We have extracted information from 6 major papers on this topic and provided them for you here.

AE is often monophasic, and instances of spontaneous recovery without immunotherapy or tumor resection have been reported. However, recovery from AE is not without sequelae, and AE-related deaths during the acute stage or follow up after discharge have also been noted. Even if patients survive without immunotherapy, they may suffer a slower recovery requiring prolonged hospitalization. Persistent cognitive impairment observed in long-term follow up suggests irreversible neuronal death and advocate prompt interruption of disease activity. \(^{1}\)

In practice, most patients are treated with glucocorticoids, intravenous immune globulin, or plasma exchange, and if there is no clinical response, rituximab and cyclophosphamide are used. Rituximab is usually effective in refractory cases, and it appears to reduce the risk of a clinical relapse, which accounts for its increasing use as an initial treatment.

The speed of recovery, degree of residual deficit, and frequency of relapse vary according to the type of autoimmune encephalitis. In a series of 577 patients with anti-NMDAR encephalitis, 53% had clinical improvement within 4 weeks, and 81% had substantial recovery (i.e., mild or no residual symptoms) at 24 months. Another study showed that patients with antiLGI1 encephalitis had a more rapid response but that only 70% had substantial recovery at 24 months.

For all types of autoimmune encephalitides, prompt immunotherapy has been associated with a favorable outcome; spontaneous clinical improvement is infrequent. The frequency of clinical relapse in the encephalitides associated with antibodies against NMDAR, AMPAR, LGI1, CASPR2, or DPPX ranges from 12 to 35%. Relapses often occur when immunotherapy is reduced or discontinued. There is anecdotal evidence that cases of anti-LGI1 or anti-NMDAR encephalitis can relapse many years after the first episode. Relapses may herald recurrence of the
associated tumor or a tumor that was missed in the initial episode. Immunotherapy and treatment of the tumor, if it was missed initially, usually results in improvement.

The rapid increase in the number of syndromes and autoantibodies identified over the past 10 years suggests that other autoimmune encephalitides have yet to be discovered. Antibody titers correlate imperfectly with the course of the disease and may remain detectable (albeit at a low titer) after clinical recovery. (2)

Anti-NMDAr recovery is often protracted with long hospital admissions. One remarkable feature of NMDAR Ab encephalitis is the prolonged recovery, with progressive improvements in cognitive domains noted for months and even years following the end of treatment.

This link takes you to Table 2 Immunotherapy response in children and older patients with N-methyl-D-aspartate antibody encephalitis - to see response/recovery. (5)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4720680/table/Tab2/?report=objectonly

Most patients with anti-NMDAR encephalitis respond to immunotherapy. Second-line immunotherapy is usually effective when first-line treatments fail. In this cohort (577 patients), the recovery of some patients took up to 18 months.

Two independent predictors of good outcome included the lower severity of symptoms assessed as no need for ICU support, and the prompt initiation of immunotherapy and tumor removal, if appropriate. A notable finding was the protracted phase of recovery that continued until the 18-
month follow-up. By establishing the last follow-up assessment at 24 months, our study likely underestimates the frequency and level of recovery because some patients had a shorter follow-up, others continued to improve after 24 months, and those with substantial improvement tended to discontinue follow-ups. For the same reasons, the frequency of mortality is likely overestimated; imputation analysis estimated 7% mortality at 24 months.

**Relapses**

Relapse of encephalitis was defined as the new onset or worsening of symptoms occurring after at least two months of improvement or stabilization.

During the 24-month follow-up, 45 patients (representing a 12% risk) had clinical relapses, which in 15 patients (33%) were multiple. Compared with the initial episode, (67%) relapses were less severe (as reflected by a lower mRS score measured at the stage of maximum severity), more frequently mono-symptomatic (35%), and resulted in fewer admissions (17%) to the ICU (all p<0.001). In 16 relapses (23%) the severity of symptoms was comparable to that of the initial episode, and in (10%) was worse. Patients without a tumor had a higher frequency of relapses than those with a tumor. If a tumor is found, removal is important because it expedites improvement and decreases relapses. (3)

Following antibody titers in the management of patients has several limitations and rarely helps guide therapy, which should be based on clinical findings as titers are not reliable markers of disease severity, but they can sometimes predict relapses and support the use of prolonged immunotherapy for prevention.

To prevent relapses and maximize the response to acute phase therapy, maintenance immunotherapy should be instituted especially if early relapses during steroid taper occur. Commonly used drugs in this phase include oral corticosteroids, IVIG, and steroid sparing agents such as mycophenolate mofetil, azathioprine, and rituximab. There are no guidelines regarding treatment duration; we typically continue maintenance therapy for 3 years after stability is achieved. It is important to remember that the prolonged use of immunosuppressive medications increases the risk of lymphoproliferative disorders, and they have also been associated with progressive multifocal leukoencephalopathy. (4)

The relapse rate in NMDAR Ab encephalitis is reported to be 12–25%, and relapses may occur months to several years after the initial episode. They are often less severe and may be mono- or pauci-symptomatic. In children, atypical presentations such as cerebellar ataxia or brainstem signs have been described. The majority of relapses occur in patients who do not have a tumor associated with NMDAR Ab encephalitis, those who received no or limited treatment for the initial episode, and those not exposed to second-line agents. Second-line immunotherapy also appears to prevent further relapses in those with a multi relapse disease course. At present, there is no clinical or paraclinical predictive marker for relapses. Although alterations in CSF Ab titers relate well to clinical changes, it is impractical and perhaps unsafe to conduct CSF analysis for
predictive purposes in well patients. Changes in serum Ab titers were not well correlated with relapses. The effects of long-term immunosuppression with oral agents such as azathioprine or CellCept (mycophenolate mofetil) on relapse rate are currently unknown. [5]

*For patients with anti-NMDAr encephalitis the NEOS Score just published December 2018. The NEOS score accurately predicts 1-year functional status in patients with anti-NMDAR encephalitis. This score could help estimate the clinical course following diagnosis and may aid in identifying patients who could benefit from novel therapies. [6]


3. Treatment and prognostic factors for long-term outcome in patients with anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis: a cohort study (2013) By: Maarten J. Titulaer, Josep Dalmau and others

4. Diagnostic and Therapeutic Approach to Autoimmune Neurologic Disorders López-Chiriboga, Flanagan (2018)

5. Antibody-Mediated Autoimmune Encephalopathies and Immunotherapies (2016) by: Matteo Gastaldi, Anaïs Thouin, and Angela Vincent

6. A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis (2018) By: Ramani Balu, MD, PhD, Lindsey McCracken, MS, Eric Lancaster, MD, PhD, Francesc Graus, MD, PhD, Josep Dalmau, MD, PhD,* and Maarten J. Titulaer, MD, PhD