Clinical Commissioning Policy: Intravenous immunoglobulin for acute disseminated encephalomyelitis and autoimmune encephalitis

Reference: NHS England: 16030/P
**NHS England INFORMATION READER BOX**

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**Description**

Not Routinely Commissioned - NHS England will not routinely commission this specialised treatment in accordance with the criteria described in this policy.

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Clinical Commissioning Policy: Intravenous immunoglobulin for acute disseminated encephalomyelitis and autoimmune encephalitis

First published: July 2016

Prepared by NHS England Specialised Services Clinical Reference Group for Specialised Immunology and Allergy

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Policy Statement
NHS England will not routinely commission intravenous immunoglobulin for acute disseminated encephalomyelitis and autoimmune encephalitis in accordance with the criteria outlined in this document. In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources. This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement
Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:
- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary
About acute disseminated encephalomyelitis (ADEM), acute transverse myelitis (acute TM) and autoimmune encephalitis (AIE)
The immune system is the body's defence against infection and disease. If a person is ill, the immune system produces anti-bodies (a special type of protein that destroys disease-carrying organisms and toxins). These antibodies attack the cause of the illness. However, if the immune system develops a problem, it can start to attack the person's own healthy tissues and organs. This is known as 'auto-immune disease'.
Acute disseminated encephalomyelitis (ADEM) is a rare auto-immune disease. It can cause a sudden, widespread attack of inflammation in the brain and spinal cord. ADEM is a result of the immune system attacking healthy 'myelin', the protective covering of the nerve fibres. ADEM usually develops quickly over hours to days. Signs may include:

- feeling sick and being sick
- headaches
- feeling irritable
- feeling sleepy
- feeling unsteady or not being able to walk
- problems with vision
- weakness or tingling in certain areas of the body
- (fits) seizures and coma - in severe cases.

ADEM is often linked with acute transverse myelitis (TM). Acute TM is an inflammation of the spinal cord. Acute TM is sudden and develops quickly over hours to days. It causes weakness in the arms and legs.

Autoimmune encephalitis (AIE) is a group of auto-immune diseases where the immune system attacks the brain - this causes inflammation. AIE is not caused by an infectious agent. Signs include:

- memory loss (amnesia)
- fits (seizures)
- mental health problems
- abnormal movements
- being unable to move (paralysis)
- problems with vision
- coma.

About current treatment

Intravenous immunoglobulin (IVIg) is a medicine that is injected into a vein. It contains a mixture of anti-bodies - extracted from the blood of thousands of blood donors. IVIg is a treatment option for the above conditions where other treatments do not work or cannot be used and is currently accessed via prior approval processes.
**About the new treatment**
An assessment of the evidence has been undertaken to consider whether there is sufficient evidence for IVlg to move to routine commissioning for this indication.

**What we have decided**
NHS England has carefully reviewed the evidence to treat ADEM, acute TM and AIE with IVlg. We have concluded that there is not enough evidence to make the treatment available at this time. (Please see guidance note on page 2).
1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission intravenous immunoglobulin (IVIg) for acute disseminated encephalomyelitis (ADEM), acute transverse myelitis (TM) and autoimmune encephalitis (AIE).

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 TM. Acute TM is an attack of inflammation of the spinal cord. Acute TM 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.

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, voltage-gate potassium channel-complex (VGKC-complex) antibody associated encephalitis, N-methyl-D-aspartate-receptor (NMDA-receptor) antibody associated encephalitis, glutamic acid decarboxylase (GAD) antibody associated encephalitis, myelin oligodendrocyte glycoprotein (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 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 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 NHS England in line with Clinical Guidelines for Immunoglobulin Use (Department of Health, 2011). ADEM and AIE are classified as ‘grey indications’: grey indications are those diseases where the evidence is weak, in many cases because the disease is rare, and treatment should be considered on a case by case basis.

2 Definitions

ADEM is a rare inflammatory demyelinating disease of the central nervous system. It is an autoimmune disorder in which the body's immune system attacks the healthy myelin covering the nerves in the brain tissue, triggered by an environmental stimulus in genetically susceptible individuals, or in response to an infection or to a vaccination.

TM is an attack of inflammation (swelling) of the spinal cord. It is an autoimmune disorder in which the body's immune system inappropriately attacks the healthy myelin covering the nerves in the spine.

AIE is used to describe a group of disorders in which the body's immune system attacks healthy tissue in the brain, causing the brain to become inflamed and swell. This group of disorders are interchangeably named encephalopathy or encephalitis and often named variably by the antigenic target.

Immunoglobulins (antibodies) are proteins in the blood that play an essential role in the body's immune system by attaching to foreign substances, such as bacteria, and assist in destroying them. Immunoglobulin is a sterile preparation of concentrated antibodies recovered from pooled human plasma (used in the treatment of diseases of the immune system).

IVIg refers to intravenous infusion of immunoglobulin.
Plasma exchange (PLEX) is an extra-corporeal procedure where blood (which consists of blood cells and a clear liquid called plasma) is taken out of the body through a needle or previously implanted catheter, and the plasma is removed from the blood by a cell separator. The blood cells are then returned to the patient along with replacement donor plasma. The patients’ own plasma, containing the disease-causing auto-antibodies, is discarded.

Grey indications within the Clinical Guidelines for IVIg are defined as immune-related disorders with limited evidence of immunoglobulin efficacy, or presumed immune-related disorders with little or no evidence of efficacy.

3 Aims and Objectives

This policy proposition aims to define NHS England's commissioning position on IVIg for ADEM / acute TM or AIE.

The objective is to ensure evidence based commissioning in the use of IVIg for the treatment of patients with ADEM, acute TM or AIE.

4 Epidemiology and Needs Assessment

ADEM, acute TM, and AIE are rare autoimmune conditions.

It is not known how many cases of ADEM there are in a year in UK (Multiple Sclerosis Society, 2012). Studies in other countries have found that it affects fewer than 4 per 1,000,000 children per year (Banwell et al., 2009; Leake et al., 2004; Pohl et al., 2007). The number of adults diagnosed each year is not known, but the disease is much less common in adulthood, and usually affects children under the age of 10 (Gupte et al., 2003).

Accurate figures are not available for TM in UK, but it is estimated that there are no more than 300 new cases each year (Brain & Spine Foundation, 2013). Although this disease affects people of all ages there are bimodal peaks between the ages of 10 to 19 years and 30 to 39 years; approximately 25% of cases are in children.

The incidence rate for encephalitis in England is estimated to be around 4-5 per 100,000 people per year (Granerod et al., 2013). In Northern Europe, while 40% of
cases are infectious and 40% are due to unknown causes, at least 20% are autoimmune, with the largest groups being anti-NMDA-receptor encephalitis (4%) and VGKC-complex antibody positive encephalitis (3%) (Granerod et al., 2010).

5 Evidence Base for ADEM / acute TM

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of IVIg for ADEM / ATM (please see guidance note on page 2).

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 ADEM included the Department of Health (DH) clinical guidelines, two systematic reviews (including the Canadian guidelines), the Australian guidelines, and a few case series.

Clinical guidelines for immunoglobulin use (DH, 2011) 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 DH 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 or computed tomography.

The Canadian guidelines on the use of 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 2g/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, 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 IVIg (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 Ravaglia 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). The literature search 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; acute partial transverse myelitis and neuromyelitis optica in the review. On the evidence for the use of IVIg in TM, 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.
6 Evidence base for AIE

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of IVlg for AIE.

What is the clinical effectiveness of IVlg 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 IVlg in AIE 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 IVlg 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.

Nosadini 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.

### 7 Documents which have informed this Policy

Department of Health clinical guidelines for immunoglobulin use (second edition update, 2011)
8 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.
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