNAIT)	Insufficient data (Category 4a)	Cochrane (Rayment 2011) winkelhorst 2017 (4 RCTs229 participants (==> in 4 RCTs:)
Guillain–Barré Syndrome including variants (GBS)	Clear evidence of benefit (Category 1)	systematic review of 9 RCTs of moderate quality
Immune thrombocytopenic purpura (ITP) — adult	Evidence of probable benefit – more research needed (Category 2a)	3 RCTs demonstrated equivalent efficacy of IVIG compared to cortico
Inflammatory Myopathies: Inclusion Body Myositis (IBM)	Evidence of probable benefit – more research needed (Category 2a)	3 CTs with negative outcome for IVIG, case reports are positive
Inflammatory myopathies: polymyositis (PM), dermatomyositis (DM) and necrotising autoimmune myopathy (NAM)	Polymyositis: Category 2a - Evidence of probable benefit - more research needed. Dermatomyositis: Category 2a - Evidence of probable benefit - more research needed NAM: Category 4a - Small case studies only, insufficient data.	Polymyositis:1 prospective cases series study of 35 adults dermatomyositis: 1RCT of low quality 15 patients NAM: no prospective trials
Kawasaki disease (mucocutaneous lymph node syndrome)	Clear evidence of benefit (Category 1)	Cochrane SR of 16 RCTs (Oates whitehead 2003)
Lambert–Eaton myasthenic syndrome (LEMS)	Evidence of probable benefit – more research needed (Category 2a)	SR of 1 RCT on 9 patients and 1 case serie of 7 patients
Multifocal motor neuropathy (MMN)	Clear evidence of benefit (Category 1)	Cochrane wih 4 RCTs, RCT of 44 patients (Hahn et al 2013)

Myasthenia gravis (MG)	Clear evidence of benefit (Category 1)	Cochrane review of 7 (RCTs) (Gajdos et al 2012
Neonatal haemochromatosis (NH)	Evidence of probable benefit – more research needed (Category 2a)	Historically controlled study (Rand 2009);
Primary immunodeficiency diseases (PID) with antibody deficiency	Evidence of probable benefit – more research needed (Category 2a)	Common variable immunodeficiency: 2 crossover double blind, 2 case series: conflicting results
Stiff person syndrome	Evidence of probable benefit – more research needed (Category 2a)	1 RCT crossover design of 16 patient

Indication with an emerging therapeutic role	**Level of Evidence**	**justification**
Acute disseminated encephalomyelitis (ADEM)	Evidence of probable benefit – more research needed (Category 2a)	Case series
Autoimmune encephalitis mediated by antibodies targeting cell-surface antigens (AMAE)	Evidence of probable benefit – more research needed (Category 2a)	Cohort study:Titulaer et al (2014);Armangue 2015, Systematic reveiw (of retrospective case series) (Nosadini et al 2015)
Autoimmune haemolytic anaemia (AIHA)	Insufficient data (Category 4a)	Review based on 3 pilot (73 patients) (Flores, G 1993); review (Norton and Roberts 2006)
Bullous pemphigoid (BP)	Evidence of probable benefit – more research needed (Category 2a)	Case series (Gaitanis, G 2012;Ahmed Dahi 2003)
Cicatricial pemphigoid (CP) or Mucous Membrane Pemphigoid (MMP)	Evidence of probable benefit – more research needed (Category 2a)	Review of case reports (72 patients):Czernik A et al, 2012
Haemophagocytic lymphohistiocytosis	Insufficient data (Category 4a)	Case series
IgM paraproteinaemic demyelinating neuropathy	Conflicting evidence of benefit (Category 2c)	2 RCTs (Dalakas 1996, Comi 2002), 6 uncontrolled sutides
Immune thrombocytopenic purpura (ITP) — in children 15 years and younger	Clear evidence of benefit (Category 1)	meta-analysis:Frommer and Madronio (2006) meta analysis on dosing 13 small RCTs: Qin YH et al 2010
Opsoclonus-myoclonus ataxia (OMA)	Insufficient data (Category 4a)	Case reports
Pemphigus foliaceus (PF)	Evidence of probable benefit – more research needed (Category 2a)	1 RCT:Amagai, 2009
Pemphigus vulgaris (PV)	Evidence of probable benefit – more research needed (Category 2a)	1 RCT:Amagai, 2009; retrospective cohort study

Post-transfusion purpura (PTP)	Insufficient data (Category 4a)	1 study in 1988
Secondary hypogammaglobulinaemia unrelated to Haematological malignancy or haemopoeitic stem cell transplant (HSCT)	Insufficient data (Category 4a)	Florescu DF. 2014; Shankar T et al. 2013
Solid organ transplantation	Clear evidence of benefit (Category 1)	Kidney:1 RCT (Jordan et al 2004); Nonrandomised clinical observational studies ((Montgomery 2011) heart,renal:Jordan et al (1998) +conensus statements
Specific antibody deficiency	Insufficient data (Category 4a)	Retrospective studies (Orange et al, 2006)
Toxic epidermal necrolysis (TEN; Lyell syndrome) / Stevens–Johnson syndrome (SJS)	Insufficient data (Category 4a)	Review (Del Pozzo-Magana 2011)
Toxic shock syndrome (TSS)	Insufficient data (Category 4a	Observational cohort studies ((Kaul et al, 1999 and Linner et al, 2014)
Indication for exceptional circumstances only	Level of Evidence	justification
Acquired haemophilia and congenital haemophilia with inhibitors (Coagulation factor inhibitors)	Evidence of probable benefit – more research needed (Category 2a)	Guidelines(Collins 2013, UK clinical guidelines)
Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)] - positive systemic necrotising vasculitis	Evidence of probable benefit – more research needed (Category 2a)	Other therpay better indicated (rituximab)
Autoimmune congenital heart block	Insufficient data (Category 4a)	Positive case reports and case series, open-label study (Friedman et al, 2010
Autoimmune neutropenia	Insufficient data (Category 4a)	Small case reports Bux et al, 1991 and Bux et al, 1998 and Getta et al, 2015
Autoimmune retinopathy (AIR)	Insufficient data (Category 4a)	Open label studies and case series (Castiblanco & Foster, 2014 and Garcia-Geremias, 2015).
Catastrophic anti-phospholipid syndrome (CAPS)	Insufficient data (Category 4a)	Retrospective analysis on European registry (Cervera et al 2016)

Childhood epileptic encephalopathy	Evidence of probable benefit – more research needed (Category 2a)	Case reports, quality of this literature is poor; Cocrane on epilepsy (Geng 2011), on focal epilepsy (Walker 2013)
Epidermolysis bullosa acquisita	Insufficient data (Category 4a)	Review of 14 of 15 patients((Gurcan, 2011); retrospective case series (Ahmed, 2012)
Graves ophthalmopathy	Evidence of probable benefit – more research needed (Category 2a)	Randomised trial (Kahaly G et al, 1996); EUGOGO guidelines
Haemolytic disease of the fetus (HDF)	Conflicting evidence of benefit (Category 2c)	Systematic review, 12 RCTs (Louis et al 2014); alternative intensive phototherapy is most effective neonatal treatment
Haemolytic transfusion reaction (hyperhaemolysis syndrome	Insufficient data (Category 4a)	Case reports
Multiple sclerosis - (MS) [relapsing remitting multiple sclerosis (RRMS)]	Evidence of probable benefit – more research needed (Category 2a)	Systematic reviews in 2004 and 2006; alternatives available
Neuromyelitis optica spectrum disorders (NMOSD	Insufficient data (Category 4a)	Very small studies (Viswanathan et al, 2015 and Elsone et al, 2014
Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or paediatric acute neuropsychiatric disorders (PANS)	Evidence of probable benefit – more research needed (Category 2a)	1 RCT (Perlmutter 1999)
Pure red cell aplasia (PRCA	Evidence of probable benefit – more research needed (Category 2a)	Case studies/case series
Pyoderma Gangrenosum (PG)	Insufficient data (Category 4a)	Small case series (Patel et al, 2015 and Cummins et al, 2007) and case reports (Cafardi & Sami, 2014 and De Zwaan et al, 2009)
Rasmussen encephalitis	Evidence of probable benefit – more research needed (Category 2a)	Retrospective case series, open label studies and 1 RCT (Bien et al, 2012)
Scleromyxedema	Insufficient data (Category 4a)	Case reports/series
Sjögren's syndrome associated neuropathy	Insufficient data (Category 4a)	Small case series/conflicting results
Susac syndrome	Insufficient data (Category 4a)	Case series (Mateen, 2012) positive results, alternative PE possibly greater efficacy (Vodopivec, 2016).

Systemic capillary leak syndrome	Insufficient data (Category 4a)	Case series (Gousseff, M, 2011; Marra, AM 2014)
Indication not support for reimbursement	Types of studies included	
Acute optic neuritis	Evidence of no probable benefit – more research needed (Category 2b)	Alternatives available
Acute rheumatic fever	Evidence of no probable benefit – more research needed (Category 2b)	
Adrenoleukodystrophy	Nil (Category 4b)	
Amegakaryocytic thrombocytopenia	Nil (Category 4b)	
Antiphospholipid syndrome (non-obstetric)	Nil (Category 4b)	
Aplastic anaemia/pancytopenia	Nil (Category 4b)	
Asthma	Evidence of no probable benefit – more research needed (Category 2b)	Alternatives available
Atopic dermatitis/eczema — adult	Evidence of no probable benefit – more research needed (Category 2b)	Alternatives available
Autism	Insufficient data (Category 4a)	
Autologous haemopoietic stem cell transplantation	Evidence of no probable benefit – more research needed (Category 2b)	Cochrane review (Raanani)
Behçet's disease	Nil (Category 4b)	
Cardiac surgery with bypass — prophylaxis	Evidence of probable benefit – more research needed (Category 2a)	Alternatives available
Congestive cardiac failure	Evidence of probable benefit – more research needed (Category 2a)	Alternatives available
Crohn's disease	Evidence of probable benefit – more research needed (Category 2a)	Alternatives available
Diabetic amyotrophy (diabetic proximal neuropathy or diabetic lumbosacral radiculoplexus neuropathy)	Insufficient data (Category 4a)	RCT stopped (not published)
Diamond Blackfan syndrome	Nil (Category 4b)	
Female infertility	Insufficient data (Category 4a)	Alternatives available
Glomerulonephritis — IgA nephritis	Evidence of no probable benefit – more research needed (Category 2b)	Alternatives available
Haemolytic uraemic syndrome	Nil (Category 4b)	
Henoch–Schönlein purpura	Nil (Category 4b)	

HIV in children	Evidence of probable benefit – more research needed (Category 2a)	Alternatives available
HIV/AIDS — adult	Evidence of no probable benefit – more research needed (Category 2b)	
Idiopathic dilated cardiomyopathy	Evidence of no probable benefit – more research needed (Category 2b)	
Linear IgA disease	Nil (Category 4b)	
Lupus cerebritis	Insufficient data (Category 4a)	
Lupus nephritis	Evidence of probable benefit – more research needed (Category 2a)	
Motor neuron disease/amyotrophic lateral sclerosis	Nil (Category 4b)	
Myalgic encephalomyelitis	Conflicting evidence of benefit (Category 2c)	1 RCT (1990)
Myocarditis in children	Insufficient data (Category 4a)	Cochrane (obinson update 2015°
Narcolepsy/cataplexy	Insufficient data (Category 4a)	
Nephrotic syndrome	Evidence of probable benefit – more research needed (Category 2a)	Alternatives available
Obsessive compulsive disorders	Insufficient data (Category 4a)	
Paraneoplastic cerebellar degeneration	Insufficient data (Category 4a)	
Paraneoplastic Subacute Sensory Neuropathy	Insufficient data (Category 4a)	Alternatives available
Polyneuropathy of critical illness	Insufficient data (Category 4a)	
Pure white cell aplasia (PWCA)	Insufficient data (Category 4a)	
Recurrent fetal loss (with or without antiphospholipid syndrome)	Clear evidence of no benefit (Category 3)	Cochrane
Rheumatoid arthritis	Conflicting evidence of benefit (Category 2c)	
Sepsis	Evidence of probable benefit – more research needed (Category 2a)	Neonatal (Brockelhurst et al 2011); adult and pediatric possible effect but check with PID or SID
Systemic lupus erythematosus (SLE)	Evidence of probable benefit – more research needed (Category 2a)	
Ulcerative colitis	Nil (Category 4b)	

6.2.2 Level of evidence categories used for categorizing and establishing the Ig Criteria

Categories	Types of studies	conclusion on evidence
1	High-quality randomised controlled trials (RCTs)	Clear evidence of benefit
2a	Some RCTs and/or case studies	Evidence of probable benefit – more research needed
2b	Some RCTs and/or case studies	Evidence of no probable benefit – more research needed
2c	High-quality RCTs with conflicting results	Conflicting evidence of benefit
3	High-quality RCTs	Clear evidence of no benefit
4a	Small case studies only	Insufficient data
4b	No included studies	-

6.3 FRANCE

6.3.1 Reimbursed indications based on licenced indications (in 2019)

reimbursed indication in France (based on licenced indications)	
primary immunodeficiency PID	agammaglobulinemie
	common variable immunodeficiency
	severe combined immunodeficiency
	hypogammaglobulinemie
	humoral immunodeficiency
Secondary Immune Deficiency SID	hypogammaglobulinemia after HSCT
	hypogammaglobulinemia and Multiple Myeloma or Chronic lymphocytic leukemia with severe recurrent infections
allogenic hematopoetic stem cell transplantation/bone marrow	
HIV with severe recurrent bacterial Infections (adult and child)	
Kawasaki disease	
Chronic Inflammatory Demyelinating Polyneuropathy	
Guillain Barre syndrome	
immune thrombocytopenia (idiopathic thrombocytopenic purpura)	
myastenia (acute)	only 1 product TEGELINE®
Multifocal Motor Neuropathy	
Wiskott-Aldrich syndrome (thrombocytopenie)	only 1 product CLAIRYG®
Birdshot retinochoroïditis	only 1 product TEGELINE®

6.3.2 *Priority list « Hiérarchisation des indications des immunoglobulines humaines polyvalentes – Version Avril 2019 »*

Hiérarchisation des indications des immunoglobulines humaines polyvalentes – Version Avril 2019

Indication ** Situation correspondant à l'AMM*	**Degré de priorité** ● Prioritaire [P] ● A réserver aux urgences vitales et/ou fonctionnelles et/ou en cas d'échec des alternatives thérapeutiques [UV] ● Non prioritaire [NP]	**Nécessité d'un avis spécialisé**		**Posologie**
		Instauration	**Renouvellement**	
Déficits immunitaires				
Déficits immunitaires primitifs*	● [P]			0,4g/kg en une perfusion toutes les 3 à 4 semaines
Neurologie				
Syndrome de Guillain-Barré* (ou variantes dont le syndrome de Miller-Fisher) chez l'enfant, et **chez l'adulte en cas de contre-indication ou d'impossibilité de recourir à des échanges plasmatiques dans les 6 heures**	● [P]			2g/kg en 2 jours ou 0,4g/kg/j sur 5 jours en cas de risque d'insuffisance rénale
Polyneuropathie inflammatoire démyélinisante chronique* (PIDC) **cliniquement évolutive** après discussion du rapport bénéfice/risque des corticoïdes, échanges plasmatiques et IgIV	● [UV]	**Avis en RCP et d'un centre de la filière FILNEMUS**	**Semestrielle par un centre de la filière FILNEMUS**	*Instauration et entretien :* 2g/kg en 2 jours ou 0,4g/kg/j sur 5 jours en cas de risque d'insuffisance rénale Cure à répéter toutes les 4 semaines pendant 3 cures avant évaluation d'efficacité. *A titre indicatif, en cas d'absence d'abord veineux ou de contre-indication par voie IV un recours à la voie SC peut être envisagé.*
Neuropathie motrice multifocale* et neuropathie sensitive et motrice multifocale avec bloc de conduction (syndrome de Lewis et Sumner) **cliniquement évolutive** nouvellement diagnostiquée ou en cours de traitement et répondant aux IgIV	● [UV]		**Rythme à adapter selon la réponse thérapeutique du patient**	
Myasthénie auto-immune grave y compris séronégative chez l'enfant, et **chez l'adulte en :** • **Cas de décompensation aiguë (si impossibilité dans les 6h de recourir à des échanges plasmatiques ou en cas d'échec ou de contre-indication)** • **Cas de maladie non contrôlée par une corticothérapie et/ou des immunosuppresseurs** • **Prévention d'une exacerbation avant geste chirurgical**	● [UV]	**Avis du centre de la filière FILNEMUS excepté pour les cas de décompensations aiguës**		1g/kg sur 1 à 3 jours

Encéphalites auto-immunes et syndromes neurologiques paranéoplasiques (dont syndromes de Lambert-Eaton et de l'homme raide)	🔵 [UV]	**Avis du réseau de centres de référence**	**Trimestrielle après 2 cures réalisées à un mois d'intervalle**	2g/kg en 2 jours ou 0,4g/kg/j sur 5 jours si risque élevé d'insuffisance rénale Durée de traitement limitée à 6 mois
Hématologie				
Purpura thrombopénique idiopathique, **traitement à réserver** uniquement **aux formes sévères chez :** • **l'adulte avec un score de Khellaf >8** et toujours **en association avec les corticoïdes** • **l'enfant avec un score de Buchanan >3 ou un taux de plaquettes < 10 g/L**	🔴 [P]	Voir PNDS		1g/kg adulte et 0,8g/kg enfant, dose unique à J1 Répéter la dose à J3 seulement si les signes de gravité persistent Formes exceptionnelles avec mise en jeu immédiate du pronostic vital (en particulier hémorragie intra-cérébrale) : 1g/kg enfant et adulte à J1 et J2 + corticoïdes + transfusion de plaquettes
Erythroblastopénie associée à une infection chronique par le parvovirus B19 chez les immunodéprimés **et responsable d'une anémie sévère (<8 g/dL)**	🔴 [P]	**Avis du réseau de centres de référence**		2g/kg en 2 jours ou 0,4g/kg/j sur 5 jours si risque élevé d'insuffisance rénale Deux cures sont nécessaires en moyenne
Maladie de Willebrand acquise associée à une gammapathie monoclonale IgG (MGUS IgG) **avec un syndrome hémorragique sévère** en cas d'échec ou d'intolérance à la desmopressine et/ou concentrés de vWF **ou nécessitant une intervention chirurgicale urgente engageant le pronostic vital ou fonctionnel**	🔴 [P]	**Avis du réseau de centres de référence**		1,2 g/kg en 3 jours soit 0,4g/kg/j
Traitement de l'allo-immunisation fœto-maternelle plaquettaire anti HPA-1a **avec antécédent avéré de thrombopénie néonatale**	🔴 [P]	**Avis spécialisé**		Perfusions hebdomadaires de 1 g/kg à partir de la 20ème semaine d'aménorrhée. En cas de risque d'hémorragie fœtale modéré, on peut envisager un traitement de début plus tardif et à une posologie de 0,5 g/kg Dans les formes très sévères, possibilité d'un début de traitement plus précoce à 2 g/kg par semaine.
Déficits immunitaires secondaires : ▪LLC*, LNH et autres avec défaut de production d'Ac **(dosage pondéral des IgG <4g/L), associées à des infections à répétition survenus malgré une antibioprophylaxie bien conduite et entraînant une hospitalisation**	🔵 [UV]	**Passage en RCP**		0,2 à 0,4 g/kg en dose unique toutes les 3 à 4 semaines. *Cas particuliers en pédiatrie :* *La fréquence d'administration et/ou la dose peuvent être augmentées afin de maintenir un taux résiduel d'IgG sérique >4 g/L notamment en cas de facteurs de risque aggravants d'hypogammaglobulinémie.*

■Myélome actif ou indolent : Prophylaxie des infections bactériennes • Quel que soit le taux d'immunoglobulines après au moins 2 épisodes infectieux bactériens fébriles avec foyer cliniquement ou radiologiquement documenté ou des hémocultures positives dans l'année, survenus malgré une antibioprophylaxie bien conduite ; • Episodes infectieux fébriles présumés bactériens non documentés mais répétés ET un taux d'immunoglobulines normales très diminué a. Si chaînes légères ou pic en béta: gamma <4g/l ; b. Si pic en gamma : dosage pondéral des classes d'Ig non impliquées <50% de la normale ■Post-traitement par cellules CAR-T anti-CD19 • Chez l'enfant : prophylaxie systématique en cas d'hypogammaglobulinémie • Chez l'adulte : supplémentation à visée curative en cas d'hypogammaglobulinémie associée à des infections sévères et répétées survenus malgré une antibioprophylaxie bien conduite.	● [UV] ● [UV]	**Passage en RCP** **Passage en RCP**		*Cf. Recommandations IFM (Octobre 2018)* 0,4 g/kg IV en dose unique toutes les 4 semaines ou 0,1g/kg SC par semaine
Allogreffe de CSH • Prophylaxie des infections bactériennes et virales en cas d'hypogammaglobulinémie (gammaglobulines sériques <4g/l) chez l'allogreffé avec donneur non apparenté ou alternatif • Quel que soit le taux d'IgG en cas de: - Pneumopathie à CMV, infection ou à haut risque d'atteinte respiratoire basse liée au VRS - Atteinte respiratoire basse liée au para- influenzae • Hypogammaglobulinémie avec des infections récurrentes avant ou après greffe de CSH	● [UV]	**Passage en RCP**		*Cf. Recommandations SFGM-TC Mars 2019* IgIV, 0,4 à 0,5g/kg par administration toutes les 3 à 4 semaines jusqu'à l'obtention d'un taux de gammaglobulines sériques > 0.4g/L IgIV 0,5g/kg un jour sur 2 pendant 2 semaines pour un total de 7 doses, en association au traitement antiviral 0,4 à 0,8g/Kg toutes les 4 semaines jusqu'à l'obtention d'un taux de gammaglobulines sériques 0.5 à 0.6 g/L
Syndrome catastrophique des antiphospholipides **en cas d'échec du traitement anticoagulant IV associé à des corticoïdes en complément ou en alternative à la plasmaphérèse**	● [UV]	**Avis du réseau de centres de référence**		2g/kg en 2 jours ou 0,4g/kg/j sur 5 jours si risque élevé d'insuffisance rénale
Anémie auto-immune hémolytique **grave en impasse thérapeutique**	● [UV]	**Avis du réseau de centres de référence**		Sur avis du réseau de centres de référence

Maladie de Willebrand acquise associée à une gammapathie monoclonale IgG (MGUS IgG) **sans syndrome hémorragique** en cas d'échec ou d'intolérance à la desmopressine et/ou aux concentrés de vWF **ou relevant d'une intervention chirurgicale programmée n'engageant pas le pronostic vital ou fonctionnel**	● [NP]	**Avis du réseau de centres de référence**		1,2 g/kg en 3 jours soit 0,4g/kg/j
Maladies infectieuses				
Prophylaxie des sujets à risque suivants, après exposition à un cas confirmé de rougeole : - femme enceinte non vaccinée et sans antécédents de rougeole, - sujet immunodéprimé quel que soit son statut vaccinal et ses antécédents avérés de rougeole, - enfants de moins de 6 mois dont la mère présente une rougeole, - enfants de moins de 6 mois dont la mère n'a pas d'antécédent de rougeole et n'a pas été vaccinée (dans le doute une sérologie maternelle IgG peut être demandée en urgence), - enfants âgés de 6 à 11 mois non vaccinés en post-exposition dans les 72 h après contact quel que soit le statut vaccinal de la mère ou ses antécédents de rougeole	● [P]			200 mg/kg en dose unique (voir recommandations du haut conseil de santé publique)
Transplantation d'organes solides (Rein, Cœur, Poumons et Cœur-Poumons)				
Traitement du rejet de greffe médié par Ac en cas d'échec ou contre-indication aux autres alternatives	● [P]			0,1g/kg après chaque plasmaphérèse, suivie par 2 g/kg à répartir sur 48h à répéter tous les mois pendant 4 mois.
Prophylaxie des rejets médiés par Ac chez les patients traités par les plasmaphérèses : - hyperimmunisés avant la greffe - ou chez les patients avec un (ou plusieurs) Ac contre le donneur (avec une MFI > 2000) après la greffe	● [UV]			1 dose de 0,1g/kg après chaque plasmaphérèse
Désimmunisation des patients hyperimmunisés en attente d'une greffe du rein, du cœur, des poumons et cœur-poumons en dehors des plasmaphérèses	● [NP]	**Avis spécialisé**		
Médecine interne				
Myopathies inflammatoires auto-immunes				
Dermatomyosite et polymyosite corticorésistantes et après échec, dépendance, intolérance ou contre-indication aux immunosuppresseurs, **avec graves troubles de la déglutition**	● [UV]	**Passage en RCP**	**Trimestrielle**	2g/kg en 2 jours ou 0,4g/kg/j sur 5 jours si risque élevé d'insuffisance rénale

Myosites à inclusion avec dysphagie **pour les patients résistants aux corticoïdes et aux immunosuppresseurs**		● [NP]	**Passage en RCP**	**Trimestrielle**	
Vascularites					
Maladie de Kawasaki*		● [P]			1.6 à 2g/kg sur 2 à 5 jours ou 2g/kg en dose unique à débuter durant les 10 premiers jours
Vascularites systémiques ANCA-positives en cas de rechute ou de résistance ou d'intolérance aux corticoïdes, immunosuppresseurs (méthotrexate, azathioprine, cyclophosphamide et rituximab)		● [NP]	**Avis spécialisé**	**Semestrielle**	
Maladies systémiques					
Syndrome de Clarkson		● [UV]			2g/kg tous les mois la 1ère année sans récidive puis diminution année après année de moitié jusqu'à 0,25g/kg puis arrêt progressif.
Dermatologie					
Pemphigus (vulgaire, foliacé/superficiel ou paranéoplasique) en impasse thérapeutique après un traitement par rituximab et/ou corticostéroïdes et/ou immunosuppresseurs		● [UV]	**Après RCP et avis du réseau de centres de référence**	**RCP et réseau de centres de référence**	Instauration : 2g/kg sur 2 à 5 jours, tous les mois pendant 6 mois Entretien (si efficace) : réduction des doses ou espacement des perfusions
Pemphigoïde des muqueuses (ex pemphigoïde cicatricielle) avec atteinte muqueuse étendue et/ou atteinte oculaire sévère et/ou atteinte laryngée, en impasse thérapeutique après un traitement de 3 à 6 mois par corticothérapie générale et/ou immunosuppresseurs et/ou rituximab ou en cas d'intolérance à ces traitements		● [UV]			
Epidermolyse bulleuse acquise (EBA) avec atteinte cutanée et/ou muqueuse étendue et/ou atteinte oculaire et/ou atteinte laryngée en échec thérapeutique après un traitement par rituximab et/ou corticostéroïdes et/ou immunosuppresseurs		● [UV]			
Nouvelle indication 2019	Mucinose Papuleuse engageant le pronostic vital: - Avec manifestations graves, notamment neurologiques ou cardiaques - Mucinose Papuleuse galopante et généralisée	● [UV]	**Avis spécialisé**		2g/kg en 4 ou 5 jours toutes les 4 à 6 semaines pendant plusieurs mois (6 à 12 cures).
Hépatologie					
Nouvelle indication 2019	Hémochromatose néonatale (hépatite allo-immune congénitale) : - en période néonatale dans les insuffisances hépatocellulaires néonatales	● [P]	**Avis spécialisé** (hépato-pédiatre,		1 g/kg après une exsanguino-transfusion de 2 masses sanguines

Indications non justifiées ou non acceptables au regard des données disponibles (liste non exhaustive)

Déficits immunitaires
Déficits immunitaires secondaires ne répondant pas aux situations pré-citées et aux critères suivants : - défaut de production d'Ac (dosage pondéral des IgG <4g/L), - associés à des infections à répétition entraînant une hospitalisation - après validation en RCP.
Neurologie
Autisme
Narcolepsie
Sclérose en plaque secondairement progressive
Hématologie
Purpura thrombotique thrombocytopénique
Hémophilie acquise
Syndrome d'activation macrophagique
Neutropénie auto-immune
Purpura thrombopénique immunologique ne répondant pas aux critères précités
Cytopénies auto-immunes en dehors des critères précités
Maladie de Willebrand acquise, associée à une gammapathie monoclonale de type IgA ou IgM
Chez les patients allo-greffés : • En prophylaxie systématique de l'infection, en l'absence d'hypogammaglobulinémie • Dans les maladies à CMV autres que la pneumopathie (ECIL7 6,7) • Dans les atteintes respiratoires hautes ou basses liées à un autre virus que le VRS ou le para-influenzae, (ECIL4 10) • Dans la prophylaxie de la maladie à CMV (ECIL 76,7) • En association au traitement préemptif anti-CMV (ECIL 7 6,7) • Dans les autres atteintes virales notamment BK virus, EBV, Influenzae, HHV6, norovirus, rotavirus, adénovirus.
Infection virale au cours du myélome multiple
Transplantation d'organes solides
Prophylaxie et traitement des rejets humoraux des organes autres que le rein, le cœur, poumons et cœur-poumons sauf justification et après avis spécialisé
Médecine interne
Lupus érythémateux systémiques
Polyarthrite rhumatoïde
Arthrite juvénile idiopathique, Maladie de Still
Syndrome de Felty
Asthme
Echecs récidivants de fécondation in vitro avec ou sans Ac anti-phospholipide
Nécrose épidermique toxique et SSJ
Urticaire et dermatite atopique
Sclérodermie systémique
Maladies infectieuses
Prévention des infections chez le grand prématuré

Syndrome d'activation macrophagique secondaire à une infection à Epstein Barr virus

Indications caduques

Rétinochoïdopathie de Birdshot *
Infections bactériennes récidivantes chez l'enfant infecté par le VIH*

6.4 CANADA

6.4.1 Guideline development in Canadian Provinces and Territories

	GUIDELINE & RECOMMENDATIONS IN CANADA				
	BRITISH COLOMBIA	**ALBERTA/MANITOBA/SASKATCHEWAN**	**ONTARIO**	**ATLANTIC PROVINCES**	**QUEBEC**
date	version 4, 29 May 2018	criteria for clinical use, April 2018	version 4, January 31,2018	May 2018	2017
author	Transfusion Medicine Advisory Group (TMAG)	Prairie Collaborative IG utilization management framework, inter-provincial medical expert committee and Institute of Health economics	Ontario Regional Blood Coordinating Network	Atlantic collaborative via the Nova Scotia Provincial Blood Coordinating Team	l'Institut national d'excellence en santé et en services sociaux (INESSS)
process	consensus of the Transfusion Medicine Advisory Group recommendations	Literature search for guidelines (sept 2017) and additional evidence from SR or primary studies critical appraisal AGREE tool + expert opinion (6 topic-specific committees) Consensus-based decisions	literature review + expert opinion (reviewed by physicians within each of the specialties Ontario IG advisory Panel)	NAC recommendations of 2007 + expert opinion (clinical advice from 307 physicians in different domains)	literature review: 25 neurological indications selected, Cochrane systematic review updated with primary studies (January 2017) (further publications to follow)
outcome	List of Approved Medical Conditions for IVIG Use	"Do", "Do Not Do", or "Do Not Know" recommendations	*indications for routine use *indications recommended not for routine use	*Indicated conditions with prerequesites *possibly indicated conditions	*Beneficial effect RCTs or meta-analyses of RCTs *efficacy inadequate *insufficient evidence

6.4.2 *Recommended indications for which there is consensus in all Provincial guidelines*

recommended indication
HEMATOLOGY
Fetal/neonatal alloimmune thrombocytopenia (FNAIT)
Haemolytic disease of Fetus or Newborn (HDFN)
Immune thrombocytopenia (adult)
Immune thrombocytopenia (paediatric)
NEUROLOGY
Chronic Inflammatory Demyelinating Polyneuropathy
Guillain Barré syndrome (including miller-fisher)
Multifocal motor neuropathy (MMN)
Myasthenia gravis
RHEUMATOLOGY
Juvenile idiopathic inflammatory myopathy (dermatomyositis)
Kawasaki disease
INFECTIOUS DISEASE
Toxic shock syndrome (streptococcal or staphylococcal)
IMMUNOLOGY
Primary Immune Deficiency (PID)
Secondary Immune Deficiency (SID)

6.4.3 *Indications for which Provincial guidelines have no consensus*

recommended indication	BRITISH COLOMBIA	ALBERTA/MANITOBA/SASKATCHEWAN	ONTARIO	ATLANTIC PROVINCES	QUEBEC (only on 25 neurological conditions)
HEMATOLOGY					
post transfusion purpura		x	x	x	
heparin-induced thrombocytopenia		x			
neonatal thrombocytopenia secondary to maternal autoimmune disorders		x			
pure red cell aplasia		x	?	?	
acquired hemophilia with factor VIII inhibitor		?	?	?	
hematological malignancy				?	
autoimmune hemolytic anemia		?	?	?	
acquired von willebrands disease			?		
allogenic bone or stem cell transplantation		x	x		
autoimmune neutropenia		?	?		
hemolytic transfusion reaction			?		
virus associated hemophagocytic syndrome			?		
hemolytic uremic synrome		?			
neonatal hemochromatosis		?			
sickle cell disease		?			
thrombotic thrombocytopenic purpura		?			
NEUROLOGY					
lambert eaton myasthenia gravis		x	?	?	x
acute Disseminated encephalomyelitis (ADEM)		x	?	?	?
anti-NMDA receptor encephalitis		x			
multiple sclerose		x		?	x remitting
IgM paraproteinemia associated neuropathy		x			?

recommended indication	BRITISH COLOMBIA	ALBERTA/MANITOBA/SASKATCHEWAN	ONTARIO	ATLANTIC PROVINCES	QUEBEC (only on 25 neurological conditions)
epilepsy - opsoclonus myoclonus ataxia (pediatric)		x			
epilepsy - opsoclonus myoclonus ataxia (adult)		?			
paraneoplastic or sporadic autoimmune encephalitis		x		?	
stiff person syndrome		x	?	?	x
sydenham chorea		x		?	
autoimmune encephalitis (NMDA or Rasmussen)		?	?	?	?
PANDAS		?	?	?	?
neuromyelitis Optica (devic disease)		?		?	?
autoimmune optic neuropathy				?	
childhood epilepsy		?			
acute flaccid myelitis		?			
aicardi goutieres syndrome		?			
diabetic amyotrophy		?			?
hashimoto encephalopathy		?			
narcolepsy/cataplexy		?			
paraneoplastic neurological syndromes		?			?
postpolio syndrome		?			
susac syndrome		?			
transverse myelitis		?			
DERMATOLOGY					
pemphigus vulgaris and variants	x	x	x	?	
autoimmune blistering diseases (pemphigus, epidermolysis bullosa acquisita)		x		?	
pyoderma gangrenosum		x		?	
scleromyxedema		x		x	

recommended indication	BRITISH COLOMBIA	ALBERTA/MANITOBA/SASKATCHEWAN	ONTARIO	ATLANTIC PROVINCES	QUEBEC (only on 25 neurological conditions)
toxic epidermal necrolysis/stevens-johnson syndrome		x	?		
systemic vasculitic syndromes (polyarteritis nodosa livedoid vasculopathy)		?		x	
chronic idiopathic urticaria		?		?	
necrobiotic xanthogranuloma				?	
pre-tibial myxederma				?	
severe lupus erythematosus		?		?	
atopic dermatitis (pediatric)		?		?	
RHEUMATOLOGY					
idiopathic inflammatory myopathy adult (dermatomyositis and polymyositis)		x	x	x	
antiphosholipid syndrome catastrophic leading to multiple organ failure		x		?	
eosinophilic granulomatosis with polyangiitis		x			
adult-onset still's disease		?		?	
sjogren syndrome		?		?	
hematophagocytic lymohistiocytosis		?		?	
scleroderma		?			
immune-mediated uveitis		?			
INFECTIOUS DISEASE					
necrotizing faciiitis		?			
IMMUNOLOGY					
hematopoetic stem cel transplant in PID		x	x		
solid organ transplant (pre-transplantation)		x	x		
solid organ transplant (peri-transplantation)		x	x		
antibody medicated rejection		x	x	x	
OTHER					
sytemic capillary leak syndrome		x			

recommended indication	BRITISH COLOMBIA	ALBERTA/MANITOBA/SASKATCHEWAN	ONTARIO	ATLANTIC PROVINCES	QUEBEC (only on 25 neurological conditions)
vasculitic syndromes		?			
congenital heart block, autoimmune (neonatal lupus)		?			
graves' disease		?			

x indicates that the guideline recommends the use of IG in this indication, but for most indications, specifications and prerequisites exist (see specific guideline)

? Indicates that the guideline has no strong recommendation, categorises it as a 'don't know indication' or is based on very limited evidence

6.4.4 Not recommended indications per Provincial Guideline

NOT RECOMMENDED	BRITISH COLOMBIA	ALBERTA/MANITOBA/SASKATCHEWAN	ONTARIO	ATLANTIC PROVINCES	QUEBEC
adrenoleukodystrophy	x	x	no list	no list	x
autism	x	x			x
inclusion body myositis	x	x			x
POEMS syndrome	x	x			x
alzheimer's disease		x			x
critical illness polyneuropathy	x	x			
HIV/aids		x			
aplastic anemia	x				
heparin induced thrombocytopenia	x	,			
amyotropic lateral sclerosis	x				
intractable childhood epilepsy	x				
paraproteinemic neuropathy (igM)	x				
sepsis,neonatal prophylaxis,		x			
clostridium difficile infection;		x			
prophylaxis for CMV, Epstein-Barr		x			

NOT RECOMMENDED	BRITISH COLOMBIA	ALBERTA/MANITOBA/SASKATCHEWAN	ONTARIO	ATLANTIC PROVINCES	QUEBEC
preventing graft-versus-host disease		x			
autologous HSCT		x			
acute optic neuritis		x			
chronic fatigue syndrome		x			
antiphospholipid syndrome (other than catastrophic)		x			
behcet disease		x			
rheumatoid arthritis		x			
progressive-secondary multiple sclerosis					x

6.5 ENGLAND

6.5.1 *Colour-coding priority system of indications for Ig use in England*

Red
High priority

Conditions	Short term	Long term
Alloimmune Thrombocytopenia (Foeto - Maternal/Neonatal)		
Chronic inflammatory demyelinating polyradiculoneuropathy		
Guillain Barre Syndrome		
Haemolytic disease of the newborn		
HSCT in primary immunodeficiencies		
Immune thrombocytopenic pupura (acute and persistent, excluding chronic)		
Kawasaki disease		
Paraprotein - associated demyelinating neuropathy (IgM, IgG or IgA)		
Primary immunodeficiences		
Specific antibody deficiency		
Thymoma with immunodeficiency		
Toxic epidermal necrolysis, Stevens Johnson syndrome		

*Updated May 2018

Blue
Medium priority

Conditions	Short term	Long term
Acquired red cell aplasia		
Autoimmune congenital heart block		
Autoimmune haemolytic anaemia		
Autoimmune uveitis		
Coagulation factor inhibitors (alloantibodies and autoantibodies)		
Haemophagocytic syndrome		
Immunobullous disease		
Inflammatory myopathies		
Multifocal motor neuropathy		
Myasthenia gravis (including Lambert - Eaton myasthenic syndrome)		
Necrotising (PVL - associated) staphylococcal sepsis		
Post - transfusion purpura		
Rasmussen syndrome		
Secondary antibody deficiency (any cause)		
Severe or recurrent clostridium difficile colitis		
Staphylococcal Streptococcal toxic shock syndrome		
Stiff person syndrome		
Transplantation (solid organ)		

Grey
Low Priority

Conditions

Immune-mediated disorders with limited evidence of immunoglobulin efficacy	Presumed immune-mediated disorders with little or no evidence of efficacy
Acute disseminated encephalomyelitis (If high dose steroids have failed)	Acquired red cell aplasia NOT due to parvovirus B19
Autoimmune encephalitis (including NMDA and VGKC antibodies, among others)	Acute idiopathic dysautonomia
Catastrophic antiphospholipid syndrome	Aplastic anaemia/pancytopenia
Cerebral infarction with antiphospholipid antibodies	Atopic dermatitis/eczema
Chronic ITP	Autoimmune neutropenia
CNS Vasculitis	Chronic facial pain
Complex regional pain syndrome	Diabetic proximal neuropathy
Intractable childhood epilepsy	Haemolytic uraemic syndrome
Neuromyotonia	PANDAS
Opsoclonus Myoclonus	Paraneoplastic disorders that are known not to be B- or T-cell mediated
Post exposure prophylaxis for viral or pathogenic infection if intramuscular injections is contraindicated, or treatment when hyper-immune Immunoglobulins are unavailable	POEMS
Pyoderma gangrenosum	SLE without secondary immunocytopenias (Including juvenile)
Systemic juvenile idiopathic arthritis	
Systemic vasculitides and ANCA disorders	
Urticaria (Severe, intractable)	

Black

Conditions
Immunodeficiency secondary to paediatric HIV infection
Autologous BMT
Adrenoleukodystrophy
Alzheimer's disease
Amyotrophic lateral sclerosis
Chronic fatigue syndrome
Critical illness neuropathy
Multiple sclerosis
Rheumatoid arthritis
Neonatal sepsis (prevention or treatment)
Sepsis in the intensive care unit not related to specific toxins or C. difficile
Asthma
Graves ophthalmopathy
IVF failure
Recurrent spontaneous pregnancy loss

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