HHS Public Access

Author manuscript

*Curr Opin Neurol*. Author manuscript; available in PMC 2023 June 01.

Published in final edited form as:

*Curr Opin Neurol*. 2022 June 01; 35(3): 415–422. doi:10.1097/WCO.0000000000001050.

# Life after Autoantibody-Mediated Encephalitis: Optimizing Follow-up and Management in Recovering Patients

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## Abstract

**Purpose of review:** Timely diagnosis and treatment is essential to optimize outcomes in patients with antibody-mediated encephalitis (AME); yet even with early diagnosis and treatment, long-term outcomes may still fall short of expectations. Identifying patients at greater risk of adverse outcomes is key to personalizing care, supporting accurate counselling of patients and family members, and informing therapeutic decisions in patients with AME. This review considers long-term outcomes in recovering patients, including approaches to measure and manage common sequelae that influence life after AME.

**Recent Findings:** Cognitive impairment, fatigue, and sleep disturbances affect most recovering AME patients. This realization highlights the need for outcome measures that encompass more than motor function. Standardized questionnaires, surveys, and clinical assessment tools may be adapted to support comprehensive and reproducible clinical assessments, and to identify patients who may benefit from additional therapies.

**Summary:** *Good* outcomes continue to be reported in recovering patients, emphasizing the high potential for recovery following AME. However, cognitive, behavioral, and physical sequelae may limit the potential for *great* outcomes following AME. Multidisciplinary follow-up is needed to recognize and treat sequelae that compromise long-term recovery and limit quality of life in recovering patients.

### Keywords

antibody-mediated encephalitis; autoimmune encephalitis; autoantibody; long-term outcome; anti-NMDAR encephalitis; LGI1

## Introduction

Antibody-mediated encephalitis (AME) may present with a wide range of clinical manifestations including psychiatric and cognitive disturbances, movement disorders, dysautonomia, and seizures.(1) Timely treatment with immunomodulatory therapies promoting antibody depletion leads to remarkable improvement in most patients with AME, [REF - WCO350307] emphasizing the critical role of antibody-mediated disruption of central nervous system neuronal cell-surface proteins, ion channels or receptors in disease

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pathogenesis,(1) and the importance of timely diagnosis and treatment. Consistent with these goals, the operationalization of practical diagnostic criteria has led to earlier recognition and treatment of these disorders.(2*) However, it remains unclear whether this approach will translate to improved long-term outcomes in recovering patients.(3)

AME patients commonly require prolonged hospitalization, multidisciplinary care, and staged escalation of immunotherapies,(4**) with most surviving to discharge. Longer-term management is decidedly more variable. Although the majority of AME patients with the two most common forms of AME—AME associated with antibodies against N-methyl-D-aspartate receptors (NMDAR) or leucine glioma inactivated-1 (LGI1) antigens(5-7)—return to independent living within 2 years of treatment,(6, 7) persistent impairments in memory and executive function are increasingly recognized, as well as serious behavioral and physical sequelae that impair quality of life for patients and caregivers.(7-11) These findings fuel ongoing debate concerning the ideal duration of immunosuppressant therapies and the role of complementary interventions in promoting recovery in patients with AME. Inevitably, achieving the best possible long-term outcomes will require a comprehensive approach that optimizes acute management, identifies patients at the highest risk of adverse outcomes who may benefit from additional therapies, and screens for and manages sequelae that compromise recovery and impair quality of life in recovering patients.

## Optimizing management of antibody-mediated encephalitis

Epidemiological studies suggest that autoimmune encephalitis is comparable to infectious encephalitis, with antibody-mediated causes accounting for an estimated 1-2 cases per 100,000 person-years.(12-14) Practical diagnostic criteria have been proposed to identify patients with *possible* and *probable* AME who may benefit from the prompt initiation of immunotherapy.(2*) These criteria encourage initiation of immunotherapy *before* the results of serum and cerebrospinal fluid (CSF) autoantibody testing return, recognizing that early induction of immunotherapy is consistently associated with favorable long-term outcomes.(2*, 10, 15, 16) Intravenous methylprednisolone, immunoglobulins, and plasma exchange should be used alone or in combination as soon as AME is suspected and contraindications excluded (i.e., active infection). These therapies may be repeated later in the disease course if a relapse is suspected.(17) Rituximab and cyclophosphamide are commonly cited as “second-line” therapies for treatment refractory patients,(5, 15, 18) although there is a trend towards early induction of rituximab (3) due to its favorable side effect profile.(19-21) Alternative therapies have been trialed in limited numbers of patients with severe disease, including bortezomib,(22, 23) tocilizumab,(24) and low dose interleukin-2.(25) However, caution is advised when basing treatment decisions on isolated reports including small numbers of patients, recognizing the inherent bias toward the publication of ‘positive’ case reports. Selecting patients who might benefit from long-term immunosuppression is challenging given the relatively low relapse rate associated with AME and the potential for adverse events associated with immunosuppressive medications, including lymphoproliferative disorders and progressive multifocal leukoencephalopathy.(26) High-quality randomized controlled trials are needed to evaluate the safety and efficacy of specific treatments in AME.(27)

## Identifying patients at risk of adverse outcomes (prognostication)

Identifying patients at greater risk of adverse outcomes or, conversely, those most likely to respond to specific therapies, is key to personalizing care in AME, supporting accurate counselling of patients and family members, and informing optimal therapeutic decision making. Accessible clinical prognostic tools and biomarkers are needed to support these efforts.

The modified Rankin Scale (mRS) is the most widely applied functional outcome measure in AME, owing to its simplicity, high inter-rater reliability,(28) and ease with which it can be retrospectively applied.(5, 15, 18) Under this rubric, patients with no disability (mRS=0), no significant disability despite symptoms (mRS=1), and those with slight disability that does not compromise their ability to manage their personal affairs (mRS=2), are said to have had a “good” outcome, while those with higher levels of impairment (mRS ≥3) are determined to have a “bad” outcome.(5, 7, 10, 18, 28)

Several variables have been shown to associate with 1-year outcomes in patients with NMDAR encephalitis, including treatment delays that extend beyond 4 weeks from symptom onset, lack of clinical improvement within 4 weeks of therapy, requirement for ICU admission, abnormalities on brain MRI, and CSF pleocytosis >20 cells/uL. Collectively, these variables comprise the anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score, with one point allocated to each variable, yielding a score from 0 to 5.(29) In a multi-center cohort study of 382 NMDAR AME patients, a low NEOS score (0-1) predicted a mRS ≤2 1-year after symptom onset. Conversely, higher NEOS scores (4-5) were associated with poorer 1-year outcomes (mRS ≥3). The NEOS score was since been validated in a Chinese population of 111 NMDAR AME patients,(30) and adapted in a recent systematic review incorporating data from 1550 patients.(3) Taken together, these findings suggest that the NEOS may identify NMDAR AME patients early in the disease course who may benefit from escalation in immunosuppressive therapies and expanded access to rehabilitative services. Additional clinical and paraclinical characteristics may also guide prognostication in NMDAR encephalitis. Infants (<2 years) and older adults (>65 years) experience a higher risk of poor outcomes,(3) a finding that may reflect differences in NMDAR subunits in the developing and aging brain.(31) The presence of dysautonomia, need for mechanical ventilation, development of status epilepticus or presence of underlying neoplasm (e.g. teratoma in NMDAR AME) may also be regarded as negative prognostic signs.(32)

Beyond NMDAR AME, small case series suggest that older age and failure to respond to first line immunotherapies may associate with worse outcomes in LGI1 AME.(33, 34) In a series including 30 recovering LGI1 AME patients, higher mRS scores were associated with smaller hippocampal volumes ~2 years following disease onset, with disease severity, treatment delays, and structural hippocampal damage associated with worse cognitive performance.(35*) Less data are available from patients with rarer forms of AME. In a systematic review including 55 patients with alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) AME, psychiatric symptoms at presentation were associated with higher mRS at follow-up. Conversely, there was a trend towards

younger age and confusion at presentation associated with “good” outcomes (mRS ≤2).(36) Older age, presence of underlying malignancy and delays in immunotherapy initiation also predict worse outcomes for patients with AME associated with autoantibodies against gamma-aminobutyric acid (GABA)-A and B-type receptors.(26, 37)

Objective measures are needed to predict outcomes in AME and monitor disease progression. Although specific disease-associated antibody titers present an attractive target, their applications are limited.(5, 7, 15, 38) Early reductions in CSF autoantibody titers may associate with better outcomes in patients with NMDAR AME. However, as antibodies persist long after clinical recovery, their utility in monitoring disease relapse and progression is unclear.(38) In LGI1 AME patients, the detection of antibodies in the CSF (not necessarily the titer) may identify patients with greater levels of inflammation, and associate with worse motor (mRS ≥3) (39-41) and cognitive outcomes.(42) This association may reflect complement-mediated neuronal injury and hippocampal atrophy,(35*) although this remains to be established in larger cohorts.

Beyond autoantibody levels, biomarkers of neuronal and synaptic injury may provide a more direct measure of the neural processes that drive outcomes in AME. In a recent multicenter study including data from 46 AME patients (NMDAR AME, n=35; LGI1/contactin-associated protein-like 2 (CASPR2) AME, n=11), combinations of CSF biomarkers of synaptic dysfunction, neuroinflammation, neuronal and neuroaxonal injury differentiated AME patients from sex- and age-similar cognitively normal individuals (n=39) with high sensitivity.(43*) Moreover, in the subset of patients with available longitudinal clinical data, markers of neuroinflammation and synaptic dysfunction at presentation associated with 1-year functional outcomes.(43*) These findings build upon a prior longitudinal study showing that higher CSF concentrations of neurofilament light chain (NfL)—a marker of neuroaxonal injury—were associated with worse long-term clinical outcomes in NMDAR AME patients.(44) Similarly, higher CSF NfL levels at diagnosis were associated with higher mRS at follow-up in patients with NMDAR or LGI1 AME.(45) Collectively, these findings suggest that CSF biomarkers may be used to stratify patients based on disease activity.

Commonly available paraclinical tests may also be adapted to support diagnosis and prognostication in patients with AME. Brain MRI may show T2-weighted FLAIR hyperintensity of the mesial temporal lobes in patients with limbic encephalitis, T1-weighted hyperintensities in the basal ganglia in patients with LGI1 AME,(46) or diffuse subcortical lesions in patients with other forms of AME (e.g., GABA-A).(2*, 47) Serial MRI may also identify patients at higher risk of cognitive sequelae, recognizing the established correlation between cerebral atrophy (especially hippocampal atrophy), disease severity, and cognitive deficits in NMDAR and LGI1 AME.(8, 35*, 48) Although most EEG findings are non-specific, the detection of “extreme delta brush” in an adult patient may support a diagnosis of NMDAR AME, intimating a more severe disease with higher risk of poor outcome.(49-51) Similarly, the detection of frontal infra-slowing preceding stereotyped motor movements (including FBDS) may suggest a diagnosis of LGI1 AME.(52)

Increasing experience with fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging suggests that patterns of hypo- or hypermetabolism in otherwise normal-appearing mesial temporal lobes may support a diagnosis of AME in selected patients,(53-56) with subsequent normalization presenting a possible surrogate for therapeutic response.(57) Although interesting, application of FDG-PET is likely to be limited due to the high costs and limited availability, challenging generalization of this technology.

## Optimizing long-term outcomes

Cognitive impairment, fatigue, and sleep disturbances are increasingly recognized as long-term complications in recovering AME patients.(7, 34, 58-60) These findings highlight the need for outcome measures that encompass more than motor function, including outcomes that are easily overlooked in standard clinical encounters, such as daily function, autonomy, and quality of life (of patient and caregiver).(61-63) Standardized questionnaires, surveys, and clinical assessment tools have been piloted in patients with AME and may be adapted to support comprehensive and reproducible clinical assessments (Table 1).

### Cognitive Deficits and Neuropsychiatric Manifestations

Cognitive impairment is pervasive following AME. Although impairment may be captured on widely available bedside tests (e.g., MoCA (65)), formal neuropsychological batteries are preferred given their superior sensitivity and domain-specific resolution. Studies to date confirm prominent deficits in attention, executive, and memory function early in recovery, with persistent deficits detectable even 5 years after treatment for NMDAR AME.(65*) Cognitive impairment is also common in patients with LGI1/CASPR2 AME, with 62% of patients showing residual dysfunction at follow-up.(7) Memory and spatial orientation seem to be more affected,(14) with severe cognitive deficits documented in subsets of patients 2 years following the acute phase of the disease.(34) Similar outcomes are reported in smaller case series of patients with AME associated with antibodies against dipeptidyl-peptidase–like protein 6 (DPPX) antigens,(66, 67) AMPAR,(68-70) and GABA-A/B receptors.(47, 71)

Studies reporting disruptions in structural (8, 35*, 72, 73) and functional connectivity (9, 35*, 48, 74) suggest a relationship between prolonged neuroinflammation and synaptic, (75) cellular,(76, 77) and network-level dysfunction and cognitive sequelae.(11) These associations are further strengthened by the consistent observation that delays in access to immunotherapy associate with worse outcomes.(10, 11, 35*) Together, these findings exemplify the importance of timely diagnosis and treatment in AME. Outside of the acute period, interventions are lacking to improve long-term outcomes. Targeted rehabilitative measures, incorporating goal-directed occupational therapy may be useful in selected patients.(4**) Ideally, these would be delivered together with lifestyle interventions known to improve cognition (e.g., physical exercise) and other potentially modifiable “dementia” risk factors.(78)

Beyond cognitive deficits, anxiety, depression,(58, 79) and psychosis (15, 80) are common contributors to functional impairment, compromising return to work or school and quality of life in recovering patients (and caregivers).(60, 81) Active screening for these AME sequelae is important, recognizing that many symptoms may improve with use of established

pharmacotherapies (e.g., selective serotonin reuptake inhibitors for anxiety and depression, (82) antipsychotics for persistent psychoses (83)) and non-pharmacological interventions (e.g., meditation, biofeedback,(4**) and counselling). A comprehensive assessment should also screen for medications (e.g., opiates, benzodiazepines, anticholinergics) or other substances (e.g., alcohol, marijuana use) that may directly or indirectly impair cognition.

## Fatigue

Fatigue is reported in up to 60% of patients with NMDARE and LGI1/CASPR2 AME,(58, 84) with high potential to compromise quality of life and return to meaningful function.(85) Interestingly the incidence of fatigue does not seem to differ between those with mRS <3 or >3 at hospital discharge, highlighting again the limitations of this tool as a marker of "good" prognosis.(58) The mechanistic underpinnings of fatigue in AME are poorly understood, although medications, sleep dysfunction, and mood disorders may all contribute.(86) Absent evidence-base therapies, a multidisciplinary approach is recommended to treat post-AME fatigue, emphasizing recognition and treatment of comorbid medical conditions, lifestyle modifications, and psychologic support.

## Sleep disorders

Systematic screening for sleep disturbances in the acute phase of AME discloses meaningful sleep complaints in upwards of 75% of patients,(87) with the potential for specific complaints to inform diagnostic testing given the putative association between specific sleep disorders (e.g., dream enactment behaviors) and specific forms of AME (e.g., LGI1 AME). (59, 88) Sleep complaints may shift over the course of follow-up, with severe insomnia in patients with acute NMDAR AME, transitioning to hypersomnia in later stages, with or without confusional arousals from non-rapid eye movement sleep.(88)

Early recognition and management of sleep disorders is important to optimize management at all stages of AME. In acutely ill patients, sleep disordered breathing may delay extubation or exacerbate autonomic dysfunction, contributing to morbidity and mortality. In recovering patients, untreated sleep dysfunction may contribute to cognitive and psychiatric complaints, worsen fatigue, and reduce quality of life. Although sleep disorders appear to improve with time from initiation of immunotherapy, insomnia, dream enactment behaviors, and hypersomnia may persist in 20% of patients,(88, 89) justifying regular screening with referral for polysomnography when appropriate.

The general approach to treatment of sleep dysfunction in AME mirrors that used in other disorders. Sleep hygiene should be encouraged, and comorbidities managed (e.g., maintenance of weight, treatment of anxiety or depression). Continuous positive airway pressure may be required to manage sleep disordered breathing. Pharmacological therapies may be required to treat insomnia (e.g., melatonin, trazodone), hypersomnolence (e.g., modafinil), or abnormal nighttime behaviors (e.g., clonazepam for dream enactment behaviors).(59)

### Seizures

Seizures are common at presentation and in follow-up in AME.(90, 91) Multiple anticonvulsant medications may be tried prior to diagnosis of AME. Refractoriness to appropriate medications may provide a useful clue to an autoimmune cause of dysfunction, particularly in young patients with new-onset status epilepticus,(2*, 90) and older patients with stereotyped involuntary motor movements (including FBDS).(92, 93) Prompt initiation of immunotherapy is essential to seizure control in select patients,(93, 94) with treatment responsiveness supporting an autoimmune-mediated cause of epilepsy.(14, 42, 94, 95) The early initiation of immunotherapy in patients with LGI1 AME associated with FBDS may even reduce the risk of long term cognitive impairment.(42)

Chronic seizures are reported in 20-40% of AME patients,(96) necessitating long-term anticonvulsant use, and other considerations (e.g., driving cessation) that may limit patients' autonomy, independence, and quality of life. Hippocampal atrophy may be a risk factor for post-AME epilepsy,(97) although other factors likely contribute.(98, 99) The higher potential for medication side effects, comorbidities, and unique reproductive considerations in recovering AME patients with epilepsy exemplify the yield of subspeciality follow-up, including epilepsy specialists.

## Conclusions

*Good* outcomes continue to be reported in recovering patients, emphasizing the high potential for sustained improvement in motor function following AME. However, impairment in other domains may limit the potential for *great* outcomes prioritized by patients and their caregivers. Longitudinal multidisciplinary follow-up is important to screen for changes in status that may indicate recurrent disease necessitating medication changes, and for common comorbidities and post-AME sequelae that may complicate recovery. Standardized clinical scales, tests, and objective biomarkers are needed to monitor disease progression, assess treatment response, and identify patients who may benefit from additional therapies, with the goal of optimizing long-term outcomes in recovering AME patients.

## Conflicts of interests:

Dr. Turcano reports no conflicts of interest. Dr. GS Day is supported by a career development grant from the NIH (K23AG064029). He owns stock (>$10,000) in ANI Pharmaceuticals (a generic pharmaceutical company). He serves as a topic editor for DynaMed (EBSCO), overseeing development of evidence-based educational content; and as a consultant for Parabon Nanolabs Inc. on a NIH-sponsored grant supporting the development of smartphone-based cognitive testing. He is the Clinical Director of the Anti-NMDA Receptor Encephalitis Foundation (Inc, Canada; uncompensated).

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**Key points**

- Antibody-mediated encephalitis (AME) represents a rapidly expanding group of disorders with a wide range of clinical manifestations. Timely diagnosis and treatment are essential to optimize short- and long-term outcomes.
- Cognitive, behavioral, and physical sequelae are common in recovering AME patients. Longitudinal multidisciplinary follow-up is recommended to recognize and treat sequelae that may compromise long-term recovery and limit quality of life.
- Objective markers are needed to measure disease severity, track progression, and identify patients who may benefit from escalation of immunotherapy or the use of other treatments.

**Table 1:**

Exemplar approaches to measure and manage contributors to long-term outcomes in recovering AME patients.

|  OUTCOMES |  TOOLS |  CLINICAL SPECIALTY |  TREATMENT |
|---|---|---|---|
| **MOTOR FUNCTION** | mRS<br>NEOS<br>CASE[†]<br>Biofluid and Neuroimaging biomarkers | Neurology; PMR, OT/PT | Rehabilitation services |
| **COGNITION** | MoCA<br>Neuropsychological testing<br>CSF biomarkers | Neurology<br>Psychiatry<br>Neuropsychology | Cognitive rehabilitation |
| **PSYCHOSIS, DEPRESSION, ANXIETY** | PHQ-9<br>GAD-7 | Neurology<br>Psychiatry<br>Neuropsychology | CBT<br>psychotropic medications |
| **FATIGUE** | FSMC<br>MFIS | Neurology<br>Psychiatry<br>PMR, OT/PT<br>Family Medicine | Cognitive rehabilitation |
| **SLEEP** | ESS; PSQI polysomnography | Sleep Medicine | Pharmacologic approach; Behavioral therapy |
| **SEIZURES** | EEG | Epilepsy specialist | Anticonvulsant therapies |

[†]An AE severity scale that assesses 9-items (seizure, memory dysfunction, psychiatric symptoms, consciousness, language problems, dyskinesia/dystonia, gait instability and ataxia, brainstem dysfunction, and motor weakness) on a 3-point scale, yielding a total CASE score of 0-27 points.(64)

AME = Antibody-Mediated Encephalitis; mRS = modified Rankin Scale; NEOS = anti-NMDAR Encephalitis one-Year Functional Status score; CASE = Clinical Assessment of Scale in Autoimmune Encephalitis score; PMR = Physical Medicine & Rehabilitation; OT = Occupational Therapy; PT = Physical Therapy; EEG = electroencephalogram; MoCA = Montreal Cognitive Assessment; CSF = cerebrospinal fluid; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = General Anxiety Disorder-7; CBT = Cognitive-behavioral therapy; FSMC = Fatigue Scale for Motor and Cognitive Function; MFIS = Modified Fatigue Impact Scale; ESS = Epworth Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index