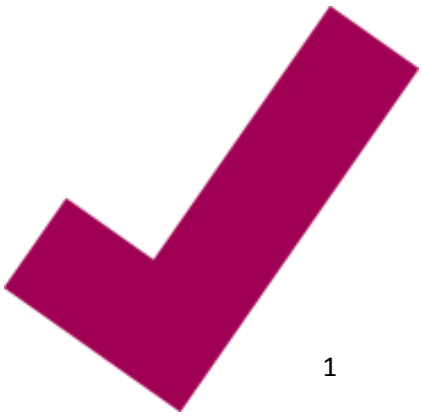
Use this style of front cover if the subject matter is sensitive e.g. abuse, sexual health and it would not be appropriate to use a person's photo.

If you need to print/photocopy multiple copies of your document, use this front cover style to reduce printing/copying costs.

A new disclaimer has been added to this template and must not be deleted.

NHS England

Evidence review: Rituximab for Paediatric autoimmune encephalitis



NHS England

Evidence review: Rituximab for Paediatric autoimmune encephalitis

First published:	December 2016
Updated:	Not applicable
Prepared by:	Public Health England on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

Acute paediatric encephalitis is a debilitating neurological disorder that develops as a rapidly progressive encephalopathy (usually in less than 6 weeks) due to brain inflammation, and represents a significant burden to patients, families and society (1). It has a mortality rate of 3.5%, and about half of the surviving children do not recover fully (2).Over the last few years an increasing number of non-infectious, mostly autoimmune, encephalitis cases have been identified, associated with antibodies targeting neuronal cell-surface antigens (1, 3). The target antigens are extracellular epitopes of synaptic receptors (including NMDAR, AMPAR and GABABR[1]) and components of trans-synaptic protein complexes (such as VGKC-complex proteins LGI1 and CASPR2[2]) (4).

Autoimmune encephalitis (AE) can affect patients at any age. In children, 46% of all cases with probable diagnosis of AE were found to be mediated by autoantibodies, against NMDAR in 27% and against VGKC-complex proteins in 17% (5). The true incidence of AE is not known, but it can be estimated that about 41 (range 30-48) cases of AE occur among children in the UK every year (using existing data on anti-NMDAR encephalitis: incidence of 0.85/million children/year; accounting for 27% of all AE; population of 12.2 million UK children).

The onset of AE is acute or subacute and most cases progress into a severe encephalopathy syndrome (1, 3) including altered mental status and a range of neurological and psychiatric symptoms. In children, about half of the cases require intensive care support, more than a half (58%) do not recover fully and experience ongoing problems (mostly cognitive and behavioural problems, and/or seizures) (5). Evidence suggests that outcomes are worse in children with antibody-positive AE than those with antibody-negative AE (71% vs 48% with ongoing problems) (5). The association with an underlying tumour depends on the type of antibodies and may vary with age and sex (3, 6).

Antibodies against cell-surface antigens can be detected in serum and cerebrospinal fluid (CSF) by cell-based diagnostic assays, most commonly using human embryonic kidney (HEK293) cells. CSF diagnostic assay is generally considered more specific than serum (3).

Anti-NMDAR encephalitis is the most frequent type of AE therefore this evidence review will focus mainly on this type of AE.

Anti-NMDAR encephalitis predominantly affects children under 18 years (around 40% of all cases) and adults younger than 45 years. There is a female gender predominance of 4:1 which is less evident in children under 12 years (1, 6-9). In young patients, the frequency of anti-NMDAR encephalitis surpassed that of any specific viral cause (9). The incidence in children under 18 years was estimated to be 0.85 per million children per year (95% confidence interval 0.64 to 1.06) (6). Some evidence described the paediatric presentation to be more ‘neurological’ than

[1] **NMDAR** N-methyl-D-aspartate receptor; **AMPAR** alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **GABABR** gamma-aminobutyric acid-B receptor

[2] **VGKC** voltage-gated potassium channel; **LGI1** leucine-rich glioma-inactivated protein 1; **CASPR2** contactin-associated protein 2

the more psychiatric presentation in adults (9), whereas other suggested neuropsychiatric presentation in 90% of children (6). However in the acute phase, most patients progress towards a similar syndrome regardless of their age, including abnormal (psychiatric) behavioural and cognitive functions, seizures, movement disorder, reduced consciousness, speech disorder, autonomic dysfunction, hypoventilation and memory deficit (1, 6, 9, 10). The disease is rarely monosymptomatic, but some cases may develop partial phenotypes. The presence of tumour, most commonly ovarian teratoma, depends on age and sex, and is most frequent (around 50%) in young women (1, 6, 9).

The diagnosis can be confirmed by the detection of IgG antibodies against the GluN1 (NR1) subunit of the NMDAR in the serum and/or cerebrospinal fluid (1, 11).

Despite the severity of the disease, more than 75% of all patients with anti-NMDAR encephalitis have a substantial recovery (i.e. recover fully or have mild sequelae), with early recognition and treatment predictive of a good outcome (6, 12). Relapses are not uncommon and may occur in 8% to 29% of patients (13).

Most types of AE have significant clinical overlap at onset and commonalities at disease presentation (3). For example limbic encephalitis, another frequent clinical syndrome characterized by memory deficits, seizures, confusion and/or psychiatric symptoms suggesting involvement of limbic system (i.e. mood changes), can be associated with a wide range of antibodies to cell-surface antigens, including synaptic receptors AMPAR and GABABR, and VGKC-complex proteins LGI1 and CASPR2 (1, 3, 14), as well as with antibodies against intracellular (onconeural) antigens, such as glutamic acid decarboxylase (GAD) (1).

Impairment in all these conditions appears to be associated with the degree of active inflammation, and therefore the mainstay of treatment is immunosuppression. First-line immunotherapies generally consist of corticosteroids (intravenous and oral), intravenous immunoglobulin (IVIg) and/or plasma exchange (PLEX). Second-line treatment is usually administered when the response to first-line therapy is inadequate or when the disease is known to be severe or relapsing. It typically includes rituximab, cyclophosphamide, azathioprine, mycophenolate mofetil or others (3). Patients are also treated with tumour resection if this is present.

Rituximab

Rituximab is a chimeric monoclonal antibody against CD20-positive B cells that induces B-cell depletion (15, 16). It does not affect innate immune system, immunoglobulin or T-cell activity (15).

In the UK, rituximab has been NICE approved for use in suppressing autoimmune disorders. To date there has been no randomized clinical trials of rituximab treatment in paediatric neurological inflammatory disease, leading to off-label use in severely ill children (15). It is generally given as a second-line immunotherapy when patients with severe or refractory disease fail the first-line therapy (3).

There is no agreed protocol for the use of rituximab. It is recommended to give a total dose of 1500-2000 mg/m^2 (body surface area calculation) in either two or four

divided doses to achieve a biological effect. Variable dosing regimens are being utilized across different treatment centres, with a weekly dose of 375 mg/m^2 intravenously for 4 weeks being the most commonly used regimen. The rationale for repeat rituximab dosing is based on clinical diagnosis and the perceived risk of relapses (15).

Some countries follow specific therapeutic guidelines for rituximab use in paediatric autoimmune disorders. The French Reference Centre of Paraneoplastic Neurological Syndromes recommends to intervene early with second-line immunotherapy when patients do not respond to first-line treatment. In paediatric patients, rituximab is used with a dose 375 mg/m^2, and repeatedly given if no substantial improvement after 10 days (13).

Despite an apparent benefit in many patients (e.g. 87% of paediatric cases with AE and inflammatory CNS disease experienced definite, probable and possible benefit), rituximab is considered as a broad-acting immunosuppressive agent. Treating clinicians are alerted of the potential adverse events, particularly anaphylactic reactions to rituximab or other murine proteins, its interaction with live vaccines (whilst receiving rituximab or several months following vaccination), and infectious side effects (such as viral reactivations, bacteraemia and sepsis) due to secondary effects of B-cell depletion on T-cell function. The rate of infectious complications in children treated with rituximab varies based on underlying diagnosis (with the highest rate in children with primary immunodeficiencies and the lowest rate in children with autoimmune diseases) and was estimated to be 7.2% in children with a range of autoimmune disorders (17). In children with anti-NMDAR encephalitis in particular, infusion adverse events were recorded in 12.5% and serious infections in 7.6% of cases (15).

2. Summary of results

A total of 11 studies were considered in this evidence review which fit the selection criteria and view from the Policy Working Group. These studies described, within their limitations, the efficacy and safety of rituximab and/or (second-line) immunotherapy on a total of 552 children. Rituximab was uses alone or in combination with other first and second line immunosuppressive therapies.

The retrospective observational multi-centre study of 144 children (Dale et al. (2014))(15) provided the best available evidence for using rituximab in treatment of children with autoimmune and inflammatory CNS disorders. In the study, 87% of all patients and 97% of patients with anti-NMDAR encephalitis had some form of benefit from rituximab treatment used as second-line, especially when received early. 17% of patients had modified Rankin Scale (mRS) of 0-2 (considered to be a good neurological disability score) at rituximab initiation compared to 74% at outcome. The change in mRS 0-2 was greater in patients given rituximab early compared to those treated later. The study reported a total of three deaths (2%), of which two occurred due to infectious adverse event.

In addition, the large prospective cohort study of 577 all age patients including 211 children (Titulaer et al. (2013))(9) found that 78% of patients with anti-NMDAR encephalitis who failed first-line and received second-line immunotherapy (with rituximab and/or cyclophosphamide) had good outcome at 24 months, compared to 55% of patients who failed first-line and did not receive second-line therapy. Early treatment was associated with good outcome ($p<0.001$). Furthermore the use of immunotherapy ($p=0.038$) and use of second-line immunotherapy in patients without tumour ($p=0.007$) were associated with fewer relapses. Overall 30 of 501 patients died, including 6 of 177 children. At 24 months' follow-up, 10% mortality rate was estimated (24 deaths among 252 patients who were followed up at 24 months').

The other nine studies discussed in the results are smaller and also provide indirect evidence in relation to the target population or rituximab treatment.

Rituximab used as second-line therapy was generally well tolerated with 2-3% of patients reporting severe infusion and infectious adverse effects of grade 4 or more Dale et al. (2014)(15). However long-term use of rituximab appears to be less safe as suggested by Brenton et al. (2016)(7).

It should be noted that all studies (including the large cohorts) presented in this evidence review are low grade studies and have significant limitations that affect generalisability of results and their application in clinical practice. There are no studies that compare the effects of individual immunotherapies, thus it is not possible to ascribe therapeutic benefits solely to rituximab. Furthermore, it is unclear if children with anti-NMDAR encephalitis are more likely to benefit, whether use of rituximab has any benefits over different second-line therapies such as cyclophosphamide, or at which stage of disease it should be used (acute, subacute or chronic).

Better quality evidence is needed to investigate the safety and efficacy of rituximab monotherapy in children with autoimmune CNS disorders (and anti-NMDAR

encephalitis in particular), to compare rituximab with other immunotherapies, to determine the most optimal dosage regimen and timing of rituximab therapy to yield maximum benefit, and to standardise diagnostics and safety monitoring.

3. Methodology

This evidence review provides a summary of the best available evidence for using rituximab treatment in paediatric autoimmune encephalitis (AE), mainly anti-NMDAR encephalitis. A search of Medline, Embase, CINAHL, Cochrane Library, NHS Evidence and TRIP database was performed in September 2016 for studies published in the English language since 1990. Details of the search strategy are provided in Section 9.

As anticipated no randomised controlled trials were identified for use of rituximab treatment in children with AE/anti-NMDAR encephalitis. Thus we considered and included lower grade studies providing the most up to date and available direct and indirect evidence (i.e. uncontrolled prospective or retrospective cohort studies or case series).

The search primarily focused on rituximab treatment and paediatric anti-NMDAR encephalitis. However the evidence investigating this particular treatment for this condition was scarce, hence the search was extended and included related studies reporting findings of combined immunotherapy (rather than rituximab alone) and studies looking at AE in which anti-NMDAR diagnosis formed part of the cohort. Furthermore, we aimed to look at the use of rituximab as second-line treatment, although in some studies rituximab was used as a third-line or long-term therapy. A summary of the preliminary resources and results of the search is presented below.

Source	Results
NHS EVIDENCE (GUIDANCE ONLY)	13 (of 1 is a duplicate and not included)
COCHRANE	1 (a trial, not Cochrane review – not included)
TRIP DATABASE (GUIDELINES ONLY)	11
MEDLINE	9
EMBASE	67 (of which 7 are duplicates and not included)
CINAHL	0

- total number of hits identified in the search: 93
- number of articles retrieved for which abstracts were considered: 55
- number of articles appraised: 15
- number of articles included: 11

Guidelines were not included in this appraisal. Studies and case series reporting less than five patients were excluded. A total of 15 references primarily considering the efficacy and/or safety of individual treatments were appraised. As we were unable to retrieve a full text article for two of those references that were conference abstracts (Parnes et al. 2015(18); De Blander et al. 2013(19)), we did not include those in the results due to insufficient information available to support the presented findings. Furthermore, another two studies (Sartori et al. 2015(10); Irani et al. 2010(20)) were excluded as the number of patients treated with rituximab was less than five, thus too small for deducting any level of significance.

A total of 11 articles appraised and included were also graded in accordance with NHS England guidance on conducting evidence reviews 2016.

4. Results

A total of eleven articles were considered in the discussion of the efficacy, safety and cost effectiveness of rituximab treatment. All the studies contained indirect evidence with regards to the research question either in relation to the treatment or the target population (children with anti-NMDAR encephalitis).

No studies containing direct or indirect evidence on cost effectiveness of use of rituximab for children suffering with anti-NMDAR encephalitis were found. Studies where less than five patients received rituximab treatment and where a full text article was not available were excluded.

Only one study (a retrospective descriptive cohort) assessed the utility and safety of rituximab treatment in children with autoimmune and inflammatory encephalitis of which anti-NMDAR encephalitis was a subgroup (Dale et al. (2014))(15). One other study (a prospective controlled observational cohort) investigated rituximab treatment in adult population with limbic encephalitis of which patients with NMDAR-Ab were a subgroup and was included for consideration (Lee et al. (2016))(16) as advised by the Policy Working Group.

Nine other studies that were identified reported the use of immunotherapy (including but not exclusively focusing on rituximab) in children or all-age cohort where children were a subgroup of patients with anti-NMDAR encephalitis. These were:

- 1 large prospective observational cohort study by Titulaer et al. (2013)(9);
- 1 large retrospective descriptive study Dalmau et al. (2008)(21);
- 1 prospective observational cohort study by Wright et al. (2015)(6);
- 5 small retrospective descriptive studies by Brenton et al. (2016)(7), Zekeridou et al. (2015)(13), Hacohen et al. (2014)(22), Armangue et al. (2013)(11); Florance et al. (2009)(8);
- 1 systematic review of immunotherapy for autoimmune encephalitis associated with antibodies to cell surface antigens by Nosadini et al. (2015)(3).

The main results of the 11 articles are summarised in the below table.

Publication	Design	Population	Treatment	Sample size	RTX second-line		Median age	Median f-up	Outcomes									
					%	n			Benefit from rituximab		mRS 0-2 at initiation vs outcome		mRS 0-2		Full recovery (mRS=0)		Relapse		Death	
									%	n			%	n	%	n	%	n	%	n
Dale et al. (2014)	Retrosp. descriptive cohort	Children with autoimmune & inflammatory encephalitis	Rituximab	144 total			8 y	1.65 y	**87%**	125	**17% vs 74%**				**28%**	40			**2%**	3
				39 NMDAR-Ab			8.7 y	1.3 y	**97%**	38	**5% vs 80%**				**18%**	7			**5%**	2
				Anti-NMDAR cases treated early (n=25)							**8% vs 92%**									
				Anti-NMDAR cases treated late (n=14)							**0% vs 57%**									
									mRS improvement		**mRS 0-2 in nonrespond.***									
Lee et al. (2016)	Prosp. controlled observational cohort	Adults with limbic encephalitis	Rituximab	80 with RTX			43 y	22.5 m	**76%**	61	**60%**	33/55	**69%**	55			**13%**	10		
				81 controls			47 y	25.1 m	**54%**	44	**22%**	6/27	**63%**	51			**7%**	6		
				p-value					0.011		0.001		0.442				0.284			
Titulaer et al. (2013)	Prosp. observational cohort	All age with anti-NMDAR encephalitis	Immunotherapy	577 all-age	**20%**	101/501	21 y	24 m					**81%**	203/252	**~50%**	**	**12%** in 2y	45	**10%**	30
				Cases who failed first- & received second-line Rx									**78%**	43/55						
				Cases who failed first- & did not receive second-line Rx									**55%**	32/58						
				211 children	**24%**	42/177							**~86%**	**	**~58%**	**				6
Dalmau et al. (2008)	Retrosp. descriptive	All age with anti-NMDAR encephalitis	Immunotherapy	100 (22 children)	**10%**	10	23 y	17 m					**75%**	75	**47%**	47	**15%**	15	**7%**	7
Wright et al. (2015)	Prosp. observational cohort	Children with anti-NMDAR encephalitis	Immunotherapy	31	**19%**	6	8 y	at least 12 m							**63%**	19/30	**23%**	7		
															[a]**78%**	18/23				
															[b]**13%**	1/7				
Brenton et al. (2016)	Retrosp. descriptive	Children with anti-NMDAR encephalitis	Immunotherapy	10	**60%**	6	13 y	at least 12 m							**60%**	6	**0%**	0		
Zekeridou et al. (2015)				36	**72%**	26	10 y	24 m							**56%**	20	**8%**	3		
Hacohen et al. (2014)				46	**11%**	5	10.5 y	30 m							**32%**	15	**33%**	15		
															[c]**0%**	0	[c]**20%**	1		
Armangue et al. (2013)				20	**35%**	7	13 y	17.5 m							**60%**	12	**15%**	3	**5%**	1
Florance et al. (2009)				32	**19%**	6	13 y	4.5 m							**29%**	9	**25%**	8		
Nosadini et al. (2015)	Systematic review	Patients with autoantibodies to neuronal cell-surface antigens	Immunotherapy	905 with anti-NMDAR	No new evidence on treatment of anti-NMDAR encephalitis as review consists of studies discussed above: Zekeridou et al. (2015); Wright et al. (2015); Hacohen et al. (2014); Dale et al. (2014); Titulaer et al. (2013); Florance et al. (2009); Dalmau et al. (2008); plus Irani et al. (2010) (excluded from results and discussion of this review as only 2 patients treated by rituximab)															
					Results of all reviewed articles suggest that: • The use of immunotherapy (rather than no therapy) is associated with a better outcome. • Early commencement of immunotherapy favours a better neurological outcome. • The use of second-line immunotherapies appears to be beneficial, more commonly associated with a better outcome and lower relapse rates.													

*Nonresponders, i.e. patients with inadequate response to first-line treatment (82 of all 161 patients); **Number not available, percentage estimated from Figure 3 and Figure S4; [a]Patients diagnosed early; [b]Patients diagnosed late; [c]Patients who received rituximab

5. Discussion

Clinical effectiveness

The retrospective multi-centre study by Dale et al. (2014)(15) was the only significant research investigating the efficacy of rituximab in treatment of children with autoimmune and inflammatory disorders of the central nervous system (CNS). They reported a definite, probable or possible benefit from rituximab in 87% (125/144) of all children and 97% (38/39) of children in the NMDAR-Ab cohort. After a median follow-up of 1.65 years after administration of rituximab, 28% (40/144) of patients achieved full recovery and 2% (3/144) died. In the NMDAR-Ab cohort, the median follow-up was 1.3 years, 18% (7/39) recovered fully and 5% (2/39) died.

Dale et al. (2014) also evaluated clinical disease state at rituximab initiation versus outcome, and found that 17% of cases had mRS of 0-2 at rituximab initiation, compared to 74% at outcome. In the NMDAR-Ab cohort, 5% of cases had mRS of 0-2 at initiation and 80% at outcome. The change in mRS 0-2 at initiation versus outcome as greater in patients who received rituximab early compared to those who received it late. In the NMDAR-Ab patients who received rituximab 8% had mRS of 0-2 at initiation and 92% at outcome, compared to those who received it late and had a change from 0% to 57%.

The prospective controlled observational study by Lee et al. (2016)(16) evaluated the efficacy of rituximab as a second-line immunotherapy in adults with autoimmune limbic encephalitis. In their comparative analysis, functional improvement (of the mRS score) occurred more frequently in patients treated with rituximab (61/80; 76%) compared to the control group without it (44/81; 54%) (P-value=0.011). However rituximab group did not achieve more favourable mRS (i.e. mRS of 0-2) at last follow-up compared the control (69% vs 63%, p-value=0.442). Additional monthly rituximab therapy and partial response to first-line immunotherapies were associated with mRS improvements and favourable mRS score.

Lee et al. (2016) found the effect of rituximab to be the same regardless of autoantibody status. Among patients (from both rituximab and control groups) who did not respond to the first-line immunotherapy, rituximab treatment resulted in more favourable outcome compared to patients without rituximab (60% (33/55) vs 22% (6/27), p=0.001). Relapse rate was similar in rituximab and control groups (13% (10/80) vs 7% (6/81), p=0.284).

Titulaer et al. (2013)(9) prospectively studied so far the largest multi-institutional cohort of patients (both children and adults) with anti-NMDA receptor encephalitis. A total of 101/501 (20%) patients received rituximab (alone or in combination). Of those, 84% were treated with 375 mg/m^2 of rituximab weekly for 4 weeks. In children under 18 years, 42/177 (24%) received rituximab.

The study found that 81% (203/252) of patients had good outcome (mRS of 0-2) and approximately 50% fully recovered at 24 month follow-up. Predictors of good

outcome were early treatment and no admission to intensive care unit. Of patients who failed first-line and received second-line therapy, 78% (43/55) had good outcome at 24 months, compared to 55% (32/58) of patients who failed first-line and did not receive second-line therapy. In children, predictors of good outcome and the magnitude of effect of second-line immunotherapy were similar to those of the entire cohort.

They reported that during the 24 month follow-up, 45 patients had clinical relapse (representing a 12% risk within 2 years), of whom 15 (33%) had multiple relapses. The use of immunotherapy (p=0.038) and use of second-line immunotherapy in patients without tumour (p=0.007) were associated with fewer relapses. Overall 30 of 501 patients died, including 6 of 177 children. At 24 months' follow-up, 10% mortality rate (24 deaths among 252 patients who had 24 months' follow-up) was estimated. There were significant issues with follow up over the 24 month period (50% of all patients and 56% of patients who received second line immunotherapies were lost to follow-up) therefore the findings need to be interpreted with caution.

The retrospective study by Dalmau et al. (2008)(21) investigated a cohort of 100 patients (both children and adults) with anti-NMDAR encephalitis where rituximab was used as one of the second-line treatment options. Overall, 47/100 (47%) of patients achieved full recovery and 75/100 (75%) had good outcome with mRS of 0-2 after a median follow-up of 17 months. Seven patients died as a result of the neurological disorder. 15% had one or more relapses in median of 24 months. Only 10/100 (10%) patients received rituximab as a second-line treatment. The authors discussed that 13/17 patients unresponsive to first-line immunotherapy responded to rituximab (n=6), cyclophosphamide (n=5), or both (n=2).

Wright et al. (2015)(6) conducted a prospective observational study investigating immunotherapy for paediatric anti-NMDAR encephalitis. Overall, 19% (6/31) of study patients received rituximab (either alone or in combination with cyclophosphamide), 63% (19/30) achieved full recovery and 23% (7/30) had a clinical relapse. Patients who were diagnosed and treated early were more likely to make a full recovery. At last follow-up, 78% (18/23) of patients who were diagnosed early made full recovery compared with 13% (1/7) of late diagnosed patients (p=0.002).

The study did not find a difference in the long-term outcome between children with anti-NMDAR encephalitis who received second-line immunotherapy or not. On the other hand the evidence suggested that treatment with corticosteroids and IVIg only may not be sufficient as 4/5 patients who were diagnosed early but did not fully recover and 6/7 who had a clinical relapse received steroids and IVIg only as their initial treatment.

In the five smaller retrospective studies by Brenton et al. (2016)(7); Zekeridou et al. (2015)(13); Hacohen et al. (2014)(22); Armangue et al. (2013)(11); Florance et al. (2009)(8), the authors investigated immune therapy for anti-NMDAR encephalitis in children, the proportion of patients who received rituximab as second-line treatment (either alone or in combination with cyclophosphamide) varied, ranging from 11% in the study by Hacohen et al. (2014) and 19% by

Florance et al. (2009) to 60% in the study by Brenton et al. (2016) and 72% by Zekeridou et al. (2015).

Similarly the proportion of patients who achieved complete recovery from the initial disease at last follow-up differed. Florance et al. (2009) and Hacohen et al. (2014) found that less than a third of all cases had full recovery (29% and 32% respectively) whereas the other three studies reported full recovery in more than half of their cases (56% in Zekeridou et al. (2015) and 60% in Brenton et al. (2016) and Armangue et al. (2013)). Proportion of children who experienced neurological relapse(s) ranged from zero (Brenton et al. (2016)) to 33% (Hacohen et al. (2014)).

Overall the studies with high proportion of children treated with rituximab (72% in Zekeridou et al (2015) and 60% in Brenton et al. (2016)) reported higher recovery (56% and 60%) and lower relapse (8% and 0%) rates. However the study by Zekeridou et al. (2015) with the highest rate of second-line rituximab treatment concluded that their outcome was very similar to the outcome reported in other series with lower rate of second-line treatment. It should be noted though that rituximab dosage used in this study was lower than the recommended total dose of 1500 mg/m^2 which might have confounded their findings and could explain the lack of effect on outcome of increased rituximab usage within their cohort.

Hacohen et al. (2014) who reported only a few cases taking rituximab (5/46) found that none of the 5 rituximab patients had a full recovery. However only 1/5 (20%) rituximab patients had a relapse, compared with 14/41 (34%) patients without rituximab.

Armangue et al. (2013) found that all 7 patients who received rituximab responded to treatment without further relapses. One case who had 5 previous episodes received rituximab and cyclophosphamide followed by mycophenolate mofetil during episode 6 and substantially improved with no further relapses eight months after rituximab. The authors also reported that one case treated with first-line therapy only died as a result of the neurological disorder.

Florance et al. (2009) looked at initial response to treatment with rituximab and/or cyclophosphamide and found that 4/7 patients started to improve shortly after treatment initiation (3 received both rituximab and cyclophosphamide,1 received cyclophosphamide only) and the other three had slow improvement not clearly related to the treatments (2 with rituximab only and 1 with both).

The systematic review of immunotherapy for autoimmune encephalitis associated with antibodies to cell surface antigens by Nosadini et al. (2015)(3) reviewed primary studies according to the type of antibody. The overall results suggested that:

- The use of immunotherapy (rather than no therapy) is associated with a better outcome.
- Early commencement of immunotherapy favours a better neurological outcome.
- The use of second-line immunotherapies also appears to be beneficial, more commonly associated with a better outcome and lower rates of

relapses.

The summary of literature review on the treatment of anti-NMDAR encephalitis included eight studies; of those, seven were discussed above (Zekeridou et al. (2015); Wright et al. (2015); Hacohen et al. (2014); Dale et al. (2014); Titulaer et al. (2013); Florance et al. (2009) and Dalmau et al. (2008)) and one by Irani et al. (2010) was excluded from results and discussion of this review as only 2 two patients were treated by rituximab (but is included in Section 7: Evidence Summary Table). This review did not provide any new evidence for treatment of anti-NMDAR encephalitis.

Safety and tolerability

The retrospective observational multi-centre study by Dale et al. (2014) provided the best available evidence for safety and tolerability of rituximab treatment in children with autoimmune and inflammatory CNS disorders. Hematologic and immunologic measurements were recorded in the majority of children. A total of 119/124 (96%) patients had B-cell depletion after rituximab (the actual values were not recorded), which persisted >12 months in 12 children. 27 patients had documented hypogammaglobulinemia. There was no difference in hematologic and immunologic effects between younger and older children, except an increased rate of hypogammaglobulinemia in children ≤5 years.

The study reported infusion adverse events (AEs) in 18/144 (12.5%) children. Of those, three cases had a grade 4 reaction (anaphylaxis) that was resolved without complication with standard therapy. One patient with infusion-related fever had a transient exacerbation of seizures. One other patient was unable to tolerate rituximab due to worsening hypersensitivity. There was no difference in infusion AEs between those on antihistamine prophylaxis and those without it, and no increased risk in younger children (≤5 years).

Infectious side effects were recorded by Dale et al. (2014) in 11/144 (7.6%). Of those, two patients had a grade 5 AE (death; both were patients with anti-NMDAR); two a grade 4 AE (life-threating or disabling); and remaining seven a grade 3 AE (hospitalisation or intravenous antibiotics). Grade 4 &5 infectious AEs occurred a median of 30 days (range 3-38) after rituximab initiation. There was no difference in infectious AEs between those on antibiotic prophylaxis and those without it, and no increased risk in younger children (≤5 years).

In the prospective controlled observational study by Lee et al. (2016), hematologic effects of rituximab were observed in all 80 patients who developed B-cell near-complete depletion (assessed via CD19 count) during rituximab therapy. 37 (46%) patients had transient lymphopenia which was neither severe nor sustained (≥6 months). No serious infusion-related and infectious adverse effects (AEs) were reported by the authors. 5/80 patients (7%) had non-severe infusion-related AEs; four had rash (grade 1) and one dyspnea and palpitations (grade 2). And 9/80 patients (11%) had non-severe infectious AEs; all had pneumonia (grade 3) at median of 30 days (range 2-60) after rituximab initiation. Finding were not reported in relation to the prescription of antihistaminic and acetaminophen.

In the large prospective observational cohort study by Titulaer et al. (2013) with a follow-up period of 24 months, only four serious adverse events were reported due to second-line therapy, including one anaphylaxis and one infection due to rituximab, and one infection and one severe lymphopenia due to cyclophosphamide. No treatment-related deaths or irreversible complications were identified. A significant number of patients (56% of those who received second-line therapy) were lost to follow-up, thus the findings need to be interpreted with caution.

The study by Zekeridou et al. (2015) with the highest proportion of second-line rituximab treatment (72%; 26/36 cases received rituximab) followed up patients for 24 months, however the adverse effects occurred early on with three (11.5%) serious adverse events observed due to rituximab. Two cases had severe allergic reaction and one case had severe sepsis with death 10 days after rituximab treatment (this case presented with multi-resistant pulmonary infection).

In the study by Brenton et al. (2016), 5/10 children experienced adverse events due to chronic immunosuppression, ranging from severe headache to septic shock. These complications appeared at least 4 months post hospitalisation and resulted in further hospitalisation. Of those five children, 3 were receiving rituximab as a long-term therapy. Two patients stopped long-term immunotherapy for these concerns.

In the other smaller studies, no significant side effects were reported in patients treated with rituximab by Wright et al. (2015), Armangue et al. (2013) and Florance et al. (2009).

Adverse events or side effects were not reported by Dalmau et al. (2008), Hacohen et al. (2014) and Nosadini et al. (2015).

Evidence strengths and limitations

Autoimmune encephalitis (AE) in children is a rare condition that is becoming more recognised in the last 10 years. Therefore it is not surprising that there is a lack of large studies or studies of high level of quality. Existing evidence is mostly derived from uncontrolled mainly retrospective studies prone to bias and confounding. Furthermore, very limited evidence exists for rituximab treatment, its efficacy and safety in children with AE specifically related to anti-NMDAR disorders.

The studies included in this evidence review are low grade studies and have significant limitations that affect their generalisability and application to clinical practice. The majority are uncontrolled observational studies (generally case series), which are subject to bias and confounding. Most studies either lack in methodology or clarity on the data (e.g. large loss to follow-up, lack of adjustments for variation in dosage, time of treatment start and duration etc.) to support conclusions drawn for our group of interest.

Three of the observational studies were undertaken prospectively, which may reduce some sources of bias and confounding. However the prospective study by

Lee et al. (2016) investigated one specific type of autoimmune encephalitis in adult population, thus findings do not necessarily apply to children population and should be interpreted with caution. The prospective study by Titulaer et al. (2013) was conducted with patients of all ages and could not adjust for the effect of individual treatments. And the third prospective study Wright et al. (2015) had a relatively small sample size of 31 children and did not focus on rituximab treatment (only 19% (6/31) of children received rituximab).

As is usual for a rare disease, many of the studies had small sample sizes for deducing any level of significance or generalising findings. Even the two larger studies by Dale et al. (2014) and Titulaer et al. (2013) which included more than 100 children and provide the most useful evidence had several limitations. The study by Dale et al. (2014) assessed the utility of rituximab in a cohort of patients with heterogeneous CNS disorders. Titulaer et al. (2013) only reported the combined effect of first-line immunotherapy and second-line therapy where applicable, and could not compare the effect of individual treatments. Furthermore, their main findings focused on the all-age cohort rather than children population.

Crude markers of disability such as the modified Rankin Scale (mRS) were used as outcome measures in the majority of studies. The mRS is an acceptable measure, but the grading in our group of studied patients may have been affected by factors such as comorbidities and the socio-economic status which were not accounted for. Moreover, in some of the smaller studies, for example by the Brenton et al. (2016) and Florance et al. (2009), the outcome measures were not clearly defined.

Only two studies by Dale et al. (2014) and Lee et al. (2016) evaluated the utility of rituximab monotherapy for autoimmune CNS disorders. As mentioned above, the study by Dale et al. (2014) was limited by the fact that it assessed the utility of rituximab in a cohort of patients with heterogeneous CNS disorders. Moreover, patients received other immunotherapies before and after rituximab; thus evaluating the therapeutic effect of a single agent was inaccurate. The study by Lee et al. (2016) was conducted among adult population with one specific condition (autoimmune limbic encephalitis) thus findings can only be accepted on the basis of similar mechanism of action by depletion of B-cells and reduction of autoimmune response as a result.

The remaining nine studies reported patients who received a combination of different treatments (first-, second-, sometimes third-line and long -term immunotherapy) and outcomes were often reported for the whole cohort with no differentiation between cases who did and did not receive rituximab as second-line treatment. Therefore ascribing therapeutic benefits to rituximab was not possible.

Rituximab is known to be associated with numerous adverse effects. Dale et al (2014) provided the best available evidence for safety and tolerability of rituximab treatment in children with autoimmune and inflammatory CNS disorders, reporting infusion adverse events in 12.5% and infectious side effects in 7.6% of children treated with rituximab. In contrast, Lee et al. (2016) did not record any serious

(grade 4 or more) infusion-related and infectious adverse effects, but as noted above there are significant limitations with the reporting of these outcomes due to loss to follow-up. In addition this study was conducted among adults rather than children. Also Titulaer et al. (2013) in his large cohort reported only four serious adverse events due to second-line therapy, including one anaphylaxis and one infection due to rituximab. Again this study included patients of all ages; nevertheless 37% of those were under 18 years. Also long-term use of rituximab seems to be less safe as suggested by Brenton et al. (2016).

The three larger studies by Dale et al. (2014), Lee et al. (2016) and Titulaer et al. (2013) found that a variety of rituximab dosage regimens were employed. Dosage of 375 mg/m^2 weekly for 4 weeks was the most commonly used regimen in studies by Dale et al. (2014) and Titulaer et al. (2013). A median rituximab cycle was 5 weeks (interquartile range 4-6.75 weeks) was reported in the study of the adult population by Lee et al. (2016). The other studies provided no information on rituximab dosage regimen, except for the French study by Zekeridou et al. (2015) where the dosage regimen was likely to have followed the French recommendation of a dose 375 mg/m^2, repeatedly given if no substantial improvement was noted after 10 days.

Better quality evidence is needed to investigate the safety and efficacy of rituximab monotherapy in children with autoimmune CNS disorders (or anti-NMDAR encephalitis in particular), to compare rituximab with other immunotherapies, to determine the most optimal dosage regimen and timing of rituximab therapy to yield maximum benefit, and to standardise laboratory diagnostics, symptomatic assessment (for cognition and physical ability) as well as hematologic and safety monitoring.

6. Conclusion

Efficacy and safety should be taken into account when considering the place of rituximab in treating AE encephalitis (anti NMDAR). There is a lack of high-quality evidence to ascertain the added beneficial effect of rituximab (either in the acute or chronic stage) as best optional treatment in children anti-NMDAR encephalitis.

From the large observational study by Dale et al. (2014)(15) investigating rituximab monotherapy, 87% of children with autoimmune and inflammatory encephalitis (and 97% of children with anti-NMDAR encephalitis) had some form of benefit from rituximab treatment used second-line, especially when received early. The large prospective cohort study by Titulaer et al. (2013)(9) found that 78% of patients with anti-NMDAR encephalitis who failed first-line and received second-line immunotherapy (with rituximab and/or cyclophosphamide) had good outcome at 24 months, compared to 55% of patients who failed first-line and did not receive second-line therapy.

Early diagnosis and early treatment were associated with better outcomes. Dale et al. (2014)(15) found that the change in mRS 0-2 was greater in patients given rituximab early compared to those treated later. Titulaer et al. (2013)(9) found early treatment to be a predictor of good outcome and Wright et al. (2015)(6) reported a higher proportion of full recoveries in patients diagnosed and treated early. Evidence also suggested that the use of immunotherapy and use of second-line immunotherapy/rituximab was associated with fewer relapses (9, 11, 21, 22).

The death rate reported ranged between 2%-10% (9, 11, 15, 21). Most patients died as a result of their neurological disorder and due to very low numbers and data limitations it was not possible to draw any conclusions.

The limited evidence supports the use of rituximab second-line especially in children with severe refractory or relapsing autoimmune encephalitis who fail or inadequately respond to the first-line therapy. However no evidence compares the effects of individual immunotherapies, thus it is not possible to ascribe therapeutic benefits solely to rituximab. Furthermore, it is unclear which children are more likely to benefit, which dosage regimen is the most optimal and whether or when rituximab has any benefits over different second-line therapies such as cyclophosphamide.

Rituximab was generally well tolerated in short-term studies. In the study by Dale et al. (2014)(15), 12.5% of children were reported with infusion AEs (2% with severe infusion AEs of grade 4) and 7.6% with infectious side effects (3% with severe infectious AEs of grade 4 or 5). In the large cohort study by Titulaer et al. (2013)(9), only two patients (approximately 2%) reported anaphylaxis or infection due to rituximab. However long-term use of rituximab seems to be less safe as suggested by Brenton et al. (2016)(7), thus more studies in this area are needed in order to draw any conclusions,

Better quality evidence, for example from multicentre clinical trials, is needed to investigate the safety and efficacy of rituximab monotherapy in children with

autoimmune CNS disorders (and anti-NMDAR encephalitis in particular), to compare rituximab with other immunotherapies, to determine the most optimal dosage regimen and timing of rituximab therapy to yield maximum benefit, and to standardise laboratory diagnostics and safety monitoring.

7. Evidence Summary Tables

Table 1: Use of rituximab in treatment of autoimmune and inflammatory CNS disorders in children									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**

Dale et al. 2014
 	
Children's Hospital at Westmead, University of Sydney, Australia
	P1
	
	Multi-centre (15 centres) retrospective cohort study to assess the utility and safety of rituximab in children with autoimmune and inflammatory (A&I) CNS disorders.
		144 children A&I CNS disorders of which anti-NMDAR encephalitis (n=39). 3/39 anti-NMDAR patients had ovarian teratoma.
		
		Median age at first neurological presentation was 8 years (range 0.7–17), 8.7 years for the anti-NMDAR cohort (range 1.6-17). 103/144 patients were female (29/39 of the anti-NMDAR cohort).
		
		Most patients had prolong and relapsing disease course prior to first rituximab infusion, 138 patients were treated with one or more doses of corticosteroids, 104 received one or more courses of IVIg, 43 received single or multiple doses of cyclophosphamide and 21 underwent plasma exchange. In the anti-NMDAR cohort, 37 patients had steroids, 34 IVIg, 11 PLEX, 8 cyclophosphamide, and 4 MMF/azathioprine
			Rituximab was administered at a median age of 9.9 years (range 1.6-17.9 years). Before rituximab usage, the duration of disease was a median of 0.5 years (range 0.05-9.5 years) and the median modified Rankin Scale (mRS) was 3 (range 0-5 where 0-2 was considered a marker of good outcome) at rituximab initiation.
			
			A variety of dosage regimens were employed, with 375 mg/m^2 weekly for 4 weeks being the most commonly used regimen (n=57).
			
			Total duration of follow-up was 307 patient-years after rituximab administration (median 1.65 years, range 0.1-8.5 years). For anti-NMDAR patients, the median follow-up was 1.3 years (range 0.4-4.5).
			
			There were repeat courses of rituximab for
				Primary
				
				Safety
					Hematologic and immunologic effects	Measurements were recorded in 124/144 patients. 119/124 (96%) had B-cell depletion after rituximab (the actual values were not recorded), which was present >12 months in 12 children. 27/124 had documented hypogammaglobulinemia.
						
						There was no difference between younger and older children, except an increased rate of hypogammaglobulinemia in children ≤5 years.
							4	Indirect (in relation to target population)	The primary aim was to define safety of rituximab but this was a survey based methodology with significant weaknesses using a dubious classification of benefit.
									
									• Uncontrolled/unblinded retrospective observational study
									• Multiple confounders present, thus ascribing therapeutic benefits and risks to rituximab is inaccurate:
									  ○ Patients suffered from heterogeneous CNS disorders of different severity
									  ○ Most patients received other immunotherapies (before, with or after rituximab) and rituximab in different dosage regimes
									• Clinician's subjective assessment of treatment benefit
									• Crude markers of disability (mRS) used, mRS is poorly sensitive outcome measure when evaluating cognitive and neurodevelopmental difficulties, especially in

				Primary Safety	Infusion adverse events (AEs)	18/144 (12.5%) had recorded infusion AEs. Of those, 3 patients had a grade 4 reaction (anaphylaxis) that was resolved without complication with standard therapy. One patient with infusion-related fever had a transient exacerbation of seizures. One patient was unable to tolerate rituximab due to worsening hypersensitivity. There was no difference in infusion AEs between those on antihistamine prophylaxis and those without it, and no increased risk in younger children (≤5 years).			

Table 1: Use of rituximab in treatment of autoimmune and inflammatory CNS disorders in children									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		prior to rituximab. Anti-NMDAR diagnostic markers were CSF NMDAR Ab (n=34), serum NMDAR Ab (n=5) and teratoma (n=3).	prevention of relapse and reduction of corticosteroids, but the timings were not reported.	Primary Safety	Infectious side effects	11/144 (7.6%) had recorded infectious complication. Of those: 2 patients had a grade 5 AE (death; both were anti-NMDAR patients); 2 children a grade 4 AE (life-threating or disabling); and 7 children a grade 3 AE (hospitalisation or IV antibiotics). Grade 4 &5 infectious AEs occurred a median of 30 days (range 3-38) after rituximab initiation. There was no difference in infectious AEs between those on antibiotic prophylaxis and those without it, and no increased risk in younger children (≤5 years).			very young children • Relatively short follow-up Haematological and immunological measures were not consistent in relation to time or ascertainment of methodology used. There is a significant potential of data skewing in relation to start and duration of treatment which is not accounted for. Overall results are heterogeneous and cannot be used to extrapolate on the general population.
				Primary Clinical effectiveness	Clinician's subjective classification of response to rituximab	45/144 patients had a definite benefit from rituximab, 49 probable benefit, 31 possible benefit, 17 no or unclear benefit and 2 worsened. In the anti-NMDAR cohort, 38/39 patients had a benefit from rituximab (16 definite, 16 probable and 6 possible benefit), 1 had no benefit.			
					Modified Rankin Scale (mRS)	Median mRS was 2 (range 0-5) at outcome determination. The percentage of patients with mRS of 0-2 was variable between subgroups, but showed a general improvement. The change in mRS 0-2 at rituximab initiation and outcome, and the change in median mRS			

Table 1: Use of rituximab in treatment of autoimmune and inflammatory CNS disorders in children									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						was greater in those who received rituximab early compared to those who received it late. In anti-NMDAR patients, 25/39 who received rituximab early had a change in mRS 0-2 from 8% to 92%, compared to14 who received it late and had a change from 0% to 57%.			
					Overall clinical outcome	After a median follow-up of 1.65 years (1.3 for anti-NMDAR patients) after rituximab; 3/144 (2%) patients died (2 anti-NMDAR patients who died of AEs and one case of GAD Ab encephalitis who died of refractory status epilepticus); 101 (70%) had residual problems incl. cognitive or motor impairment or psychiatric disease and 16 continued to experience seizures. 40 (28%) children fully recovered. 32/39 anti-NMDAR patients had ongoing disability (incl. the two deaths). 11/39 anti-NMDAR patients were on other therapies at last clinical visit (rituximab n=10, steroids n=4, IVIG n=6 and MMF n=1).			

Table 2: Use of rituximab in treatment of autoimmune limbic encephalitis in adults									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Lee et al. 2016 Dpt. of Neurology, Biomedical Research Institute, Seoul National University Hospital, South Korea	P1 Controlled observational cohort study to evaluate the efficacy and safety of rituximab as a second-line immunotherapy and to determine factors associated with favourable outcomes in patients with autoimmune limbic encephalitis (ALE).	This study included 80 patients with clinical diagnosis of ALE treated with (at least 3 cycles of) rituximab as second-line therapy between May 2012 and Oct 2014 and followed up for at least 9 months. 30/80 patients had synaptic (27 NMDAR and three LGI1), 15 paraneoplastic and 35 no autoantibodies. Mean age was 43 ±18.4 years (range 16-80). 38/80 patients were female and 12 had tumour (4/27 anti-NMDAR had ovarian teratoma). Prior to rituximab, all patients underwent first-line treatment for a median of 2 (IQR 1-2) cycles at 6.8 ±13.4 months from symptom onset, consisting of corticosteroids, IVIg, and/or plasmapheresis. Median mRS was 3 (IQR 3-4) at initiation of rituximab. Further 81 patients who underwent first-line immunotherapy but not rituximab during the same time period were reviewed as a control group.	All 80 patients received rituximab (375 mg/m^2 weekly for 4 weeks) after incomplete response to or relapse after first-line immunotherapy. Patients also received antihistamine and acetaminophen to prevent/ameliorate infusion-related adverse events. Median rituximab cycle was 5 weeks (IQR 4-6.75 weeks). Mean follow-up period was 22.5 ±12.2 months (range 9-36 months). Mean lag of rituximab administration was 12.1 ±8.7 months from symptom onset. 48 (60%) patients received rituximab early (within 4 weeks of last first-line treatment or relapse detection) and 43 (54%) had additional monthly rituximab therapy. 12 (15%) patients received steroids concomitantly with rituximab.	Primary Clinical effectiveness	Modified Rankin Scale (mRS): mRS improvement (decrement of mRS at last follow-up compared to rituximab initiation); favourable mRS of 0-2 worse outcome mRS of 3-4	At last follow-up, a median mRS of 2 (IQR 1-3) was observed. 61/80 (76%) patients showed mRS improvement and 55 (69%) displayed favourable mRS. *Factors associated with favourable outcomes:* Patients with mRS improvement at last follow-up were younger compared to those without such improvement. Additional monthly rituximab cycles and partial response to first-line immunotherapy were associated with mRS improvements and favourable mRS scores. mRS of 4-6 at the worst recorded neurologic status predicted an unfavourable mRS score. *Comparative analysis:* Effect of rituximab in the antibody-negative and paraneoplastic autoantibody group were comparable to those in the synaptic autoantibody group. Rituximab group showed more mRS improvement compared to the control, but did not achieve more favourable mRS at last follow-up. When treatment and control patients (n=161) grouped, among those who did not respond first-line immunotherapy	4	Indirect (in relation to target population)	• Unblinded non-randomised observational study, but prospective follow-up • Relatively small sample size • Mainly adult population; children were included age 16-18 years, but this group was not differentiated in reported outcomes • Relatively short follow-up period • The paraneoplastic group (low rate of cancer) in the study population may confound some comparative analysis • mRS is poorly sensitive outcome measure when evaluating cognitive and neurodevelopmental difficulties, especially in very young children • There is potential for non-independence (several measures of clinical markers per individual) • The anti-NMDAR cohort is not easily identifiable as a group • Selection bias as rituximab group had a higher rate of cognitive and behavioural symptoms and underwent more cycles of standard first line therapies which are noted confounders • Although there appears to

Table 2: Use of rituximab in treatment of autoimmune limbic encephalitis in adults									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						(n=82) rituximab resulted in more favourable outcome compared to patients without rituximab (60% vs 22%, p=0.001).			be significant differences in outcomes for the rituximab group the confidence interval is very wide suggesting issues with accuracy • Cannot generalise the finding from this study although autoimmune mechanisms is ascertain by depletion of B lymphocytes (CD19)
				Primary Clinical effectiveness	Relapse	10/80 (12.5%) patients relapsed with 8.4 ±3.1 months of delay.			
				Secondary Safety	Hematologic effects	All 80 patients had B-cell near-complete depletion (assessed via CD19 count) during rituximab therapy. 37 (46%) patients had transient lymphopenia which was neither severe nor sustained (≥6 months).			
					Adverse events	No serious infusion-related and infectious adverse effects (AEs) were reported. 5/80 patients (7%) had infusion-related AEs; four with rash (grade 1) and one with dyspnea and palpitations (grade 2). 9/80 patients (11%) had infectious AEs; all with pneumonia (grade 3) at median of 30 days (range 2-60) after rituximab initiation. Finding were not reported in relation to the prescription of antihistaminic and acetaminophen.			

Table 3: Use of immunotherapies incl. rituximab in treatment of anti-NMDA receptor encephalitis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Titulaer et al. 2013 Dpt. of Neurology and Neurosciences, Hospital of the University of Pennsylvania, USA; Dpt. of Neurology, hospital Clinic, The University of Barcelona, Spain	P1 Multi-institutional observational cohort study to assess presentation of disease, spectrum of symptoms, immunotherapies used, timing of improvement and long-term outcome in patients with anti-NMDA receptor encephalitis.	577 all age patients tested positive for NMDAR antibodies in serum and/or CSF between Jan 2007 and Jan 2012. Median age at disease onset was 21 years (range 8 months to 85 years). 468 patients (81%) were female; 211 (37%) were children under 18 years and 28 (5%) were ≥ 45 years. 220 patients (38%) had underlying neoplasm, of whom 93% were female aged 12-45 years and of which 94% were ovarian teratomas. Patients presented with a spectrum of symptoms, categorised in 8 groups. Children presented with behavioural disorders, seizures and movement disorders. However within 4 weeks of symptom onset, most cases progressed towards a similar syndrome regardless of their age and 87% (498/571) developed four or more of the eight groups of symptoms. During the first month of disease, 86% of patients	501 of all 577 patients were followed-up for at least 4 months (median 24 months, range 4-186) and their treatment effects and outcomes were assessed at months 4, 8, 12, 18 and 24, using the mRS. Of the 501 patients; 462 (92%) were treated with first-line immunotherapy (most commonly (44%) steroids plus IVIg), 10 (2%) with tumour removal without immunotherapy, and 29 (6%) were not treated. 125 of 221 who failed first-line immunotherapy received second-line therapy (most commonly rituximab or cyclophosphamide or both; 84% of cases treated with weekly rituximab received 4 cycles of 375mg/m^2 and 73% of cases treated with monthly cyclophosphamide received 3-6 cycles of 750mg/m^2). A total of 101 patients received rituximab (alone or in combination). Of those, 71 were from non-neoplastic cohort. The remainder of non-	Primary Clinical effectiveness	Modified Rankin Scale (mRS) Good outcome (mRS of 0-2) Treatment failure (mRS≥4)	Of all 501 patients with ≥4 month follow up, 394 had mRS of 0-2 (median 6 months, IQR 2-12) and 30 died. At 24 month follow-up, 81% (203/252) had good outcome and 10% (24/252) died. Predictors of good outcome were early treatment and no admission to ICU. Of the 125 patients who failed first-line and received second-line therapy, 84 had mRS of 0-2 (median 10 months, IQR 6-21) during first 24 months. At 24 months, 78% (43/55) had a good outcome. Of the 96 patients who failed first-line and did not receive second-line therapy, 49 had mRS of 0-2 (median 15 months, IQR 7-not achieved) during first 24 months. At 24 months, 55% (32/58) had good outcome. In 177 children, predictors of good outcome and the magnitude of effect of second-line immunotherapy were similar to those of the entire cohort.	4	Indirect (in relation to target population and treatment)	• Uncontrolled, non-randomised observational study, but prospective follow-up and large sample size • Due to last follow-up at 24 months, the study may: o underestimate frequency and level of recovery as some patients had a shorter follow-up and others continued to improve after 24 months o overestimate the mortality (imputation analysis estimated mortality of 7% at 24 months) • The effect of individual treatments could not be compared, hence sole rituximab treatment effects is unclear • There is lack of allocation concealment • Children and adults assessed together, no specific children outcomes • mRS is poorly sensitive outcome measure when evaluating cognitive and neurodevelopmental difficulties, especially in very young children • Significant loss to follow up between 4 and 24
				Primary Clinical effectiveness	Relapse	During the 24 month follow-up, 45 patients had clinical relapse (representing a 12% risk within 2 years), of whom 15 (33%) had multiple relapses. Compared with the initial episode, 46/69 (67%) relapses were less severe, 24 (35%) mono-symptomatic, 16 (23%) similar and 7 (10%) worse.			

Table 3: Use of immunotherapies incl. rituximab in treatment of anti-NMDA receptor encephalitis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		had the modified Rankin Scale (mRS) of 5 and further 12% had mRS of 4. 90% of cases had abnormal EEG, 33% abnormal MRI and 79% abnormal CSF.	respondents (96/221) had no additional treatment.			The use of immunotherapy in the initial episode, use of second-line therapy and teratoma identified at presentation were associated with a lower frequency of relapses.			months, from 125 to 55 patients in the cohort that received second-line therapy • The results are heterogeneous in relation to the population of interest and treatment, thus they could not be generalised
				Secondary Safety	Side-effects	Four serious adverse events were reported due to second-line therapy incl. one anaphylaxis and one infection due to rituximab, and one infection and one severe lymphopenia due to cyclophosphamide. No treatment-related deaths or irreversible complications were identified.			

Table 3: Use of immunotherapies incl. rituximab in treatment of anti-NMDA receptor encephalitis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Brenton et al. 2016 University of Virginia, Dpt. of Neurology, USA	P1 Retrospective descriptive case series of children diagnosed with anti-NMDA receptor encephalitis to further characterize and classify the presentation and disease course and illustrate the approach to the long-term management.	This review included 10 children who were diagnosed between Jan 2010 and Aug 2013, based on clinical symptoms plus CSF and/or serum positivity for the NMDA receptor antibody. (1/10 had also voltage gated potassium channel complex Ab.) Median age at presentation was 13 years (range 6–17 years). 8/10 patients were female. Prodromal symptoms were noted in 7/10 patients. All children had altered mental status, 9 experienced seizures (focal in 8/9 cases), 7 dysautonomia and 5 psychosis (halluc./ delusions). Two patients were found to have an ovarian teratoma and none experienced a neurological relapse at 12 months after immunotherapy.	In the acute phase all children received first-line corticosteroid treatment combined with IVIg in 6 cases. After a median of 8-day observation, 9 children received second-line treatment, of which 6 had rituximab (alone or in combination). Further two received rituximab as a third-line. All 10 children received chronic treatment of various drugs and dosage, incl. rituximab (n=5); of duration with a median of 12 months (range 6-48). Two patients with the ovarian teratoma underwent surgical excision in the chronic phase.	Primary Clinical effectiveness	Recovery	6/10 patients had full recovery from the initial disease. The remaining 4 patients continue to experience mild persistent behavioural abnormalities and one also requires antiseizure medication for persistent seizures.	3	Indirect (in relation to treatment)	• Very small sample size • Uncontrolled descriptive study • Strong selection bias • Patients received different treatments, thus ascribing therapeutic benefits to rituximab is not possible • Unexplained inconsistency of relapse rate compared to other research • Solely descriptive design, thus no outcomes measured • Observational evidence, not generalizable
				Primary Clinical effectiveness	Relapse	No patients experienced a neurological relapse despite all patients being free from immunotherapy for at least 12 months at the time of the review.			
				Secondary Safety of chronic treatment	Side effects	5/10 experienced adverse events (ranging from severe headache to septic shock) due to chronic immunosuppression (at least 4 months post immunosuppression), resulting in further hospitalisation. 3/5 patients with side effects were receiving rituximab as a chronic therapy. 2 patients stopped the chronic immunotherapy for these concerns.			
Zekeridou et al. 2015	P1 Retrospective case series describing treatment and outcome of	This study included 36 children with anti-NMDA receptor encephalitis whose presence of NMDA-R-Abs in CSF was confirmed in French PNS Reference Center	All patients received first-line treatment (corticosteroids, IVIg and/or plasma exchange). Median time to first treatment was 19 days.	Primary Clinical effectiveness	Initial improvement	In the 26 cases treated with rituximab, median duration between first rituximab administration and first sign of improvement was 24 days (range 5-150).	3	Indirect (in relation to treatment)	• Uncontrolled retrospective study • Small sample size limiting statistical analysis in subgroups

Table 3: Use of immunotherapies incl. rituximab in treatment of anti-NMDA receptor encephalitis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
French Reference Center of Paraneoplastic Neurological Syndromes, HospicesCivils de Lyon, Hopital Neurologique, France	children with anti-NMDA receptor encephalitis.	between Jan 2007 and Dec 2012. Mean age was 10 years (range 1–17). 22/36 patients were ≤12 years old and 26 were female. 52% of patients had prodromal symptoms. 50% (18/36) presented with seizures and 31% (11/36) with psychiatric symptoms. During acute disease, psychiatric and cognitive symptoms were present in 92% of cases, seizures in 86% and movement disorders in 82%. Autonomic dysfunction was more frequent in females than males (50% vs 0%) and chorea in cases ≤12 years (52% vs 0%). CSF abnormal in 91%, EEG in 92% and MRI in 31% of cases. One patient had ovarian teratoma. Compared to 71 adult patients tested in the same Center, children cases had fewer tumour, presented more frequently seizures, had less psychiatric and more abnormal movement symptoms at	81% of cases received second-line therapy; 26 patients rituximab and 5 cyclophosphamide (of those, 3 cases had both). Median time between first- and second-line therapy was 26 days. *Note French therapeutic recommendation: Perform early second-line immunotherapy when patient did not respond to first-line treatment; for paediatric cases: rituximab with a dose 375 mg/m^2, repeat if no substantial improvement after 10 days.* 6/36 patients received long-term immunosuppression (5 azathioprine and 1 mycophenolate mofetil). Follow-up period was 24 months (at 24 months data available in 31/36 patients).	Primary Clinical effectiveness	Good outcome (mRS ≤2)	30/36 patients (83%) had good outcome at last follow-up. Median time between treatment onset and good outcome was 6 months. Age >12 years was a predictor of good outcome (p=0.03).			• Patients received different treatments, and although these were at defined timelines, ascribing therapeutic benefits directly to rituximab is with certainty not possible • mRS is poorly sensitive outcome measure when evaluating cognitive and neurodevelopmental difficulties, especially in very young children • Nearly 14% of patients were lost to follow up at 24 months. • More frequent and earlier use of second-line immunotherapy, especially rituximab, as per French guidance recommendation; however outcomes appear to be similar to those reported in other studies where second-line treatment was used less often • Observational evidence, not generalizable
					Complete recovery (mRS of 0)	20/36 patients (56%) achieved complete recovery at last follow-up. Median time between treatment onset and complete recovery was 24 months. Initial mRS≤3 was a predictor of complete recovery (p<0.01)			
				Primary Clinical effectiveness	Relapse	3/36 children presented with relapse (at 4, 12 and 24 months). Of those, one patient had first-line treatment only, and two had second-line before their relapse. There were no multiple relapses observed.			
				Secondary Safety	Adverse events	Three serious adverse events were observed due to rituximab: 2 cases had severe allergic reaction; 1 case had severe sepsis with death 10 days after rituximab (presented with multi-resistant pulmonary infection).			

Table 3: Use of immunotherapies incl. rituximab in treatment of anti-NMDA receptor encephalitis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		disease onset compared with adults.							
Wright et al. 2015 John Radcliffe Hospital, University of Oxford, UK; Birmingham Children's Hospital, UK	P1 UK-wide prospective surveillance study reporting clinical features, management and neurological outcomes of NMDAR-Ab-mediated encephalitis in children.	This study included 31 children with NMDAR-Ab encephalitis (defined by clinical presentation and NMDAR antibodies in serum and/or CSF) from 13 different centres. Eight cases presented during the 13-month study period and 23 were historical. Median age was 8 years (range 22 months-17 years)). 23/31 patients (74%) were female. Male cases were older (median 11 years) and had more frequently partial phenotypes. 29/31 children (90%) had good premorbid health. There was no significant family history of autoimmune disease. 90% (28/31) of patients presented with	24 cases were diagnosed (and treated) within 8 weeks of symptom onset (median time 3 weeks for early diagnosis) and 7 were diagnosed late (over 6 months). All 31 patients received steroids, 22 (71%) had IVIg and 9 (29%) plasma exchange (PLEX). 10 (32%) received second-line immunotherapy using cyclophosphamide (n=3), rituximab (n=3), both (n=3) and mycophenolate mofetil (n=1). Four treatment group were identified: a/ Steroids+IVIg (n=19) b/ Steroids+IVIg+PLEX (n=2)	Primary Clinical effectiveness	Modified Rankin Scale (mRS)	The median mRS score was 4 at nadir (range 2–5) and 1 (range 0–4) at1-year follow-up for patients diagnosed early, and 5 at nadir (range 2–5) and 2 (range 0–5) at 1-year follow-up for patients diagnosed late.	3	Indirect (in relation to treatment)	• Unblinded non-randomised observational study, but prospective follow-up • Relatively small sample size • Relatively short follow-up period • Strong survey based selection and reporting bias • Patients received different treatments, thus ascribing therapeutic benefits directly to rituximab is not possible • Unexplained inconsistency of symptoms at presentation suggestive of selection bias. • No difference found in the long-term outcome between patients who
					Full recovery (mRS of 0)	At last follow-up, 18 of the 23 patients who were diagnosed early made full recovery compared with 1 of 7 late diagnosed patients (78% vs 13%, p=0.002). 4 of 5 patients who were diagnosed early and did not fully recover received only steroids+IVIg as treatment. 89% (8/9) of patients who received PLEX fully recovered compared with 47% without PLEX (p=0.049) (this may be confounded by additional second-line immunotherapy in 7/9 patients with PLEX).			

Table 3: Use of immunotherapies incl. rituximab in treatment of anti-NMDA receptor encephalitis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		behavioural change and/or neuropsychiatric features. During acute disease, seizures and movement disorders were seen in 68% (21/31) of cases and sleep dysfunction in 52% (16). 7 cases had partial phenotype without encephalopathy (4 psychiatric and 3 movement disorder). One patient had ovarian teratoma. EEG was abnormal in 93% of cases, MRI in 35% and CSF in 45%.	c/ Steroids+IVIg+2nd line (n=3) d/ Steroids+IVIg+PLEX+ 2nd line (n=7) 18/31 (58%) patients responded to immunotherapy within 30 days, but in 3 patients it took up to 90 days. Follow-up period ranged from12 to 60 months.	Primary Clinical effectiveness	Relapse	7/31 patients (23%) had a clinical relapse. Of those, 6 received steroids+IVIg only as their initial treatment. The median time to relapse was 12.5 months (range 2–60). The clinical presentation at relapse was milder in severity. Additional second-line or long term immunotherapy was needed in 4/7 patients who relapsed. One patient had more than one relapse, the other 3 recovered fully.			received second-line immunotherapy or not. • Observational evidence, not generalizable
				Secondary Safety	Side effects	No significant treatment complications/side effects were reported in any of the 31 patients.			
Hacohen et al. 2014 Nuffield Dpt. of Clinical	P1 Retrospective study to report clinical and radiologic findings of children with NMDAR antibodies and	The study included a cohort of 46 paediatric patients (≤18 years) with a range of NMDAR-Abs-associated neurologic syndromes. 28/46 had typical NMDAR-Ab encephalitis and 18 had other NMDAR-Ab associated CNS	41/46 cases received immunotherapy: steroids (n=36), IVIg (n=23), PLEX (n=14). 10/46 cases received second-line therapies: Rituximab (n=5), Cyclophoshamide (n=2), MMF (n=5),	Secondary Clinical effectiveness	Recovery	15/46 patients had full recovery (mRS=0) and 31/46 had a range of persisting deficits (mRS 1-5). None of the 5 patients treated with rituximab had a full recovery.	2	Indirect (in relation to treatment)	• Study focused on findings of children with NMDAR antibodies and white matter disorders rather than treatment and outcomes of the whole cohort – the data summarised here are mainly based on one table output in the article

Table 3: Use of immunotherapies incl. rituximab in treatment of anti-NMDA receptor encephalitis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Neurosciences, John Radcliffe Hospital, University of Oxford, UK	white matter disorders (study period 2009-2013 of referrals to Oxford Radcliffe Hospital).	disorder. 10 cases were found to have significant white matter involvement (with or without anti-NMDAR encephalitis). In the white matter patients, 6/7 with serial samples available had a positive relationship between NMDAR-Ab titres and severity of clinical symptoms. Median age was 10.5 years (range 1-18); 32 were female. 1/46 cases had ovarian teratoma.	Azathioprine (n=1). Median length of follow-up was 30 months (6–60).	Secondary Clinical effectiveness	Relapse	15/46 patients relapsed. 1/5 patients who were treated with rituximab had a relapse.			• Retrospective observational study, not generalizable • Very small sample size and relatively short follow-up period • Patients received different treatments and only a few patients treated with rituximab, thus ascribing therapeutic benefits directly to rituximab is not possible
Armangue et al. 2013 Service of Neurology, University of Barcelona, Spain	P1 Retrospective study to report clinical features of paediatric patients with anti-NMDAR encephalitis	The study included 20 children (≤18 years) with anti-NMDAR encephalitis confirmed in CSF (and serum in 9 patients), using 2 different tests, between Jan 2008 and Feb 2012. Median age was 13 years (range 8 months-18 years), 70% were female. 11/20 patients had prodromal symptoms. Initial symptoms were neurologic (usually dyskinesias or seizures) in 12/20 patients, psychiatric or cognitive in 8 patients. Neurologic presentations were more	All 20 patients received first-line therapy: steroids (n=20), IVIg (n=15), plasma exchange (n=1). 7 patients had second-line therapy with rituximab (alone n=5 or in combination with cyclophosphamide n=2), due to unsatisfactory response to first-line drugs in 6 patients and multiple relapses in 1 case. The median number of rituximab treatment was 4 weekly doses (range 4-6) and of cyclophosphamide cycles 5.5 monthly doses (range 4-7).	Primary Clinical effectiveness	Pediatric Cerebral Performance Category (PCPC) scale 1: Full recovery 2: Mild disability 3: Moderate disability 4: Severe disability 5: Coma 6: Death	At disease peak, median degree of disability was 4 (all patients had ≥4, and one had 6 (death). At last follow-up, 17/20 patients (85%) had substantial recovery (PCPC of 1 or 2). Of those, 12 fully recovered (8-12 months after symptom onset in 8 cases, and 3-5 months in 4 cases) and 5 had minimal residual deficits. 2/20 (10%) had moderate or severe deficits, and 1 (5%) died. All 7 patients who received rituximab responded to treatment without further relapses. The deceased patient was treated with intravenous steroids and IVIG without effect.	3	Indirect (in relation to treatment)	• Retrospective observational study, not generalizable • Very small sample size and relatively short follow-up period • No uniform systematic treatment approach - patients received different treatments and only a few patients treated with rituximab, thus ascribing therapeutic benefits directly to rituximab is not possible

Table 3: Use of immunotherapies incl. rituximab in treatment of anti-NMDA receptor encephalitis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		frequent in patients <12 years than ≥12 years (67% vs 55%). One month from onset, all patients had abnormal movements and alterations of behaviour and speech. Ovarian teratoma was identified in 2 patients (both ≥12 years). EEG was abnormal in 90% of patients and MRI in 45%. Lymphocytic pleocytosis was present in 70% of patients.	3 patients received other immunotherapy (mycophenolate mofetil n=2 and tacrolimus n=1). Median follow up period was 17.5 months (range 4-149).			Median time from the start of immunotherapy until first sign of improvement was 11.5 days (2-176).			
				Primary Clinical effectiveness	Relapse	3/20 patients (15%) had relapses either prior or after the diagnosis of the disorder. One case who had 5 previous episodes received rituximab and cyclophosphamide followed by mycophenolate mofetil during episode 6 and substantially improved with no further relapses eight months after rituximab.			
				Secondary Safety	Side effects	None of the patients who received rituximab had significant side effects of the treatment.			
Florance et al. 2009 Division of Neurology, Dpt. of Pediatrics, Hospital of Philadelphia, USA	P1 Retrospective study to report clinical features of anti–NMDAR encephalitis in patients ≤18 years	The study included 32 children with anti-NMDAR encephalitis (confirmed antibodies reacting with extracellular epitopes of NR1 in CSF or serum). Median age was 14 years (range23 months-18 years); 6 were male. 8/32 cases had ovarian teratomas (all female, only one case was ≤14 years). 28/32 patients presented	All 8 cases with tumour had a resection. 30/31 cases had immunotherapy consisting of a combination of corticosteroids, IVIg or plasma exchange. 7 cases refractory to first-line treatment received rituximab (n=2), cyclophoshamide (n=1) or both (n=4). Median follow-up was 4.5 months (2-14.5).	Clinical effectiveness	Response to treatment with rituximab and/or cyclophoshamide	4/7 patients started to improve shortly after treatment initiation (1 with cyclophosphamide, 3 with both) and the other three had slow improvement not clearly related to the treatments. These treatments were well tolerated.	2	Indirect (in relation to treatment)	• Retrospective observational study, not generalizable • Very small sample size and very short follow-up period • Patients received different treatments and only a few patients treated with rituximab, thus ascribing therapeutic benefits to rituximab is not possible
				Clinical effectiveness	Recovery Full recovery if patient returned to all activities; substantial improvement if mild	Outcome was assessable in 31 patients (1 was lost to follow-up). 9/31 patients had full recovery and 14/31 had substantial improvement. Median time from symptom presentation to initial			

Table 3: Use of immunotherapies incl. rituximab in treatment of anti-NMDA receptor encephalitis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		with behavioural or personality changes, sometimes associated with seizures (n=6). On admission, 53% had severe speech deficits. Eventually, 77% developed seizures, 84% movement disorders, 86% autonomic instability. CSF was abnormal in 29/31 cases, EEG in 25/25 and brain MRI in 10.			deficits persisted.	improvement was 6 weeks (range 2–28). Full recovery occurred more common in patients who had a teratoma that was removed than in those without it (5/8 vs 4/23, p=0.03).			
				Clinical effectiveness	Relapse	25% of patients had one (n=5) or more relapses (n=3) in median of 24 months (range 1-96). Four patients relapsed while on or after completing immunotherapy; the other 4 more than 1 year after recovery.			
Dalmau et al. 2008 Dpt. of Neurology, Hospital of the University of Pennsylvania, USA	P1 Retrospective study to analyse the clinical and immunological features of patients with the anti-NMDA-receptor encephalitis.	This study included 100 patients with anti-NMDAR encephalitis (confirmed by NMDAR antibodies in serum and/or CSF). Median age was 23 years (range 5-76). 91/100 were female. 22/100 were children: one male (11 years), 21 female (median 15 years, range 5-18). 86/100 patients had prodromal symptoms. All presented with psychiatric symptoms or memory problems. During acute disease, 76 patients had seizures, 88 unresponsiveness, 86	Tumour resection n=51 Immunotherapy n=92: Corticosteroids (n=76), IVIg (n=62), PLEX (n=34), Rituximab (n=10) Cyclophoshamide (n=9) Azathioprine (n=1) Median follow-up was 17 months (1–194).	Secondary Clinical effectiveness	Response to treatment	13 of 17 patients unresponsive to corticosteroids, IVIg and/or PLEX responded to cyclophosphamide (n=5), rituximab (n=6), or both (n=2).	3	Indirect (in relation to treatment and target population)	• Not focused on children or treatment and outcomes, thus insufficient detail in this regard and ascribing therapeutic benefits to rituximab is not possible • Retrospective observational study, not generalizable • Very small sample size and short follow-up period • Observational study that raises questions the role of prodromal events as triggers of immune response
				Secondary Clinical effectiveness	Modified Rankin Scale (mRS) and mini-mental state examination (MMSE)	47/100 patients had full recovery (mRS=0; MMSE 29-30), 28 mild stable deficits (mRS 1-2; MMSE 25-28), 18 severe deficits and 7 died as a result of the neurological disorder Patients who received early tumour treatment (usually with immunotherapy) had better outcome (p=0.004) and fewer neurological relapses (p=0.009) than the rest of the patients. Two patients died before tumour assessment.			

Table 3: Use of immunotherapies incl. rituximab in treatment of anti-NMDA receptor encephalitis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		dyskinesias, 69 autonomic instability and 66 hypoventilation. 59% of patients (58/98, 57 females, 12 children) had tumours, mostly ovarian teratomas (n=49). 57/58 developed neurological symptoms before tumour diagnosis (median 8 weeks, range 1–380). CSF was abnormal in 95/100 cases, EEG in 92 and brain MRI in 55.		Clinical effectiveness	Relapse	15/100 patients had one to three relapses. Median time between initial presentation and last relapse was 18 months (range 1–84). Relapses were less common in patients with early tumour treatment than in other patients (p=0.009). None of the patients was receiving immunotherapy at the time of the neurological relapse.			
Nosadini et al. 2015 Kids Research Institute at the Children's Hospital at Westmead, University of Sydney, Australia	R1 Systematic review on immune therapy in autoimmune encephalitis associated with antibodies to cell surface antigens including NMDA receptor, to appreciate use and type of immunotherapy, its efficacy and possible benefit of early and aggressive treatment. *The 8 studies included in the 'Anti-NMDAR*	The study presented 11 reviews of autoimmune encephalitis syndromes defined by the autoantibody; only 1 review of 'Anti-NMDAR antibodies' is relevant, thus summarised here. The 'Anti-NMDAR antibodies' review included 8 studies published between 2008 and 2015. It reported a total of 905 patients (80% females, 47% ≤18 years), 577 of which were described in one large case series by Titulaer 2013.	92% of patients (766/829) received immune therapy: steroids in 83% of patients, IVIg in 66% and PLEX in 31%. In the large case series, steroids and IVIg were often given together (in 44% of cases). 34% of patients (229/684) received second-line immunotherapy: rituximab in 24% of patients (195/828), cyclophosphamide in 15% and other immunotherapies in 9%. 11% of patients (85/758) relapsed and 5.1% (40/783) died.	Clinical effectiveness	Response to treatment and neurological outcome	Results in the reviewed articles suggest: • The use of immunotherapy (rather than no therapy) is associated with a better outcome. • Early commencement of immunotherapy favours a better neurological outcome. • The use of second-line immunotherapies also appears to be beneficial, more commonly associated with a better outcome and lower rates of relapses. • On the other hand, in one series (Zekeridou 2015) with a higher use of second-line immunotherapy (mostly rituximab) the outcome was very similar to the outcome reported in other series with lower rate of second-line treatment.	3	Indirect (in relation to treatment and target population)	*The 8 studies included in the 'Anti-NMDAR antibodies' review are presented individually in this table (see Dalmau 2008, Florance 2009, Irani 2010, Titulaer 2013, Dale 2014, Hacohen 2014, Wright 2015, Zekeridou 2015), thus not a new evidence or different population.* • Relatively small sample size in relation to rituximab usage and children • Retrospective uncontrolled nature of the presented data • Variable, non-standardized outcome measures, heterogeneous dosage and follow-up duration hamper the comparison of outcomes • Literature inherent bias,

Table 3: Use of immunotherapies incl. rituximab in treatment of anti-NMDA receptor encephalitis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	antibodies' review are presented in this table individually.					• A considerable reduction in relapse rate occurred over time, from 15% in a cohort reported in 2008 to 9% in 2013. • Similarly, the rate of severe deficits or death at follow-up from 25% to 21% in these series, possibly due to earlier and more aggressive therapy with increased disease recognition over this time.			incl. severity and reporting bias Only 1 review ('Anti-NMDAR antibodies') is relevant; other reviews focused on different autoantibody syndromes, included no or very few children and/or no or very few patients treated with rituximab (≤5 cases).

8. Grade of evidence table

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Benefit from rituximab - recorded by the attending clinician as 'definite', 'probable' or 'possible improvement', 'no benefit', or 'disease worsening during therapy'	**Dale et al. 2014**	4	Indirect (in relation to target population)	C	This outcome measure was subjectively classified by clinicians without a pre-treatment agreed classification thus open to interpretation and variability. The study by Dale et al. 2014 is the only study using this outcome measure. It included 144 children with autoimmune and inflammatory CNS disorders treated with rituximab as second-line therapy; of those 39 had anti-NMDAR encephalitis. 125/144 patients had a benefit from rituximab (45 definite, 49 probable and 31 possible benefit), 17 patients had no or unclear benefit and 2 worsened. In the anti-NMDAR cohort, 38/39 patients had a benefit from rituximab (16 definite, 16 probable and 6 possible benefit), 1 had no benefit. This was an uncontrolled retrospective observational study with multiple confounders present and poor methodology in the measurement of benefit, thus ascribing therapeutic benefits to rituximab is inaccurate.
Modified Rankin Scale (mRS) - described as neurological disability: 0 No symptoms at all; 1 No significant disability despite symptoms: able to carry out all usual duties and activities; 2 Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance; 3 Moderate disability: requiring some help, but able to walk without assistance; 4 Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance; 5 Severe disability: bedridden, incontinent, and	**Dale et al. 2014**	4	Indirect (in relation to target population)	C	The study by Dale et al. 2014 used the mRS to evaluate disease state at initiation and following rituximab treatment and to report on full recovery. It included 144 children with autoimmune and inflammatory CNS disorders treated with rituximab as second-line therapy; of those 39 had anti-NMDAR encephalitis. The change in mRS 0-2 at rituximab initiation and outcome was greater in those who received rituximab early compared to those who received it late. In anti-NMDAR patients, those who received rituximab early (n=25) had a change in mRS 0-2 from 8% to 92%, compared to those who received it late (n=14) and had a change from 0% to 57%. The median mRS was 2 (range 0-5) at outcome determination. Full recovery corresponded to mRS=0. After a median follow-up of 1.65 years after rituximab, 40 (28%) children fully recovered. In the anti-NMDAR cohort, the median follow-up was 1.3 years and 7/38 (18%) fully recovered. This was an uncontrolled retrospective observational study with multiple confounders present, thus ascribing therapeutic benefits to rituximab is inaccurate. The study by Titulaer et al. 2013 used the mRS to report on good neurological outcome corresponding to mRS 0-2. It included 577 patients (211 children) with anti-NMDAR encephalitis treated with different immunotherapies. Of those, 501 patients (177 children) were followed-up for at least 4 months and had their treatment effects and outcomes assessed. 101/501 (20%) patients (42/177; 24% children) received rituximab (alone or in combination). Overall 394/501 patients had good outcome with mRS of 0-2. At 24 month follow-up, 81% (203/252) had good outcome. Predictors of good outcome were early treatment and no admission to ICU. At 24 months, 78% (43/55) of patients who failed first-line and received second-line therapy had a good
	Titulaer et al. 2013	4	Indirect (in relation to target population and treatment)	C	
	Lee et al. 2016	4	Indirect (in relation to target population)	C	
	Dalmau et al. 2008	3	Indirect (in relation to target population and treatment)	C	
	Wright et al. 2015	3	Indirect (in relation to treatment)	C	
	Zekeridou et al. 2015	3	Indirect (in relation to treatment)	C	
	Hacohen et al. 2014	2	Indirect (in relation to treatment)	C	

requiring constant nursing care and attention; 6 Dead					outcome, compared to 55% (32/58) of patients who failed first-line and did not receive second-line therapy. In children, predictors of good outcome and the magnitude of effect of second-line immunotherapy were similar to those of the entire cohort. This was an uncontrolled though prospective observational study, with large sample size but significant loss to follow up. Children and adults assessed together and the effect of individual treatments could not be compared, hence sole rituximab treatment effect is unclear.
Paediatric Cerebral Performance Category (PCPC) scale PCPC of 1 (full recovery) or 2 (substantial recovery)	**Armangue et al. 2013**	3	Indirect (in relation to treatment)	C	The PCPC scale is not as precise as objective measures such as functional status scale but it is used significantly in PICU settings. The study by Armangue et al. 2013 is the only study using this outcome measure. It included 20 children with anti-NMDAR encephalitis treated with different immunotherapies. 7/20 (35%) children received rituximab (alone or in combination). At last follow-up, 17/20 patients (85%) had substantial recovery. Of those; 12 fully recovered (8-12 months after symptom onset in 8 cases, and 3-5 months in 4 cases). This was a retrospective observational study; with a very small sample size thus its findings cannot be generalizable. Patients received different treatments and only a few patients were treated with rituximab, thus ascribing therapeutic benefits directly to rituximab is not possible.
Full recovery (no scale specified)	**Brenton et al. 2016**	3	Indirect (in relation to treatment)	C	Outcomes were recorded in relation to change of clinical symptoms from such as abnormal behaviour, dyskinesia and movement disorders or seizures. The study by Brenton et al. 2016 is the best study that reported on this outcome. It included 10 children with anti-NMDAR encephalitis treated with different immunotherapies. 6/10 (60%) children received rituximab (alone or in combination). 6/10 patients had full recovery from the initial disease. This was a retrospective descriptive study, with a very small sample size, not generalizable. Patients received different treatments and only a few patients were treated with rituximab, thus ascribing therapeutic benefits to rituximab is not possible.
	Florance et al. 2009	2	Indirect (in relation to treatment)	C	
Ongoing disability / Persisting deficits	**Dale et al. 2014**	4	Indirect (in relation to target population)	C	Outcomes were recorded in relation to change of clinical symptoms from such as abnormal behaviour, dyskinesia and movement disorders or seizures. The study by Dale et al. 2014 is the best study that reported on this outcome. It included 144 children with autoimmune and inflammatory CNS disorders treated with rituximab as second-line therapy; of those 39 had anti-NMDAR encephalitis. After a median follow-up of 1.65 years after rituximab, 101/144 (70%) children had residual problems incl. cognitive or motor impairment or psychiatric disease and 16 continued to experience seizures. In the anti-NMDAR cohort, the median follow-up was 1.3 years and 32/39 (82%) patients had ongoing disability (incl. two deaths). This was an uncontrolled retrospective observational study with multiple confounders present, thus ascribing therapeutic benefits to rituximab is
	Hacohen et al. 2014	2	Indirect (in relation to treatment)	C	
	Armangue et al. 2013	3	Indirect (in relation to treatment)	C	

					inaccurate.
Initial improvement / Response to treatment with rituximab	**Zekeridou et al. 2015**	3	Indirect (in relation to treatment)	C	Initial improvement was defined as treatment within 15 days from symptom onset and other studies use mRS as a measure for outcomes. The study by Zekeridou et al. 2015 measured improvement in relation to mRS. It included 36 children with anti-NMDAR encephalitis treated with different immunotherapies. 29/36 (81%) children received second-line therapy and 26/36 (72%) rituximab (alone or in combination). Median time between first and second-line therapy was 26 days (range 7-198). In the 26 cases treated with rituximab, median duration between first rituximab administration and first sign of improvement was 24 days (range 5-150). This was a retrospective observational study, with a small sample size, not generalizable. Patients received different treatments, and despite more frequent and earlier use of second-line immunotherapy, especially rituximab, ascribing therapeutic benefits directly to rituximab is with certainty not possible.
	Armangue et al. 2013	3	Indirect (in relation to treatment)	C	
	Dalmau et al. 2008	3	Indirect (in relation to target population and treatment)	C	
	Florance et al. 2009	2	Indirect (in relation to treatment)	C	
Relapse	**Titulaer et al. 2013**	4	Indirect (in relation to target population and treatment)	C	Relapse is defined as the new onset or worsening of symptoms occurring after at least 2 months of improvement or stabilisation. The study by Titulaer et al. 2013 is the best study that reported on this outcome. It included 577 patients (211 children) with anti-NMDAR encephalitis treated with different immunotherapies. Of those, 501 patients (177 children) were followed-up for at least 4 months and had their treatment effects and outcomes assessed. 101/501 (20%) patients (42/177; 24% children) received rituximab (alone or in combination). During the 24 month follow-up, 45 patients had clinical relapse (representing a 12% risk within 2 years), of whom 15 (33%) had multiple relapses. Compared with the initial episode, 46/69 (67%) relapses were less severe, 24 (35%) mono-symptomatic, 16 (23%) similar and 7 (10%) worse. The use of immunotherapy in the initial episode, use of second-line therapy and teratoma identified at presentation were associated with a lower frequency of relapses. This was an uncontrolled though prospective observational study, with large sample size but significant loss to follow up. Children and adults assessed together and the effect of individual treatments could not be compared, hence sole rituximab treatment effect is unclear.
	Lee et al. 2016	4	Indirect (in relation to target population)	C	
	Dalmau et al. 2008	3	Indirect (in relation to target population and treatment)	C	
	Wright et al. 2015	3	Indirect (in relation to treatment)	C	
	Brenton et al. 2016	3	Indirect (in relation to treatment)	C	
	Zekeridou et al. 2015	3	Indirect (in relation to treatment)	C	
	Hacohen et al. 2014	2	Indirect (in relation to treatment)	C	
	Armangue et al. 2013	3	Indirect (in relation to treatment)	C	
	Florance et al. 2009	2	Indirect (in relation to treatment)	C	
Death	**Dale et al. 2014**	4	Indirect (in relation to target population)	C	The study by Dale et al. 2014 is the best study that reported on this outcome. It included 144 children with autoimmune and inflammatory CNS disorders treated with rituximab as second-line therapy; of those 39 had anti-NMDAR encephalitis. After a median follow-up of 1.65 years (1.3 for anti-NMDAR patients) after rituximab, 3/144 (2%) patients died (2 anti-NMDAR patients who died of AEs and one case of GAD Ab encephalitis who died of refractory status epilepticus). This was an uncontrolled retrospective observational study with multiple confounders present, thus ascribing therapeutic benefits to rituximab is inaccurate.
	Titulaer et al. 2013	4	Indirect (in relation to target population and treatment)	C	
	Dalmau et al. 2008	3	Indirect (in relation to target population and treatment)	C	
	Armangue et al. 2013	3	Indirect (in relation to treatment)	C	

Hematologic (and immunologic) effects	**Dale et al. 2014**	4	Indirect (in relation to target population)	C	Outcomes were assessed from blood tests. B-cell depletion was assed using CD19 count. The study by Dale et al. 2014 is the best study that reported on this outcome. It included 144 children with autoimmune and inflammatory CNS disorders treated with rituximab as second-line therapy; of those 39 had anti-NMDAR encephalitis. Measurements were recorded in 124/144 patients. 119/124 (96%) had B-cell depletion after rituximab (the actual values were not recorded), which was present >12 months in 12 children. 27/124 had documented hypogammaglobulinemia. There was no difference between younger and older children, except an increased rate of hypogammaglobulinemia in children ≤5 years. This was an uncontrolled retrospective observational study with multiple confounders present, thus ascribing therapeutic benefits to rituximab is inaccurate.
	Lee et al. 2016	4	Indirect (in relation to target population)	C	
Adverse events / Side effects	**Dale et al. 2014**	4	Indirect (in relation to target population)	C	Infusion AEs were any unwanted hypersensitivity or allergic reactions that occurred during rituximab infusion, classified using CTCAE v4.0. Infectious AEs included any infectious complications that may have been attributed to rituximab usage, classified using CTCAE v4.0 The study by Dale et al. 2014 is the best study that reported on this outcome. It included 144 children with autoimmune and inflammatory CNS disorders treated with rituximab as second-line therapy; of those 39 had anti-NMDAR encephalitis. 18/144 (12.5%) had recorded infusion AEs. Of those, 3 patients had a grade 4 reaction (anaphylaxis) that was resolved without complication with standard therapy. One patient with infusion-related fever had a transient exacerbation of seizures. One patient was unable to tolerate rituximab due to worsening hypersensitivity. There was no difference in infusion AEs between those on antihistamine prophylaxis and those without it, and no increased risk in younger children (≤5 years). 11/144 (7.6%) had recorded infectious complication. Of those: 2 patients had a grade 5 AE (death; both were anti-NMDAR patients); 2 children a grade 4 AE (life-threating or disabling); and 7 children a grade 3 AE (hospitalisation or IV antibiotics). Grade 4 &5 infectious AEs occurred a median of 30 days (range 3-38) after rituximab initiation. There was no difference in infectious AEs between those on antibiotic prophylaxis and those without it, and no increased risk in younger children (≤5 years). This was an uncontrolled retrospective observational study with multiple confounders present, thus ascribing therapeutic benefits to rituximab is inaccurate.
	Lee et al. 2016	4	Indirect (in relation to target population)	C	
	Titulaer et al. 2013	4	Indirect (in relation to target population and treatment)	C	
	Wright et al. 2015	3	Indirect (in relation to treatment)	C	
	Brenton et al. 2016	3	Indirect (in relation to treatment)	C	
	Zekeridou et al. 2015	3	Indirect (in relation to treatment)	C	
	Armangue et al. 2013	3	Indirect (in relation to treatment)	C	

Nosadini et al. 2015 was not included in the 'Grade of evidence' table as it does not provide any new evidence for treatment of anti-NMDAR encephalitis

9. Literature Search Terms

Due to the small number of patients with this condition, high quality evidence is not anticipated thus the search will extend to include low grade studies.

Search terms:

Autoimmune encephalitis, rituximab, paediatric, NMDAR, non-inflammatory, antibody specific and non-antibody specific encephalitis

Search strategy *Indicate all terms to be used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	All paediatric patients <18 years (or mixed population where children are part of the cohort) with a definite or probable diagnosis of autoimmune encephalitis who: • Are not (or inadequately) responsive to first line immunotherapy in the acute phase • Relapse whilst on or off maintenance therapy
I – Intervention Which intervention, treatment or approach should be used?	Rituximab alone or as combination therapy in early treatment on acute phase (within three months of becoming symptomatic) or relapsing disease
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	First Line (in the first 6weeks of presentation): • Corticosteroids, intravenous immunoglobulin (IVIG) or plasma exchange (PLEX), either sequentially of in combination. First Line (**after** the first 6 weeks of presentation): • Corticosteroids, intravenous immunoglobulin (IVIG) or plasma exchange (PLEX), either sequentially of in combination. Second line: • Cyclophosphamide(in selected cases), Azathioprine and Mycophenolate Mofetil (MMF) as maintenance therapy Relapse (with first line therapy) Relapse with rituximab therapy
O – Outcomes	*Critical to decision-making:*

What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	1. Reduction in mortality 2. improvement of severity of disease as measured by the change in modified Rankin Scale (mRS); including reduction in seizures (where present), halt in cognitive impairment and improvement (measured with age appropriate validated scales like Baileys) and halt of motor skills damage and improvement (measured with mRS) 3. improvements in level of disability at specified follow-up interval,(6 months, 1 year and 2 years) often with mRS 4. prevention of further relapse or reduction of relapse rate in patients when compared to baseline when treatment initiated at relapse 5. reduction of auto antibody in serum and/or CSF in autoantibody + cases at 3 months *Important to decision-making:* 6. Drug toxicity 7. Prevention of further relapsing when treating patients with recurrence of disease. (with 2 year of acute episode and onward) 8. Cost effectiveness
Assumptions / limits applied to search	
Inclusion Criteria	1990, English, Age specific – Studies with children alone or mixed population where children are part of the cohort, Side effects
Exclusion Criteria	

10. Search Strategy

MeSH descriptor: [Encephalitis] explode all trees
rituximab
AND
encephalitis
AND
(autoimmune OR non inflammatory OR NMDA OR NMDAR OR "N methyl D" OR "antibody specific" OR "non antibody specific")
AND
(pediatric OR paediatric OR child OR children

11. Evidence selection

- Total number of hits identified in the search: 93
- Total number of articles retrieved for which abstracts were considered: 55
- Total number of articles appraised: 15
- Total of articles included: 11

12. References

1. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. The Lancet Neurology. 2016;15(4):391-404.
2. Pillai SC, Hacohen Y, Tantsis E, Prelog K, Merheb V, Kesson A, et al. Infectious and Autoantibody-Associated Encephalitis: Clinical Features and Long-term Outcome. Pediatrics. 2015;135(4):e974.
3. Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother. 2015;15(12):1391-419.
4. Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology. 2011;77:179-89.
5. Hacohen Y, Wright S, Waters P, Agrawal S, Carr L, Cross H, et al. Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. J Neurol Neurosurg Psychiatry. 2013;84(7):748-55.
6. Wright S, Hacohen Y, Jacobson L, Agrawal S, Gupta R, Philip S, et al. N-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. Arch Dis Child. 2015;100(6):521-6.
7. Brenton JN, Kim J, Schwartz RH. Approach to the Management of Pediatric-Onset Anti-N-Methyl-d-Aspartate (Anti-NMDA) Receptor Encephalitis: A Case Series. J Child Neurol. 2016;31(9):1150-5.
8. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti–N-Methyl-D-Aspartate Receptor (NMDAR) Encephalitis in Children and Adolescents. Ann Neurol. 2009;66(1):11-8.
9. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. The Lancet Neurology. 2013;12(2):157-65.
10. Sartori S, Nosadini M, Cesaroni E, Falsaperla R, Capovilla G, Beccaria F, et al. Paediatric anti-N-methyl-D-aspartate receptor encephalitis: The first Italian multicenter case series. Eur J Paediatr Neurol. 2015;19(4):453-63.
11. Armangue T, Titulaer MJ, Malaga I, Bataller L, Gabilondo I, Graus F, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr. 2013;162(4):850-6 e2.
12. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. The Lancet Neurology. 2011;10:63-74.
13. Zekeridou A, Karantoni E, Viaccoz A, Ducray F, Gitiaux C, Villega F, et al. Treatment and outcome of children and adolescents with N-methyl-D-aspartate receptor encephalitis. J Neurol. 2015;262(8):1859-66.
14. Miya K, Takahashi Y, Mori H. Anti-NMDAR autoimmune encephalitis. Brain Dev. 2014;36(8):645-52.
15. Dale RC, Brilot F, Duffy LV, Twilt M, Waldman AT, Narula S, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology. 2014;83:142-50.
16. Lee W-J, Lee S-T, Byun J-I, Sunwoo J-S, Kim T-J, Lim J-A, et al. Rituximab treatment for autoimmune limbic encephalitis in an institutional cohort. Neurology. 2016;86:1683-91.
17. Kavcic M, Fisher BT, Seif AE, Li Y, Huang Y-S, Walker D, et al. Leveraging Administrative Data to Monitor Rituximab Use in 2875 Patients at 42 Freestanding Children's Hospitals across the United States. J Pediatr. 2013;162:1252-8.
18. Parnes M, Stocco A, Nguyen T, Teruya J, Graf J, Muscal E. Does a Standardized Multidisciplinary Approach Improve Outcomes for Children with NMDA Receptor Antibody

Encephalitis? A Preliminary Assessment of a Single Center Experience (I6-5E). Neurology. 2015;84(14):Supplement I6-5E.
19. De Blander H, Falaschi L, Clement R, Postaire M, Bourget P. Anti-NMDA receptor encephalitis: Pharmaceutical care and clinical follow-up in pediatrics. Int J Clin Pharm. 2013;35:1251-351.
20. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain. 2010;133(Pt 6):1655-67.
21. Dalmau D, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. The Lancet Neurology. 2008;7:1091–98.
22. Hacohen Y, Absoud M, Hemingway C, Jacobson L, Lin JP, Pike M, et al. NMDA receptor antibodies associated with distinct white matter syndromes. Neurol Neuroimmunol Neuroinflamm. 2014;1(1):e2.