NHS England

Evidence Review:

Intravenous immunoglobulin for acute disseminated encephalomyelitis

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Contents

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is a rare autoimmune disease of the central nervous system, marked by widespread inflammation in the brain and spinal cord. ADEM typically damages the myelin sheaths covering the nerves of the central nervous system, which, as a result, destroys the white matter. It is often triggered by a viral infection or vaccination, and is therefore is sometimes referred to as post-infectious or post-immunization acute disseminated encephalomyelitis.

Post-infectious or antibody mediated conditions are often associated with acute transverse myelitis (ATM). ATM is an attack of inflammation of the spinal cord. ATM is sudden and develops rapidly over hours to days, causing weakness in the arms and legs, which can range from a mild 'heavy' feeling in one limb, to complete paralysis in all four limbs.

Human immunoglobulin is a sterile preparation of concentrated immunoglobulins recovered from pooled human plasma or serum obtained from outside the UK, tested and found non-reactive for hepatitis B surface antigen and for antibodies against hepatitis C virus and human immunodeficiency virus (types 1 and 2). Intravenous immunoglobulin (IVIg) is proposed as a treatment option for the above indications where the condition is unresponsive to first line treatments such as steroid therapy or plasma exchange (PLEX), or first line treatments are contra-indicated.

A global shortage of human immunoglobulin and the rapidly increasing range of clinical indications for treatment with immunoglobulins has resulted in the need for a Demand Management programme for IVIg in the UK. IVIg is commissioned by NHSE in line with Clinical Guidelines for Immunoglobulin Use (Department of Health, Second edition update, July 2011). ADEM and AIE are classified as grey indications, and IVIg is not currently routinely commissioned by NHS England for these conditions. Grey indications are those diseases where the evidence is weak, in many cases becuse the disease is rare, and treatment should be considered on a case by case basis.

2. Summary of results

What is the clinical effectiveness of IVIg for ADEM / ATM, when used a) instead of PLEX in those who haven't responded to steroids alone, b) for patients who are critically ill and need to optimise treatment urgently (i.e. in combination with steroids), or c) in poor responders to steroid and PLEX?

Clinical effectiveness of IVIg for patients with ADEM

The evidence review on use of intravenous immunoglobulin for patients with acute disseminated encephalomyelitis (ADEM) included the Department of Health clinical guidelines, two systematic reviews (including the Canadian guidelines), the Australian guidelines, and a few case series.

Clinical guidelines for immunoglobulin use (Department of Health (DoH), England, second edition 2008, 2011 update) was based on expert panel review and systematic literature search for articles published between 1996-2006 and ADEM was one of the conditions included in the review. The evidence review included a search of articles published from 1996-2006 and articles for inclusion for review were assessed by a panel of experts.

According to the above DoH guidelines ADEM is a "grey" indication (grey indications are those diseases for which the evidence is weak, in many cases because the disease is rare) and may be considered for acute disseminated encephalomyelitis where high-dose corticosteroids or plasma exchange have failed (grade C recommendation, level III evidence).

The evidence relating to ADEM in these guidelines appears to have been based on two studies: Kleiman et al 1995 and Sahlas et al 2000. Based on these studies, the guidelines conclude IVIg might provide benefit in ADEM, particularly in patients who have failed to respond to high dose corticosteroids. According to the guidelines, IVIg may be considered where high-dose corticosteroid therapy or plasma exchange has failed and there is abnormal white matter on magnetic resonance imaging (MRI)/computed tomography.

The Canadian guidelines on the use of intravenous immune globulin (IVIg) for neurologic conditions (Feasby et al, 2007) were developed by expert panel review of a systematic literature search for articles published between 1996-

2004. ADEM was one of the 22 conditions included in the review.

These guidelines recommend IVIg
1. As a reasonable option as second-line therapy for monophasic ADEM in patients who do not respond to high-dose corticosteroids,
2. In patients with monophasic ADEM who have contraindications to steroids and
3. May be considered as an option to eliminate steroid dependency or for those patients who fail to respond, or have contraindications, to steroids in relapsing ADEM.

These guidelines recommend a total dose of 2 g/kg given over 2 to 5 days for adults and over 2 days for children for these indications.

The evidence in these guidelines for use of IVIg in children is based on 14 case reports (9 monophasic ADEM and 5 relapsing ADEM) consisting of 25 cases and in adults from 6 case reports (5 monophasic ADEM and 1 relapsing ADEM) consisting of 10 cases.

The majority of paediatric case reports involved children with monophasic ADEM. Overall, 70% (14/20) of children with monophasic ADEM completely recovered following administration of IVIg or IVIg plus corticosteroids. Of the five cases of relapsing ADEM, two children completely recovered after IVIg and the three others showed improvement. Two children with relapsing ADEM required monthly IVIg to maintain their response. Overall, 50% (4/8) of adults with monophasic ADEM completely recovered following treatment with IVIg. Both adults with relapsing ADEM showed marked improvement following IVIg.

The guideline does not define the definition of a ‘recovery’ or ‘improvement’ which are the primary outcomes of the intervention.

In making these recommendations the Guidelines acknowledge the evidence for IVIg in the treatment of ADEM is limited. However, given the number of positive cases reported, the Expert Panel opinion was that IVIg is a reasonable option as second-line therapy for monophasic ADEM in patients who do not respond to high-dose corticosteroids.

Criteria for the clinical use of intravenous immunoglobulin in Australia (Commonwealth of Australia, National Blood Authority, second edition in 2012) guidelines and recommendations were based in the same studies as the Canadian review, and drew the same conclusions.

Vitalti et al 2015 is a systematic review of evaluation of the usefulness of immunotherapy including IVIg in children undertaken through an electronic literature search of MEDLINE via PubMed interface, SCOPUS, Google Scholar, the Cochrane Library for articles published from inception to February 2015.

The review identified 5 case reports and an article summarising the Canadian guidelines (Feasby et al 2007). The 5 cases reported in the review by Vitalti were also included in the Canadian and Australian reviews. Nishikawa et al 1999, an observational case study of three children, aged 2 to 5 years affected by ADEM, reported successful treatment using high dose IVIg (400 mg/Kg/day) in 5 consecutive days, with an improvement of their consciousness in 14 hours, 2 days and 4 days respectively. Another observational study on 4 paediatric patients affected by corticosteroid-resistant ADEM (with no improvement after receiving a 3-5 day course of high dose intravenous methylprednisolone) showed rapid improvement after administration of IVIgg (Pradhan et al 1999). Imitaka G et al (2014) have reported a case of successful treatment of steroid-resistant ADEM in a 10-month-old infant with five days of 400 mg/kg/day of IVIg, with complete recovery. Treatment of relapsing ADEM with maintenance therapy of monthly IVIg is also reported in two case reports (Hahn et al 1996, Mariotti 2003).

Similar to results in the Canadian and Australian review, the authors report that children with ADEM who did not respond to first line treatment with corticosteroids responded following treatment with IVIg. However the review doesn’t include definition of non-response to cortico-steroids or define precisely a positive response to IVIg. Overall the level of evidence from the review is low as it derives from case reports and the lack of clarity in reporting outcomes is a limitation to its generalisability.

Three further case series not reported in the above systematic reviews were identified: Ravaglia et al 2007, Incecik et al 2013 and Erol et al 2013.

The study by Ravalgia is a prospective case series of 65 patients with ADEM studied over an 8 year period. Of the

65, 25 received IVIg because they were steroid resistant (19 patients) or steroid contraindicated (5 patients). Outcomes were defined as either good or bad in relation to functional capacity such as walking, bladder function and cognition. Among the steroid resistant group 10/19 patients (53 %) found IVIg was effective, the clinical improvement beginning within the end of the five-day cycle, without relapses. Prominent effects of IVIg were detectable on motor dysfunction. Milder onset disability (p=0.013) and lower CSF albumin (p=0.006) were predictors of IVIg response. Among steroid-free patients, 3/5 were responsive to IVIg. Some of the limitations of the study were the lack of a control arm, and the lack of random assignment of treatment raising the question of bias. In addition, the disease itself can be self-limiting and there is a possible synergistic effect between steroids and IVIg which cannot be excluded in the 19 patients who received both drugs.

The study by Incecik included 15 children with ADEM who were identified between 2004 and 2010 in a Turkish hospital. Of the 15, 3 were treated with IVIg (all in different ways – one short course of IVIg alone, the other two both received prednisolone, one of whom also had plasmapheresis). The study reported that all 3 patients treated with IVIg recovered from neurological deficits. The evidence level of this study is 4 due to the small number, lack of pooling of data of results and lack of definition of primary outcome i.e. “recovery”.

The study Erol et al 2013 was a retrospective case series of 15 children with ADEM admitted to a single institution in Turkey. Three of the fifteen children were treated with IVIg following poor response to treatment with a standard protocol of 3 to 5 days of intravenous administration of methylprednisolone. The study reported that 14 children recovered, although follow up ranged from 0.6 to several years. There was no subgroup analysis by IVIg group. This is evidence of level 3-4 due to the small number of IVIg patients, lack of clarity regarding outcome definition and variable periods of follow up.

Clinical effectiveness of IVIg for patients with transverse myelitis

There is very limited published evidence on IVIg in transverse myelitis (TM). We identified only one systematic review which is a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and a large number of single case reports which were excluded from the review. None of the three national guidelines (England, Canada, and Australia) include IVIg for TM in their list of indications.
The American study is a well-designed systematic review of clinical evaluation and treatment options for TM. Authors include other diseases of TM syndrome including acute complete transverse myelitis (ACTM); acute partial transverse myelitis (APTM) and neuromyelitis optica (NMO) in the review. On the evidence for the use of IVIg in transverse myelitis, the authors concluded that based on case reports, small case series, and retrospective reviews IVIg and other therapies may have potential benefit such as aborting TM attacks, promoting functional recovery, or reducing the frequency of additional attacks. However they conclude that there is insufficient evidence to determine the efficacy of IVIg (and other agents such as azathioprine, cyclophosphamide) in alleviating TM attacks (Level 4 evidence).

The evidence review also identified a protocol for an ongoing multicentre randomised controlled trial of IVIg versus standard therapy for the treatment of Transverse Myelitis in adults and children (STRIVE). This study by Absoud et al 2015 is currently recruiting patients and results of the study are awaited.

For the sake of completeness the references from the study protocol were searched for any other published evidence on use of IVIg in TM and there was very little found.

What is the cost effectiveness of IVIg for ADEM / ATM, when used a) instead of PLEX in those who haven’t responded to steroids alone, b) are critically ill and need to optimise treatment urgently (i.e. in combination with steroids), or c) in poor responders to steroid and PLEX?

There is no published available on cost effectiveness of IVIg in ADEM/TM.

3. Research questions

What is the clinical effectiveness of IVIg for ADEM / acute TM, when used a) instead of PLEX in those who haven’t responded to steroids alone, b) are critically ill and need to optimise treatment urgently (i.e. in combination with steroids), or c) in poor responders to steroid and PLEX?

What is the cost effectiveness of IVIg for ADEM / acute TM, when used a) instead of PLEX in those who haven't responded to steroids alone, b) are critically ill and need to optimise treatment urgently (i.e. in combination with steroids), or c) in poor responders to steroid and PLEX?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and intervention				Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Clinical Population	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
3	Systematic + Meta Analysis	not reported	IVIg	Patients with diagnosis of ADEM	Clinical effectiveness of the intervention	not defined but authors recovery from neurological deficits as measure of outcome	Authors report all patients recovered following IVIg treatment but there is no clear	none	-	Vitaliti, Giovanna; Tabatabaie, Omidreza; Matin, Nassim; Ledda, Caterina; Pavone, Piero; Lubrano, Riccardo; Falsaperla, Raffaele. The usefulness of immunotherapy in paediatric neurodegenerative disorders: A systematic review of literature data. Hum Vaccin Immunother 2015;0(0):0.	none	as in primary outcome	This is a systematic review of evaluation of usefulness of immunotherapy including IVIg in children undertaken through an electronic literature search of MEDLINE via PubMed interface, SCOPUS, Google Scholar, the Cochrane Library for articles published from inception to February 2015. The review identified 4 case reports and an article summarising the Canadian guidelines (Feasby et al 2007). The 4 case reported in the review by Vitalti were also included in the Canadian and Australian reviews. Similar to results in the Canadian and Australian review, the authors report children with ADEM who did not respond to first line treatment with corticosteroids responded following treatment with IVIg. However the review doesn't include definition of non response to corticosteroids or the definition of a response to IVIg. Overall the level of evidence from the review is at 4 due to case reports and lack of clarity in reporting outcomes it's generalisability are limited
3	Systematic	25 children and 10 adults	IVIg	Children and adults with ADEM	Cost effectiveness	none reported but authors state recovery from neurological deficits	Overall, 70% (14/20) of children with monophasic ADEM completely recovered following administration of IVIg or IVIg plus corticosteroids. Of the five cases of relapsing ADEM, two children completely recovered after IVIg and the three others showed improvement. Two children with relapsing ADEM required monthly IVIg to maintain their response. Overall, 50% (4/8) of adults with monophasic ADEM completely recovered following treatment with IVIg. Both adults with relapsing ADEM showed marked improvement following IVIg.	none	-	Feasby, Tom; Banwell, Brenda; Benstead, Timothy; Bril, Vera; Brouwers, Melissa; Freedman, Mark; Hahn, Angelika; Hume, Heather; Freedman, John; Pi, David; Wadsworth, Louis. Guidelines on the use of intravenous immune globulin for neurologic conditions. Transfus Med Rev 2007;21(2 Suppl 1):S57-107.	none reported	as in primary outcome	This is a artcle reporting on the development of Canadian 2004 guidelines for use of immunoglobulin The Canadian guidance on use of IVIg is based on Expert Panel review consisting of systematic literature search for articles published between1996-2004. ADEM was one of the 22 conditions included in the review. The Guidelines recommend IVIg 1. As a reasonable option as second-line therapy for monophasic ADEM in patients who do not respond to high-dose corticosteroids, 2. In patients with monophasic ADEM who have contraindications to steroids and 3. May be considered as an option to eliminate steroid dependency or for those patients who fail to respond, or have contraindications, to steroids in relapsing ADEM. Dose and Duration: The Guidelines recommend a total dose of 2 g/kg given over 2 to 5 days for adults and over 2 days for children. The evidence for use of IVIg in children is based on 14 case reports ((9 monophasic ADEM and 5 relapsing ADEM) consisting of 25 cases and in adults from 6 case reports (5 monophasic ADEM and 1 relapsing ADEM) consisting of 10 cases. The majority of paediatric case reports involved children with monophasic ADEM. Overall, 70% (14/20) of children with monophasic ADEM completely recovered following administration of IVIg or IVIg plus corticosteroids. Of the five cases of relapsing ADEM, two children completely recovered after IVIg and the three others showed improvement. Two children with relapsing ADEM required monthly IVIg to maintain their response. Overall, 50% (4/8) of adults with monophasic ADEM completely recovered following treatment with IVIg. Both adults with relapsing ADEM showed marked improvement following IVIg. The guideline does not define the definition of a 'recovery' or 'improvement' which are primary outcomes of the intervention. In making these recommendation the Guidelines acknowledge the evidence for IVIg in the treatment of ADEM is limited, however, given the number of positive cases reported, the Expert Panel opinion was that IVIg is a reasonable option as second-line therapy for monophasic ADEM in patients who do not respond to high-dose corticosteroids.
4	Case series	15	IVIg	Children with ADEM	Clinical effectiveness of the intervention	not defined but authors report recovery from neurological symptoms as an outcome	3/15 who received IVIg following failure of standrad treatment with steroids all recovered	none	none	İncecik, Faruk; Hergüner, M. Özlem; Altunbaşak, Şakir. Acute disseminated encephalomyelitis: an evaluation of 15 cases in childhood. Turk. J. Pediatr. 2013;55(3):253-259.	none reprted	as in primary outcome	This is retrospective case reports which included 15 children with ADEM identified between 2004-2010 in a Turkish hospital. Of the 15 and 3 were treated with IVIg (one received only IVIg for 5 days; second received IVIg along with plasmapheresis and oral prednisolone following treatment with IV methyl prednisone and the third received IVIg plus oral prednisolone following treatment with IV methyl prednisolone). Authors report in all the 3 patients treated with IVIg patients recovered from neurological deficits. The evidence level of this study is 4 due to small number, lack of pooling of data of results and lack of definition of primary outcome i.e recovery.

3	Case series	15	IVIg	ADEM	Clinical effectiveness of the intervention	not defined but authors report recovery from neurological symptoms as an outcome	3/15 who received IVIg following failure of standrad treatment with steroids all recovered	none	none	Erol, Ilknur; Ozkale, Yasemin; Alkan, Ozlem; Alehan, Fusun. Acute disseminated encephalomyelitis in children and adolescents: a single center experience. Pediatr. Neurol. 2013;49(4):266-273.	none reprted	as in primary outcome	Study Erol et al 2013 is a retrospective case series of 15 children with acute disseminated admitted to single institution in Adana, Turkey. Three of the fifteen children were treated with IVIg following poor response to treatment with standard protocol of 3 to 5 days of intravenous administration of methylprednisolone. Authors report, after a follow-up period ranging from 0.6 to years, all but one child recovered. One child who did not recover was subsequently diagnosed as having multiple sclerosis. There is no subgroup analysis by IVIg group. This is evidence level 3-4 study due to small number of IVIg patients and poor reporting on outcomes
4	Systematic	3	IVIg	patients with ADEM	Clinical effectiveness of the intervention	clinical improvement in symptoms	Not specifically reported in the DoH report but authors report that 'anecdotal evidence suggests that IVIg might provide benefit in acute disseminated encephalomyelitis], particularly in patients who have failed to respond to highdose corticosteroids	none	-	Department of Health. Clinical guidelines for immunoglobulin use. 0 2nd edition 2008 and updated in 2011;0(0):2nd edition 2008 and updated in 2011.	-	as in primary outcome measure	The DoH guidelines were originally published in 2006? And 2nd edition which was published in 2008 was updated in 2011. The recommendations in the guideline were based on a systematic review. ADEM is one of the Grey indication ((Grey indications are those diseases for which the evidence is weak, in many cases because the disease is rare.The DoH recommend IVIg may be considered for acute disseminated encephalomyelitis where high-dose corticosteroids or plasma exchange have failed (grade C recommendation, level III evidence). The evidence ADEM in the Guidelines appears to have been based on two studies mentioned in the Guidelines; Kleiman et al 1995 and Sahlas et al 2000 Based on these studies the Guidelines conclude IVIg might provide benefit in acute disseminated encephalomyelitis, particularly in patients who have failed to respond to high dose corticosteroids. Guidelines recommend IVIg at 0.4 g/kg/day for 5 days may be considered where high-dose corticosteroid therapy or plasma exchange has failed and there is abnormal white matter on magnetic resonance imaging (MRI)/computed tomography.Evidence level 4 as conclusions are based on 2 case reportswith small sample size.
2-	Case series	not mentioned	IVIg	Tranverse myelitis and related diseases	Clinical effectiveness of the intervention	none defined	Authors conclude that Case reports, small case series, and retrospective reviews have suggested potential benefits of a variety of other agents to abort TM attacks, promote functional recovery, or influence the future predilection of additional attacks. There is insufficient evidence to determine the efficacy of azathioprine, cyclophosphamide, and IVIg in alleviating TM attacks (Class IV studies).	none	-	Scott, T. F.; Frohman, E. M.; De Seze, J.; Gronseth, G. S.; Weinshenker, B. G.; Therapeutics and Technology Assessment Subcommittee of American Academy of Neurology. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2011;77(24):2128-2134.	none	as in primary outcome	This is a well designed systematic review of clinical evaluation and treatment options for transverse myelitis. Authors include other disease of TM syndrome including acute complete transverse myelitis(ACTM); acute partial transverse myelitis(APTM); neuromyelitis optica (NMO). The study is presented with objective and sercah methodology including database, methodolgy for selecting article. However there is description for metanalysis, quality assesment or testing hetrogenety. On the use of IVIg in transverse myelitis authors conclude that based on case reports, small case series, and retrospective reviews have suggested potential benefits of a variety of other agents to abort TM attacks, promote functional recovery, or influence the future predilection of additional attacks. However there is insufficient evidence to determine the efficacy of IVIg (and other agents such as azathioprine, cyclophosphamide) in alleviating TM attacks (Class IV studies).
3	Case series	24/65 cases receiving IVIg (19 steroid resistant +5 steriod contraindated patients)	IVIg0.4 g/kg/day for 5 days	Adults with ADEM	Clinical effectiveness of the intervention	outcome: (a) good (e. g. normal walking or need of unilateral help, normal or mildly compromised bladder function, normal or mildly compromised cognitive function); (b) bad (walking with double assistance or wheelchair, severe bladder dysfunction, severe cognitive dysfunction).	Among steroid resistances group 10/19 patients (53 %) IVIg were effective, the clinical improvement beginning within the end of the five-day cycle,without relapses. Prominent effects of IVIg were detectable on motor dysfunction. Milder onset disability (p=0.013) and lower CSF albumin (p=0.006) were the predictors of IVIg response. Among steroid-free patients, 3/5 were responsive to IVIg	none reported	-	Ravaglia, Sabrina; Piccolo, Giovanni; Ceroni, Mauro; Franciotta, Diego; Pichiecchio, Anna; Bastianello, Stefano; Tavazzi, Eleonora; Minoli, Lorenzo; Marchioni, Enrico. Severe steroid-resistant post-infectious encephalomyelitis: general features and effects of IVIg. J. Neurol. 2007;254(11):1518-1523.	none mentioned	as in p[rimary outcome measure	This is prospective case series of 65 patients with ADEM over a 8 year period. Of the 65, 25 reccieved IVIg because they were steroid resistant (19) or steroid contrindicated(5). Among steroid resistances group 10/19 patients (53 %) IVIg were effective, the clinical improvement beginning within the end of the five-day cycle,without relapses. Prominent effects of IVIg were detectable on motor dysfunction.Milder onset disability (p=0.013) and lower CSF albumin (p=0.006) were the predictors of IVIg response. Among steroid-free patients, 3/5 were responsive to IVIg. Someof the limitation of the study as this study was not controlled and the treatments were not randomly assigned, t effects documented in the IVIg-responder patients could have occurred by chance. Other one being the disease could be self-limiting. Also a possible synergistic effect between steroids and IVIg cannot be excluded in the 19 patients who received both drugs.

2-	Systematic	not mentioned	IVIg	patients with ADEM	Clinical effectiveness of the intervention	not defined but authors report recovery from neurological symptoms as an outcome	Authors conclude that on review of multiple case series of IVIg use for paediatric ADEM found that children with monophasic ADEM completely recovered after administration of IVIg or IVIg plus corticosteroids. In recurrent ADEM, children either completely recovered after IVIg, or showed improvement. Adults with monophasic or recurrent ADEM recovered after treatment with IVIg.	none	-	Commonwealth of Australia, National Blood Authority . Criteria for the clinical use of intravenous immunoglobulin in Australia Second Edition July 2012. 0 2012;2nd edition(0):0.	none	as in primary outcome	The Australian guidelines are based on Expert Panel review of the evidence of use if IVIg in humans and ADEM was one of the disease included. The second edition is an update of first edition published in 2007 which consisted of systematic review for evidence published until 2004.The evidence review for the second edition consisted of systematic search of databases for articles published between 2004 -2011 and the quality of articles was assessed by panel of experts using international standards. The guidelines recommend IVIg can be used in 1. ADEM unresponsive to steroid therapy or where steroids are contraindicated (e.g. suspicion of CNS infection). Assessment by a neurologist is recommended, but not mandatory. 2. Recurrent or multiphasic ADEM unresponsive to steroid therapy, or where steroid therapy has become intolerable or is contraindicated, with assessment by a neurologist mandatory The recommended induction dose of 2 g/kg in 2 to 5 divided doses and maintenance dose 0.4–2 g/kg, 4–6 weekly for recurrent or multiphasic ADEM only. The evidence for above recommendation was based on number of case report and case series consisting of 1-4 cases. The studies identified in this review were similar to Canadian review and the level of evidence of included studies was level 3-4.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	n/a
Updated search terms - Population	ADEM OR acute disseminated encephalomyelitis OR acute disseminated encephalomyelitides OR acute demyelinating encephalomyelitis OR acute demyelinating encephalomyelitides OR transverse myelitis OR transverse myelopathy OR transverse myelopathies OR tranverse myelitides
Updated search terms - Intervention	intravenous normal human immunoglobulin OR IVIG OR intravenous immunoglobulin OR intravenous immune globulin OR immune globulin intravenous OR IGIV OR intravenous immunoglobulins OR intravenous normal human immunoglobulins OR intravenous immune globulins
Updated search terms - Comparator	n/a
Updated search terms - Outcome	n/a

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	n/a
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 7. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	n/a