NHS England

Evidence Review:

Intravenous immunoglobulin for autoimmune encephalitis

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1. Introduction

Autoimmune encephalitis (AIE) is used to describe a group of disorders characterised by symptoms of limbic and extra-limbic dysfunction occurring in association with antibodies against synaptic antigens and proteins localised on the neuronal cell surface. These autoimmune conditions include, but are not limited to, VGKC-complex antibody associated encephalitis, NMDA-receptor antibody associated encephalitis, GAD antibody associated encephalitis, MOG antibody disease and Hashimoto's encephalitis. AIE symptoms include amnesia, seizures, psychosis, abnormal movements, autonomic dysregulation, hemiplegia, visual loss and coma.

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 autoantibody-associated neurological encephalitis syndromes, 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 steroids and PLEX?

Evidence for the effectiveness of IVIg in autoimmune encephalitis due to autoantibodies targeting neuronal cell surface proteins comes from one large systematic review by Nosadini et al 2015 which includes all articles published up to September 2015 and three other small sized studies not included in this review. There are no randomized controlled trials of treatment, and the majority of studies are small sized retrospective case series, except for the study by Titulaer et al which included 577 patients.

The review does not include subgroup analysis by treatment groups but provides information comparing patients receiving immunomodulatory therapy with those receiving no immunomodulatory therapy. It appears that IVIg when used in combination with other immunomodulatory treatments has better outcomes compared to patients with no immunotherapy. This appears true for encephalitis syndromes due to anti-NMDAR antibodies, anti-Capr2 antibodies, anti-GABABR antibodies, anti-GABAAR antibodies, anti-DPPX antibodies, anti-GlyR antibodies. Anti-IgLON5 encephalitis appears to be different from the other autoimmune encephalitides, with poor response to immune therapy and a high mortality rate.

Nosedini et al 2015 also concluded that early commencement of immune therapy is more commonly associated with better outcomes, and that the use of second-line immune therapies is more commonly associated with better outcomes and a lower rate of relapse, but is influenced by severity bias, as sicker patients are more likely to receive second-line therapy.

Evidence for the use of IVIg in autoimmune encephalitis due to paraneoplastic syndrome (PND) is derived from one review article by Sadeghian et al 2010 and a number of small sized studies (Vodopevic et al 2015, Moon et al 2014, Omlez et al 2013). Based on this Clinical Evidence Review, there is some evidence that the use of IVIg might have a positive impact, but as IVIg was used with other immunomodulatory treatments it is not possible to assess the specific impact of IVIg on patient outcomes. Sadeghian et al 2010 recommend IVIg use in PND affecting peripheral nervous system. Evidence level 3-4.

The main limitations of the evidence were the limited number of patients studied and the retrospective and non-standardised nature of both data and outcome measures. Most studies did not include a precise definition of patient outcomes, though a few studies used the Modified Rankin Scale to measure this. It also appears that a standardised protocol for the use of IVIg was lacking, and the majority of the studies did not present detail on the sequence of use of drugs/therapies used. In a very small number of patient studies IVIg was used as first line treatment but in most of the studies, IVIg was used in combination with steroids and/or PLEX. Due to the lack of subgroup analysis, and lack of details on sequence of use of drugs used in the treatment, the available evidence does not make it possible to reach definitive conclusions about the clinical effectiveness of IVIg in AIE.

What is the cost effectiveness of IVIg for autoantibody-associated neurological encephalitis syndromes, 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 are no published studies evaluating cost effectiveness of IVIg in autoantibody-associated neurological encephalitis syndromes.

3. Research questions

What is the clinical effectiveness of IVIg for autoantibody-associated neurological encephalitis syndromes, 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 autoantibody-associated neurological encephalitis syndromes, 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
2-	Systematic	1167	IVIg, review includes an analysis of other treaments including steriods, PLEX, and immune therpaies including azthiprine, methotrexate, tacrolimus	Auntibody related encephaloomyelitis	Clinical effectiveness of the intervention	Varied form study to study but mainly assessed in terms of Modified Rankin Scale where 0 indicates no symptoms post treatment to 5 indicating sever disability and 6 indicating death. Anti NMDAR: 92.4% received immune therapy (766/829) and IVIg was used in 66% (502/761). In the large case series by Titulaer et al., steroids and IVIg were often given together (202/462, 44%). It is reported that people who didn't receive immune therapy had significantly poorer outcomes than those who received immune therapy. Also in the largest case series consisting by Titulaer steroids and IVIg were often given together (202/462, 44%). It appears that IVIg when combined with other treatments had better outcome but is not possible to evaluate effectiveness of IVIg on its own due to lack of subgroup analysis. Anti LGI1: 97.2% (103/106) received immune therapy and IVIg was used in in 50% (53/106) There is no subgroup analysis by IVIg group. Good outcome (full recovery or mRS 0) was 27.8% (20/72) in the studies using neurological status as an outcome measure, 86.4% (19/22) patients were seizure-free in the studies using seizure status as the main outcome measure and relapses occurred in 18% patients (16/89), and death in 2.5% (4/158) patients. As above It is not possible to evaluate effectiveness of IVIg on its own due to lack of subgroup analysis. Anti-Caspr2:92.5% immune therapy (37/40, and IVIg was used in 38.1% (8/21) There is no subgroup analysis by IVIg group. Outcome data was poorly reported and authors report relapse was uncommon, and full recovery occurred in about one-fourth of patients, whereas 12.1% died (4/33 with adequate information). As above it is not possible to evaluate effectiveness of IVIg on its own due to lack of subgroup analysis. Anti-AMPAR: 95.2% (40/42), received immune therapy and IVIg was used in in 52.4% (22/42)There is no subgroup analysis by IVIg group .10.8% of patients had a full recovery (mRS 0) (4/37), whereas most cases recovered partially (25/37, 67.6%). As above It is not possible to evaluate effectiveness of IVIg on its own due to lack of subgroup analysis. Anti GABAAR: 54.5% (18/33) received first line immune therapy : and IVIg was used in 27.3% (9/33) There is no subgroup analysis by IVIg group. Patients receiving immune therapy had better outcomes than those who did not receive immune therapy (mean Rankin Score 0: 2/18, 11.1% vs. 0/12, 0%), though there was a higher rate of relapse (3/18, 16.7% vs. 1/12, 8.3%). As above It is not possible to evaluate effectiveness of IVIg on its own due to lack of subgroup analysis. Anti-GlyR antibodies: 77.3% (58/75) of patients with available data received immune therapy and IVIg in 42.6% (29/68). In the largest published series, approaches to first-line immune therapy were variable	IVIg was part of the treatment for all of the autoantibody related encepahilaitis. The proportion of patients treated with IVIg varied from 27% to 54%. Generally for most of the conditions patients treated with combination of immune therapy had better outcomes compared to patients who had no immune therapy. Due to lack of subgroup analysis by IVIg it wsa not possible to asses the impact of IVIg on the outcomes.	None	-	Nosadini, Margherita; Mohammad, Shekeeb S.; Ramanathan, Sudarshini; Brilot, Fabienne; Dale, Russell C.. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother 2015;0(0):47119.	no separate reporting for IVIg	as in primary outcome	This is a well designed systematic review of studies on encephalitis due to autoantibodies targeting neuronal cell surface proteins. The review includes studies published upto Nov 2015 on nine different types of antibodies: • There are no randomized controlled trials of treatment, and the majority of studies are small sized retrospective case series except study by Titulaer et al which include 577 patients. • The review does not include subgroup analysis by treatment groups but provides information comparing patients receiving immunomodulatory therapy vs no-immunomodulatory therapy. • However it appears IVIg when used in combination with other immunomodulatory treatments has better outcomes when compared to patients with no immunotherapy. These include encephalitis syndromes due to anti-NMDAR antibodies, anti-Capr2 antibodies, anti-GABABR antibodies, anti-GABAAR antibodies, anti-DPPX antibodies, anti-GlyR antibodies. • Anti-IgLON5 encephalitis appears to be different from the other autoimmune encephalitides, with poor response to immune therapy and high mortality rate. • Authors reommend that based on evidence early commencement of immune therapy is more commonly associated with a better outcome and the use of second-line immune therapies is more commonly associated with a better outcome and a lower rate of relapses but is influenced by severity bias, as sicker patients are more likely to receive second-line therapy. • The main limitations are the limited number of patients and the retrospective and non-standardized nature of data and outcome measures. Majority of the studies did not include definition of an outcome except few studies which uses Modified Ranskin Scale to measure outcomes. • Also it appears there is no one standard protocol for use IVIg and majority of the studies did not detail on the sequence of use of drugs/therapies used in the treatment. In very small number of patients studies IVIg was used as first line treatment but in most of the studies it IVIg were used in combination with steroids +/- PLEX. • Due lack of subgroup analysis and lack of details on sequence of use drugs used in the treatment it is not possible to answer the PICO question 1. • Study has been graded evidence level 2+ because

						but typically started with intravenous methylprednisolone followed by high-dose prednisolone, and sometimes by PE, IVIg or both. There is no subgroup analysis by IVIg group but patients who received immune therapy had higher rate of good recovery than those who were not treated (mRS 0–1: 25/44, 56.8% vs. 3/10, 30%) and a slightly lower mortality rate (3/44, 6.8% vs. 1/10, 10%). As above due to lack of subgroup analysis and considering IVIg were used in combination with other drugs it not possible to draw conclusions on effectiveness of IVIg from these studies. Anti-DPPX antibodies: 64.3% (18/28) of patients received immune therapy during the first episode of disease and IVIg in 28.6% (8/28). There is no subgroup analysis by IVIg but authors report patients who did not receive immune therapy at the first episode had worse outcomes than patients who did receive immune therapy (mRS 0–1: 0/9, 0% vs. 7/18, 38.9%) and higher rates of death (2/9, 22.2% vs. 1/18, 5.5%) despite lower rates of relapses (1/10, 10% vs 7/18, 38.9%). Similarly, patients who received second-line treatments at the first episode had better outcomes than patients who did not receive second line therapies (mRS 0–1: 4/10, 40% vs. 3/17, 17.6%) and lower rates of death (0/10, 0% vs. 3/17, 17.6%) despite similar rates of relapses (3/10, 30% vs. 5/17, 29.4%).Due to lack of subgroup analysis and considering IVIg were used in combination with other drugs it not possible to draw conclusions on effectiveness of IVIg from these studies. Anti-IgLON5 antibodies: The majority of patients received immune therapy (9/10, 90%), even though most presented late. First-line treatments were used in 90% (9/10) (steroids in 7/10, 70%; IVIg in 4/10, 40%) and second-line therapies in 70% (7/10) (rituximab in 3/10, 30%; cyclophosphamide in 4/10, 40%). Authors report a poor outcome despite use of intense immunotherapy. 70% (7/10)of patients died and remaining 3 patients had unchanged clinical picture. As above due to lack of subgroup analysis and considering IVIg were used in combination with other drugs it not possible to draw conclusions on effectiveness of IVIg from these studies. Anti mGluR5 antibodies Seventy-five percent (3/4) of patients received immune therapy. First-line treatments were administered in 75% (3/4) (steroids in 3/4, 75%, PE in 1/4, 25%) and second-line therapies in 25% (1/4) (rituximab). In the combined cohorts of anti-mGluR5-positive patients, there were no relapses and, at last follow-up (range 17 months to 4 years), 75% (3/4) of patients recovered fully and 25% (1/4) had only partially recovered. As above due to lack of subgroup analysis and considering IVIg were used in combination with other drugs it not possible to draw conclusions on effectiveness of IVIg from these studies.							of the case series and case reports with small sample sizes included in the review. However the evidence on anti NMDAR antibodies which are based on large sample size are generalizable but due to lack of subgroup analysis for IVIg subgroup it is not possible to generalise results to this subgroup.
3	Other	not imentioned	IVIg along with other immunomodulator drugs including steroids and PLEX, cyclophosphamide	paraneoplastic neurological disorder	Clinical effectiveness of the intervention	not mentioned but reported as improvement in symptoms	Authors report that IVIg had been used in variety of PNDs but mechanism of action of IVIg in PND is uncertain . Thet recommend based on and based on experience with otherneurological disorders IVIg seems most appropriate for PND affecting the peripheral nervous syste.	none	-	Sadeghian, Hamid; Vernino, Steven. Progress in the management of paraneoplastic neurological disorders. Ther Adv Neurol Disord 2010;3(1):43-52.	none reported	as in primary outcome	This is an overview article with reference to 13 artcicles that have information relating to immunomodulatory therapy in paranroplastic syndrome. With regard to IVIg in Paraneoplastic neurological disorders (PND), Authors report that IVIg had been used in variety of PNDs but mechanism of action of IVIg in PND is uncertain . Thet recommend based on and based on experience with otherneurological disorders IVIg seems most appropriate for PND affecting the peripheral nervous syste.. Evidence level 3

4	Systematic	16	IVIg	none	Clinical effectiveness of the intervention	Varied from study to study but main outcomes include Effect of IVIg: on transient seizure frequency improved neurologic condition	Granata et al 2003 N=11) -1/11(9%) transient ↓ seizure frequency >50%, improved neurologic condition, 2/11(18%) transient ↓ seizure frequency up to 50% 5/11 (46%) no effect 3/11(27%) not assessable. Korn-Lubetzki et al 2004 (n=1) -Mild improvement in symptoms Frucht et al 2001 (n=1)- Marked improvement in hyperkinetic movements Villani et al 2001 (n=1) Marked improvement (>75% ↓ seizure frequency, improved cognition Leach et al1999 (n=2) 2/2 (100%) Marked improvement in seizure frequency, hemiparesis, cognition	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	Rasmussen's encephalitis is one of the condition that is included in the list of condtions approved for use of IVIg. The approval was based on one case series and four case reports of IVIg use for Rasmussen's encephalitis. Overall, 31% (5/16) of patients showed marked improvement in symptoms following IVIg alone or in combination with additional therapies.
2-	Systematic + Meta Analysis	0	IVIg	Fisher Syndrome and related disorders	Clinical effectiveness of the intervention	none reported	-	-	-	Overell, J. R.; Hsieh, S. T.; Odaka, M.; Yuki, N.; Willison, H. J.. Treatment for Fisher syndrome, Bickerstaff's brainstem encephalitis and related disorders. Cochrane Database Syst Rev 2007;0(1):CD004761.	-	-	This Cochrane reviewand authors conclude that there are no randomised controlled trials of immunomodulatory therapy in Fisher Syndrome or related disorders on which to base practice.
3	Systematic	38 patients	IVIg	Cerebellar ataxia	Clinical effectiveness of the intervention	Not defined but outcomes reported as outcomes in clinical symptoms	1.Gluten ataxia,-Improved cerebella ataxia symptoms but not completely 2. Patients Resistance to gluten therpay- transient response to IVIg and relapse after disconitunation of treatment. 3.Cerebellar ataxia with paraneoplastic cerebellar degeneration -no response to IVIg in combination with IV methylprednisolone and cyclophosphamide, 4.Cerebellar atxia with anti -GAD antibodies-high response to combination of immonotherpaies including IVIg but remisiion in longterm. Hashimotos encephalopathy- good response to steroids and no difference bewteen different types of immunotherpaies.	none	-	Mitoma, Hiroshi; Hadjivassiliou, Marios; Honnorat, Jérôme. Guidelines for treatment of immune-mediated cerebellar ataxias. Cerebellum Ataxias 2015;2(0):14.	none reported	as in primary outcome	This is a systematic review of studies on cerebellar ataxia. The review identified 32 studies, majority of studies were case reports with 1 patients. There analysis showed IVIg and other immunotherapies had variable responses on various cerebellar ataxic conditions. 1.Gluten ataxia,-Improved cerebella ataxia symptoms but not completely 2. Patients Resistance to gluten therpay- transient response to IVIg and relapse after disconitunation of treatment. 3.Cerebellar ataxia with paraneoplastic cerebellar degeneration -no response to IVIg in combination with IV methylprednisolone and cyclophosphamide, 4.Cerebellar atxia with anti -GAD antibodies-high response to combination of immonotherpaies including IVIg but remisiion in longterm. Hashimotos encephalopathy- good response to steroids and no difference bewteen different types of immunotherapies. Overall the level of evidence is 3 as the majority of studies included had just one patient and lack of comparator.

3	Case series	5	glucocrticods and IVIg	Susac syndrome	clinical effectiveness	clinical response	Patients treated with glucocrticoids and IVIg experienced clincial pregression and further required additional immunospressive therpies	None	-	Vodopivec, Ivana; Venna, Nagagopal; Rizzo, Joseph F.; Prasad, Sashank. Clinical features, diagnostic findings, and treatment of Susac syndrome: A case series. J. Neurol. Sci. 2015;357(42036) :50-57.	none reported	as in primary outcome	This is retrospective study of 5 patients with Susac syndrome. All received corticosteroids and IVIg. Patients had no response to IVIg and corticosteroids and were further treated with additional immunosupressants. Level pf evidence=3
3	Case series	34	IVIg was one of immunomodulatory drug used along with corticosteroids, plasmapheresis, and chemotherapeutic agents such as rituximab, cyclophosphamide, mycophenolate.	autoimmune epilepsy	Clinical effectiveness of the intervention	seizure frequency	Specific autoimmune antibodies were detected in 76.5% (26) of patients; anti-VGKc in 23.5% (8); anti-NMDA-R in 20.6% (7); anti-thyroid/TPO in 14.7% (5); anti-GAD in 11.8% (4); anti-GABAB in 5.9% (2). Nine patients (26.5%) included in the study had an underlying malignancy; 2 ovarian teratomas, 2 breast cancer, 1 adenocarcinoma of the lung, 1 small cell lung cancer, 1 testicular cancer, 1 papillary thyroid cancer and 1 thymoma. 94.1% (32) patients received immunomodulatory therapies, including high dose corticosteroids (96.8%), plasmapheresis (62.5%), and IVIg (34.4%). 9 (28.1%) patients received only high dose corticosteroids as immunomodulatory therapy for acute management of recurrent seizures, whereas the remaining patients received a combination of corticosteroids with plasmapheresis and/or IVIg [Corticosteroids + plasmapheresis: 12(35.3%), Corticosteroids + IVIg + plasmapheresis: 8 (25%), Corticosteroids + IVIg 3 (9.4%)]. 63.3% (19) of patients had 50% reduction in seizure frequency (RR) at the first clinic visit, following inpatient management of acute episode. 6 (17.6%) patients had complete resolution of seizures on initial clinic follow up.	none	none	Dubey, Divyanshu; Samudra, Niyatee; Gupta, Puneet; Agostini, Mark; Ding, Kan; Van Ness, Paul C.; Vernino, Steven; Hays, Ryan. Retrospective case series of the clinical features, management and outcomes of patients with autoimmune epilepsy. Seizure 2015;29(0):143-147.	none reported	as in primary outcome	This is a retrospective case series of 34 patients with autoimmune epilepsy.Specific autoimmune antibodies were detected in 76.5% (26) of patients; anti-VGKc in 23.5% (8); anti-NMDA-R in 20.6% (7); anti-thyroid/TPO in 14.7% (5); anti-GAD in 11.8% (4); anti-GABAB in 5.9% (2). Nine patients (26.5%) included in the study had an underlying malignancy; 2 ovarian teratomas, 2 breast cancer, 1 adenocarcinoma of the lung, 1 small cell lung cancer, 1 testicular cancer, 1 papillary thyroid cancer and 1 thymoma. 94.1% (32) patients received immunomodulatory therapies, including high dose corticosteroids (96.8%), plasmapheresis (62.5%), and IVIg (34.4%). 9 (28.1%) patients received only high dose corticosteroids as immunomodulatory therapy for acute management of recurrent seizures, whereas the remaining patients received a combination of corticosteroids with plasmapheresis and/or IVIg [Corticosteroids + plasmapheresis: 12(35.3%), Corticosteroids + IVIg + plasmapheresis: 8 (25%), Corticosteroids + IVIg 3 (9.4%)]. 63.3% (19) of patients had 50% reduction in seizure frequency (RR) at the first clinic visit, following inpatient management of acute episode. 6 (17.6%) patients had complete resolution of seizures on initial clinic follow up. Overall it appears that IVIg may have some influence on the prognosis. However the generalisability of the results of IVIg is very limited because IVIg was given in combination with other treatments and also due to patient selection methods which lacks a control group and it is difficult estimate the effectiveness of IVIg.

3	Case series	36	-	anti NMDAR encephalitis	Clinical effectiveness of the intervention	improvement in neurological symptoms measured using mRs score	All patients received first-line treatment and Median time to first line treatment was 19days. The types of first-line treatment were including corticosteroids in 86 %, Intravenous immunoglobulins in 89 %, and Plasma exchange in 39 %. 81% received second-line treatment and median time from first-line to second-line treatment) was 26 days. The types of second-line treatment included rituximab in 72 %, cyclophosphamide in 14 %, and 17% received long-term immunosuppression (do not mention with what drugs). Outcome was measured using Modified Rankin scale and were considered to have good outcome if mRs score was </=2. At 12 months 83 % had a Good outcome and 24 months same proportion were reported to have Good outcome. 8% had relapses after diagnosis. The results are of outcome are not available by IVIg or any other treatment subgroups.	none	-	Zekeridou, Anastasia; Karantoni, Evgenia; Viaccoz, Aurélien; Ducray, François; Gitiaux, Cyril; Villega, Frédéric; Deiva, Kumaran; Rogemond, Veronique; Mathias, Elodie; Picard, Géraldine; Tardieu, Marc; Antoine, Jean-Christophe; Delattre, Jean-Yves; Honnorat, Jerome. Treatment and outcome of children and adolescents with N-methyl-D-aspartate receptor encephalitis. J. Neurol. 2015;262(8):1859-1866.	none reported	as in primary care	This is a prospective case series of 36 children with anti NMDAR -ab. All patients received first-line treatment and median time to first line treatment was 19 days. The types of first-line treatment were corticosteroids in 86 %, Intravenous immunoglobulins in 89 %, and Plasma exchange in 39 %. 81% received second-line treatment and median time from first-line to second-line treatment) was 26 days. The types of second-line treatments included rituximab in 72 %, Cyclophosphamide in 14 %, and 17% received long-term immunosuppression (does not mention with what drugs). Outcome was measured using Modified Rankin scale and were considered to have good outcome if mRs score was </=2. At 12 months, 83 % had a Good outcome and at 24 months same proportion were reported to have good outcome. 8% had relapses after diagnosis. The results of outcome are not available by IVIg or any other treatment subgroups. Evidence level 3 due to lack of comparator, case selection methods and small sample size. This study was included in study Nosadini et al, 2015.
3	Case series	31	First line-Steroids,IVIg, PLEX, second line - cyclophosphamide, rituximab, MMF	NMDAR-Ab-associated neurological disorders	Clinical effectiveness of the intervention	clinical improvement in symptoms based on modified Rankin scale 0=full recovery, 5=dead	All patients received steroids; 22 (71%) received IVIg, 9 (29%) received PLEX and 10 (32%) received second-line immunotherapy.Four treatment groups were identified within the whole cohort of 31 patients. The most frequently used (61%) were IVIg and steroids (Group A); PLEX was added to these in two patients (Group B). Three patients had IVIg, steroids, no PLEX, but second-line immunotherapy (Group C). Seven patients had steroids, IVIg, PLEX and second-line immunotherapy (Group D). 19/30, 63% made full recovery, 10/30, 43% made partial recovery and 1/30 made no recovery. There was no correlation between age of presentation and response to immunotherapy, and no relationship between initial response to immunotherapy and outcome at 12 months (table 1). However, 89% (8/9) patients who received PLEX during their initial treatment made a full eventual recovery compared with 47% receiving IVIg and steroids only (p=0.049, Fisher's exact test). Higher proportion Children with early diagnosis (within 8 weeks) made full recovery compared to children with late diagnosis (18/23, 78% vs 1/7,14% p=0.001	none	-	Wright, Sukhvir; Hacohen, Yael; Jacobson, Leslie; Agrawal, Shakti; Gupta, Rajat; Philip, Sunny; Smith, Martin; Lim, Ming; Wassmer, Evangeline; Vincent, Angela. N-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. Arch. Dis. Child. 2015;100(6):521-526.	authors report no significant treatment complication were reported.	as in primary outcome	This is a retrospective case series of 31 children who had NMDAR-Ab-associated neurological disorders. All patients received steroids; 22 (71%) received IVIg, 9 (29%) received PLEX and 10 (32%) received second-line immunotherapy.Four treatment groups were identified within the whole cohort of 31 patients. The most frequently used (61%) were IVIg and steroids (Group A); PLEX was added to these in two patients (Group B). Three patients had IVIg, steroids, no PLEX, but second-line immunotherapy (Group C). Seven patients had steroids, IVIg, PLEX and second-line immunotherapy (Group D). 19/30, 63% made full recovery, 10/30, 43% made partial recovery and 1/30 made no recovery. There was no correlation between age of presentation and response to immunotherapy, and no relationship between initial response to immunotherapy and outcome at 12 months (table 1). However, 89% (8/9) patients who received PLEX during their initial treatment made a full eventual recovery compared with 47% receiving IVIg and steroids only (p=0.049, Fisher's exact test). Higher proportion Children with early diagnosis (within 8 weeks) made full recovery compared to children with late diagnosis (18/23, 78% vs 1/7,14% p=0.001. Evidence level=3, as there was no comparator and retrospective nature of study. This study was included in study Nosadini et al, 2015.

3	Case series	20	Thirteen patients were treated with immunotherapy, which included intravenous immunoglobulin (IVIg) (n = 12), corticosteroids (n = 9), tacrolimus (n = 4), rituximab (n = 3), cyclophosphamide (n = 1), tocilizumab (n = 1), and mycophenolate mofetil (n = 1) (	patients with anti amphiphysin syndrome	Clinical effectiveness of the intervention	Clinical response as improvement in symptoms	Of the 20 patients, 10 patients were diagnosed with limbic encephalitis, 9 with dysautonomia, 6 with cerebellar dysfunction, and 4 with brainstem encephalitis, 4 patients had peripheral neuropathy and 1 had myelitis. 11/13 patients had favorable responses. One patient did not improve after 10 months of immunotherapy, and in one case the effect of immunotherapy could not be assessed because the patient was lost to follow-up.	none	-	Moon, Jangsup; Lee, Soon-Tae; Shin, Jung-Won; Byun, Jung-Ick; Lim, Jung-Ah; Shin, Yong-Won; Kim, Tae-Joon; Lee, Keon-Joo; Park, Kyung-Il; Jung, Keun-Hwa; Jung, Ki-Young; Lee, Sang Kun; Chu, Kon. Non-stiff anti-amphiphysin syndrome: clinical manifestations and outcome after immunotherapy. J. Neuroimmunol. 2014;274(42036) :209-214.	0	as in primary outcome	This is retrospective case series of 20 patients with anti-amphiphysin syndrome. Of the 20 patients, 10 patients were diagnosed with limbic encephalitis, 9 with dysautonomia, 6 with cerebellar dysfunction, and 4 with brainstem encephalitis, 4 patients had peripheral neuropathy and 1 had myelitis. Thirteen patients were treated with immunotherapy, which included intravenous immunoglobulin (IVIg) (n = 12), corticosteroids (n = 9), tacrolimus (n = 4), rituximab (n = 3), cyclophosphamide (n = 1), tocilizumab (n = 1), and mycophenolate mofetil (n = 1) WR to outcome 11/13 patients had favorable responses. One patient did not improve after 10 months of immunotherapy, and in one case the effect of immunotherapy could not be assessed because the patient was lost to follow-up. Evidence level 3 and with limitation to generalisability of results due retrospective nature os study, lack of comparator and small sample size. There is no subgroup analysis to assess effectiveness of IVIg.
3	Case series	15	IVIg along with steroids and PLEX	autoimmune encephalitis presenting with status epilepticus (SE), epilepsy, and cognitive decline.	Clinical effectiveness of the intervention	clinial improvement in symptoms and seizure free	NMDA receptor antibody positivity was found in seven (50%) patients, VGKC antibody in five (36%) patients, and two patients had anti-GAD and in another anti-dsDNA antibodies were found. None of the patients showed any evidence of malignancy in the periodic tumor screening done. 67% (10/15) had significant improvement and didnot have further seizures or relapse and there was one death	None	-	Pandit, Awadh Kishor; Ihtisham, Kavish; Garg, Ajay; Gulati, Sheffali; Padma, Madakasira Vasantha; Tripathi, Manjari. Autoimmune encephalitis: A potentially reversible cause of status epilepticus, epilepsy, and cognitive decline. Ann Indian Acad Neurol 2013;16(4):577-584.	none	as in primary outcome	This is a prospective case series of 15 patients with autoimmune encephalitis presenting with status epilepticus (SE), epilepsy, and cognitive decline NMDA receptor antibody positivity was found in seven (50%) patients, VGKC antibody in five (36%) patients, and two patients had anti-GAD and in another anti-dsDNA antibodies were found. None of the patients showed any evidence of malignancy in the periodic tumor screening done.. IVIg was given in 9 patients, of whom 3/9 revcived IVIg followed by streoid and in rest IVG was given along with steroids and foolowed steroid tratement. 67% (10/15) had significant improvement and didnot have further seizures or relapse and there was one death. Evidence leve 3 and limited general;isability due lack of comparator, small sample size and lack of subgroup analysis for IVIg effectiveness.

3	Case series	14 patients with anti LG1 encephalitis (12 included in the final analysis)	Steroids, IVIg, plasmapheresis, Rituximab, tacrolimus	anti LG1 encephalitis	Clinical effectiveness of the intervention	clinical improvement in symptoms based on modified Rankin scale 0=full recovery, 5=dead	7 patients received corticosteroids only. All patients responded positively with 2 showing partial response who improved with addition of IVIg. Five patients received combined therapy 4/5 has complete recovery and no relapse. The difference between two groups was not statistically different (p=0.271). Treatment initiated within 1month of symptom onset seemed to be associated with clinical outcome p=0.058; Fig. 2A). However, outcome measured by achievement of mRS=0 failed to show statistical significance (p=0.221)	brain image findings and treatment outcome	Patients without medial temporal hypermetabolism on FDG- PET scans were associated with better outcome and lower mRS (rc=−0.480, p=0.02; Fig. 2C). Recovery with mRS=0 was also related to medial temporal hypermetabolism (rb = −0.535, p=0.02; Fig. 2D). Among patients with medial temporal lesions, a unilateral lesion was associated with a favorable outcome (rc=0.898, p b 0.001; and achievement of mRS = 0 (rb = 0.750, p = 0.001. In contrast, basal ganglia hypermetabolism had no association with mRS (rc = −0.040, p = 0.907) or achievement of mRS = 0 (rb = −0.089, p = 0.774), and medial temporal lesions on MRI also failed to show association with mRS (rc=0.111, p=0.726) or recovery to mRS = 0 (rb = −0.169, p = 0.552). None of these image parameters were related to recurrence.	Shin, Yong-Won; Lee, Soon-Tae; Shin, Jung-Won; Moon, Jangsup; Lim, Jung-Ah; Byun, Jung-Ick; Kim, Tae-Joon; Lee, Keon-Joo; Kim, Young-Su; Park, Kyung-Il; Jung, Keun-Hwa; Lee, Sang Kun; Chu, Kon. VGKC-complex/LGI1-antibody encephalitis: clinical manifestations and response to immunotherapy. J. Neuroimmunol. 2013;265(42036) :75-81.	none reported	as in primary outcome	Retrospective case series of 12 paatients with anti LG1 encephalitis. 7 patients received corticosteroids only. All patients responded positively with 2 showing partial response who improved with addition of IVIg. Five patients received combined therapy 4/5 has complete recovery and no relapse. The difference between two groups was not statistically different (p=0.271). Treatment initiated within 1month of symptom onset seemed to be associated with clinical outcome p=0.058; Fig. 2A). However, outcome measured by achievement of mRS=0 failed to show statistical significance (p=0.221). Level of evidence 3 due to lack of comparator, lack of sample size and retrospective nature of study causing bias. This study is also included in review by Nosadini et al, 2015.
3	Case series	11	steroids and intervention	NMDA recepto encephalitis	Clinical effectiveness of the intervention	clinical response to treatment	based on abstract authors report 58% showed significant response to steroids and IVIg	none	-	Chakrabarty, Biswaroop; Tripathi, Manjari; Gulati, Sheffali; Yoganathan, Sangeetha; Pandit, Awadh Kishore; Sinha, Aditi; Rathi, Bhim Singh. Pediatric anti-N-methyl-D-aspartate (NMDA) receptor encephalitis: experience of a tertiary care teaching center from north India. J. Child Neurol. 2014;29(11):1453-1459.	none reported	as in primary outcome	Retospective case series of 11 patients woth NDMA repetor encephalitis. Authors report 58% responded to steroid and IVIg treatment. Evidence level 3 and with limitation to generalisability of results due retrospective nature os study, lack of comparator and small sample size. There is no subgroup analysis to assess effctiveness of IVIg.

3	Case series	13	immunomodulator treatments including IVIg.Treatment consisted of steroids in the acute phase Maintenance therapy was rituximab in 7 patients, intravenous immunoglobulin (IVIg) in 7, azathioprine in 4, mycophenolate mofetil in 3, and methotrexate in 1 (some patients received sequential therapy with different agents).	Hashimoto encephalopathy	Clinical effectiveness of the intervention	improvement in neurological symptoms including stroke like symptoms, seizures, cognitive function	Patient received steroids in the acute phase for 12 of 13 patients with rapid improvement in symptoms. Maintenance therapy was rituximab in 7 patients, intravenous immunoglobulin (IVIg) in 7, azathioprine in 4, mycophenolate mofetil in 3, and methotrexate in 1 (some patients received sequential therapy with different agents).There was complete or near complete resolution of symptoms in 12 of the 13 patients	none based on abstract	-	Olmez, Inan; Moses, Harold; Sriram, Subramaniam; Kirshner, Howard; Lagrange, Andre H.; Pawate, Siddharama. Diagnostic and therapeutic aspects of Hashimoto's encephalopathy. J. Neurol. Sci. 2013;331(42036) :67-71.	none based on abstract	as in primary outcome measure	this is retrospective case over a 13 yrs period consisting of 13 patients with Hashimoto encephalitis/ Patients received steriods and primary treatment with rapid in treatments. Patients also received other immune treatments including IVIg in 7 patients/. There is no subgroup analysis by IVIg group but authors report all 13 responded to treatment. Level of evidence is 3 and poor generalisability to lack of comparator, patuient reslection methods and lack of subgroup analysis.

3	Case series	27 (one fromauthors clinica and 26 from litertaure serach)	IVIg (revie includes an analysis of other treaments including steriods, PLEX, and immune therpaies including azthiprine, rituximab	Morvans Fibrillary \chorea	Clinical effectiveness of the intervention	Recovered- sponteneous or with treatment and death	15 patients (56%) had concurrent malignancy, 15 (79%) were positive for VGKC-Ab. Associated autoimmunity was reported in 11 patients (41%) with three having auto-antibodies only, while eight manifested clinical autoimmune diseases. Auto-antibodies to the acetylcholine receptor (n = 6), voltage-gated calcium channel (n = 2), glutamic acid decarboxylase (n = 1), phospholipid (n = 1) and muscle specific kinase (n = 1) were identified. The most common associated autoimmune disorder was myasthenia gravis (n = 5) while others included thyroid disease (n = 1), psoriasis (n = 1), myositis (n = 1) and anti-phospholipid syndrome (n=1). Four patients (36%) had clustering of auto-antibodies or autoimmune disorders that are not classically related. Mortality amongst all patients was 22% (6/27) and the prevalence of malignancy was comparable between those who died (50%) and those who recovered (57%). All patients with malignancies underwent surgery. Of those who recovered, two (9%) showed spontaneous improvement. Immunotherapy was instituted in 22 patients with 19 (86%) responding favourably and three (14%) dying. The most common first line treatment (monotherapy or in combination) was plasma exchange (PEx) (55%) followed by intravenous immunoglobulin (IVIg) (41%) and corticosteroids (32%).IVIg. Four patients (18%) required second line treatment after failing IVIg (n = 2), IVIg/ corticosteroid (n = 1) and Ex/IVIg (n = 1). One patient was treated with rituximab after failing cyclosporine. A further 14 patients required maintenance immunotherapy (monotherapy or in combination), using corticosteroids (57%); IVIg (21%); azathioprine (14%); PEx (7%) or cyclophosphamide (7%).	none	-	Lee, Will; Day, Timothy J.; Williams, David R.. Clinical, laboratory and electrophysiological features of Morvan's fibrillary chorea. J Clin Neurosci 2013;20(9):1246-1249.	none reported	as inprimary outcome	This is retrospective case series of 27 patients with Movac fibrillary chorea. 9 (41%) patients had IVIg in combination with other therapy. 3 patients had IVIg for maintance. There is subgroup analysis to assess the effectivenss of IVIg but the overall results showed 86% responded favorably with 3 patients dying. This is evedence level 3 study with limitaions to generalisability of the study due lack of comaparator, patients selection and lack of subgroup analysis
3	Case series	10	steroids and IVIg	Non viral limbic encephalitis	Clinical effectiveness of the intervention	clincial improvement	10 children with serological evidence of the presence of neuronal antibodies causing limbic encephalitis were studied. All of the 10 enrolled patients had acute onset of fever and rapid clinical deterioration. Six patients were treated with methylprednisolone pulse therapy or intravenous immunoglobulin (IVIg) at the acute stage. All had persistent neuropsychiatric symptoms and 90% developed refractory epilepsy.	none	-	Chou, I.-Jun; Wang, Huei-Shyong; Lin, Jainn-Jim; Kuo, Chang-Fu; Lin, Kuang-Lin; Chou, Min-Liang; Hung, Po-Cheng; Hsieh, Meng-Ying; Lin, Yun-Tong; CHEESE Study Group. Limbic encephalitis in Taiwanese children and adolescence: a single center study. Pediatr Neonatol 2013;54(4):246-253.	none reported in abstract	as in primary outcome	This cross-sectional study describes the clinical manifestation and the serological evidence of the presence of neuronal antibodies in 10 Taiwanese children with limbic encephalitis. All of the 10 enrolled patients had acute onset of fever and rapid clinical deterioration. Six patients were treated with methylprednisolone pulse therapy or intravenous immunoglobulin (IVIg) at the acute stage. All had persistent neuropsychiatric symptoms and 90% developed refractory epilepsy. Evidence leve 3. due retrospective case selection, small sample size. Also there is results by IVIg available from the abstarct.

2-	Case series	501	t line (steroids, IVIg, pasmapheresis) ,second line (rituximab, cyclophosphamide) and tumour removal	anti NMDAR encephalitis	Clinical effectiveness of the intervention	clinical improvement measured modified Rankin scale	577 patients (1-85 years, median 21) were studied, 212 were children (<18 years). Treatment effects and outcome were assessable in 501 (median follow-up 24 months): 472 (94%) underwent first-line immunotherapy or tumor removal, resulting in improvement within four weeks in 251 (53%). Of 221 patients who failed first-line therapy, 125 (57%) received second-line immunotherapy resulting in better outcome than those who did not (OR 2·69, CI 1·24-5·80, p=0·012). During the first 24 months, 394/501 reached good outcome (mRS 0-2; median 6 months), and 30 died. At 24 month follow-up 204/252 (81%) had good outcome.. Predictors of good outcome were early treatment (OR 0·62, CI 0·50-0·76, p<0·0001) and lack of ICU admission (OR 0.12, CI 0·06-0·22,p<0·0001). 45 patients had one or multiple relapses (representing a 12% risk within 2 years); 46/69 (67%) relapses were milder than previous episodes (p<0·0001). . Comparing children ,18 yrs with adults, the time between symptom onset and initiation of treatment was shorter in children (21 versus 28 days, p=0·007, Overall the outcome was similar to that of adults (p=0·92,)	none separately reported	-	Titulaer, Maarten J.; McCracken, Lindsey; Gabilondo, Iñigo; Armangué, Thaís; Glaser, Carol; Iizuka, Takahiro; Honig, Lawrence S.; Benseler, Susanne M.; Kawachi, Izumi; Martinez-Hernandez, Eugenia; Aguilar, Esther; Gresa-Arribas, Núria; Ryan-Florance, Nicole; Torrents, Abiguei; Saiz, Albert; Rosenfeld, Myrna R.; Balice-Gordon, Rita; Graus, Francesc; Dalmau, Josep. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12(2):157-165.	reported as in primary outcome (relapse)	as in primary outcome	This is a large multinational, multicentre prospective study of 501 pateints with anti NMDAR antibody encephalitis. 472 (94%) underwent first-line immunotherapy or tumor removal, resulting in improvement within four weeks in 251 (53%). Of 221 patients who failed first-line therapy, 125 (57%) received second-line immunotherapy resulting in better outcome than those who did not (OR 2·69, CI 1·24-5·80, p=0·012). During the first 24 months, 394/501 reached good outcome (mRS 0-2; median 6 months), and 30 died. At 24 month follow-up 204/252 (81%) had good outcome.. Predictors of good outcome were early treatment (OR 0·62, CI 0·50-0·76, p<0·0001) and lack of ICU admission (OR 0.12, CI 0·06-0·22,p<0·0001). 45 patients had one or multiple relapses (representing a 12% risk within 2 years); 46/69 (67%) relapses were milder than previous episodes (p<0·0001). Comparing children ,18 yrs with adults, the time between symptom onset and initiation of treatment was shorter in children (21 versus 28 days, p=0·007, Overall the outcome was similar to that of adults (p=0·92,). Level of evidence=2-. This is a well designed study with primary objective, patient selection methods and measurement of outcome using mRsclae. The study also considted of larger sample size and the outcome reported for various subgroups including type of treatment and age grpoup. TThe only limitation from a PICO perspective are that results are not valaibal; by IVIg treatment group so not possible to answer PICO question 1. This is study was also included in the study of Nosadini et al, 2015.

3	Case series	20	streroids, IVIg, plasmapheresis	anti NMDAR encephalitis	Clinical effectiveness of the intervention	clinical improvement measured using Pediatric Cerebral Performance Category Scale" (PCPC, relapse	During the first episode of encephalitis, 19 (95%) patients received first-line immunotherapies (one patient was only treated at third relapse). All patients received at least a short course of high-dose steroids (median 1, range 1–3 courses), followed in 13 patients by oral steroid tapering for a median of 12 weeks (range 3–47). In addition, 14 patients received intravenous immunoglobulin (IVIg; median 2 cycles, range 1–12) and one patient had plasmapheresis. At last follow up all patients had received immunotherapy: 20 had first-line therapies (steroids, IVIg and/or plasma exchange), and 7 (35 %) second-line therapies (rituximab alone or combined with cyclophosphamide). After a median follow up of 17.5 months (4–149), 17 (85%) patients had substantial improvement (PCPC of 1 or 2: 60% complete recovery and 25% minimal residual deficits), 2 (10%) moderate or severe disability (PCPC of 3 or 4) and 1 died. The two patients with moderate or severe disabilities at follow-up of 4 and 9 months were showing improvement. 3 patients developed relapse.	None reported	-	Armangue, Thaís; Titulaer, Maarten J.; Málaga, Ignacio; Bataller, Luis; Gabilondo, Iñigo; Graus, Francesc; Dalmau, Josep; Spanish Anti-N-methyl-D-Aspartate Receptor (NMDAR) Encephalitis Work Group. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J. Pediatr. 2013;162(4):850-856.e2.	non eseparately reported	0	Thi is a retrospective caase series of 20 children with anti NDMAr encepahilitis. During the first episode of encephalitis, 19 (95%) patients received first-line immunotherapies (one patient was only treated at third relapse). All patients received at least a short course of high-dose steroids (median 1, range 1–3 courses), followed in 13 patients by oral steroid tapering for a median of 12 weeks (range 3–47). In addition, 14 patients received intravenous immunoglobulin (IVIg; median 2 cycles, range 1–12) and one patient had plasmapheresis. At last follow up all patients had received immunotherapy: 20 had first-line therapies (steroids, IVIg and/or plasma exchange), and 7 (35 %) second-line therapies (rituximab alone or combined with cyclophosphamide). After a median follow up of 17.5 months (4–149), 17 (85%) patients had substantial improvement (PCPC of 1 or 2: 60% complete recovery and 25% minimal residual deficits), 2 (10%) moderate or severe disability (PCPC of 3 or 4) and 1 died. The two patients with moderate or severe disabilities at follow-up of 4 and 9 months were showing improvement. 3 patients developed relapse. Evidence level 3- due retspective case selection, lack of comparator and small sample size. The results are also not available by IVIg so not possible to answer PICO question. This study is study included in review by Nosadini et al 2015.
2-	Case series	83	IVIg 400mg/kg/day for 5 days plus standard care	Children with acute encephalitis complicated by myocarditis	Clinical effectiveness of the intervention	mortality, Heart Ejection fraction	Mortality was lower in the IVIg group [n = 1 (3.8 %)] patients compared with the standard care group [n = 13 (22.8 %)] with a relative risk of 0.17 (95 % CI = 0.02, 1.22). The difference in mortality reached borderline significance (p = 0.05). At discharge, mean (SD) ejection fraction improved from 32.8 % (6.31 %) to 49.5 % (9.04 %) in group I patients, which was significantly greater than that of group II (p = 0.001).	none	-	Bhatt, Girish Chandra; Sankar, Jhuma; Kushwaha, K. P.. Use of intravenous immunoglobulin compared with standard therapy is associated with improved clinical outcomes in children with acute encephalitis syndrome complicated by myocarditis. Pediatr Cardiol 2012;33(8):1370-1376.	none based on abstract	as in primary outcome	Theis is a well designed non randomised prospective study with a comparator. A total of 83 consecutive children with AES complicated by myocarditis were enrolled. Diagnosis of myocarditis was based on clinical, electrocardiogram, and echocardiogram findings. Patients were allocated to the two groups based on the days of the week: Those presenting on Monday and Friday were allocated to IVIg treatment (group I), and those presenting on the other days of the week to standard care (group II). Group I (n = 26) patients received IVIg at a dose of 400 mg/kg/day for 5 days in addition to standard care. A viral etiology could be established in 14 children, with the 2 most common agents isolated being Coxackie virus and enterovirus. Mortality was lower in the IVIg group [n = 1 (3.8 %)] patients compared with the standard care group [n = 13 (22.8 %)] with a relative risk of 0.17 (95 % CI = 0.02, 1.22). The difference in mortality reached borderline significance (p = 0.05). At discharge, mean (SD) ejection fraction improved from 32.8 % (6.31 %) to 49.5 % (9.04 %) in group I patients, which was significantly greater than that of group II (p = 0.001). Level of evidence 2-. As authors mention IVIg seems to have benefical effect but further validation are required involving randomised control trail in a larger sample size.

3	Case series	10	variuos immunomodulators including steroid and IVIg. Nine patients received corticosteroids (seven intravenously, two orally), intravenous immunoglobulins (IVIg) or combinations of both Median time from disease manifestation until treatment was 4 months (0–18 months) for steroids and 18 months (0.5–33 months) for IVIg. The median doses were 55 mg/kg methylprednisolone-equivalent (range 15–410 mg/kg) and 2 g/kg IVIg (range 2–2.8 g/kg).	Children with limbic encephalitis	Clinical effectiveness of the intervention	clinical improvement in symptoms	Authors report only two patients showed clinical improvement	none	-	Haberlandt, E.; Bast, T.; Ebner, A.; Holthausen, H.; Kluger, G.; Kravljanac, R.; Kröll-Seger, J.; Kurlemann, G.; Makowski, C.; Rostasy, K.; Tuschen-Hofstätter, E.; Weber, G.; Vincent, A.; Bien, C. G.. Limbic encephalitis in children and adolescents. Arch. Dis. Child. 2011;96(2):186-191.	-	as in primary outcome	This is retrospective case study of 10 children with limbic encephalitis with with different type of antibodies. All patients were treated with steroid and 4 patients received IVIg. Only 2/10 patients showed clinical improvement at the end of 24 months and neither of them had received IVIg. This is a level 3 evidence study with limited generalisability due to small sample size, lack of compararor and lack of subgroup analysis.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	n/a
Updated search terms - Population	Population part 1: (encephalitis OR encephalopathy) AND (antibody OR autoimmune OR autoantibody OR antibodies OR autoantibodies) OR population part 2: (NMDA OR NMDAR OR Caspr2 OR LGI1 OR VGKC OR hashimoto OR MOG) AND (encephalitis OR encephalopathy OR antibody OR autoimmune OR autoantibody OR antibodies OR autoantibodies)
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