

# Autoimmune encephalitis in Intensive Care Unit: A Review Article

Ashraf Alsawareah<sup>1</sup>, Omar Yousef<sup>2</sup>, Omar Ismail<sup>3</sup>, Razan Aburumman<sup>2</sup>,  
Ahmad Hanandeh<sup>2</sup>, Ahmad Mahadeen<sup>4</sup>

## BACKGROUND

Autoimmune encephalitides (AE) are immunologic diseases of the central nervous system (CNS) with or without meningeal and peripheral nervous system involvement(1). Earliest reports go back to 1934 when cerebellar and spinal degeneration were associated with bronchial carcinoma (2). It has since been reported with other malignancies and various autoantibodies (3).

The incidence of AE has been increasing over the past decade and is now considered a common cause of encephalitis (4). One US study found the incidence of AE comparable to that of viral encephalitis (5). Patients with AE often require intensive care unit (ICU) level care for management of seizures, psychiatric and behavioral symptoms, autonomic instability, coma, and respiratory failure (6–10). Appropriately recognizing ICU patients with AE helps hasten treatment and accordingly improves outcomes (6–11). This review aims to provide intensivists with a toolkit to better recognize, diagnose, and manage patients with AE in the ICU.

We will specifically be focusing on the complications of this condition, which are often encountered in the ICU setting that intensivists should be aware of and familiar with their management, such as seizures, altered mental status and behavioral/psychiatric issues, respiratory failure, and dysautonomia.

<sup>1</sup> Faculty of Medicine, The Hashemite University, Zarqa, Jordan

<sup>2</sup> Jordan University Hospital, Amman, Jordan

<sup>3</sup> Faculty of Medicine, The University of Jordan, Amman, Jordan

<sup>4</sup> Department of Neurology, University of Mississippi Medical Center, Madison, Mississippi

Financial support/ funding source: None  
Conflict of interest: No conflict of interest.

Corresponding Author:  
Omar Ismail  
School of medicine, University of Jordan,  
Amman, Jordan

email: omar.moh.isml@gmail.com

## PATHOPHYSIOLOGY

The pathophysiology of AE shares fundamental similarities with most autoimmune diseases at a basic level, involving an adaptive immune response directed against an antigen within the nervous system (12). Two crucial elements underlie this autoimmune entity: an immunological trigger and an underlying genetic predisposition (13). The various sources of triggers have led to different classifications for AE, including primary autoimmune, paraneoplastic, and para-infectious (12).

In primary autoimmune cases, there is no apparent autoimmune trigger, such as a viral infection or tumor, representing the majority of AE cases. This fact has prompted investigations into a genetic predisposition to AE, with certain human leukocyte antigen (HLA) genes implicated. For instance, Anti-LGI1 encephalitis is strongly associated with HLA-DR7 and HLA-DRB4 (14,15).

Paraneoplastic AE develops when cancer cells express antigens shares with neuronal cells, leading to the antibody-mediated recruitment of immune cells to these neuronal structures (16,17). It is most frequently observed in small-cell lung cancer but can also occur in other types of cancers (18,19). Parainfectious AE is mediated by an enhanced or abnormal immune response to an infection that triggers the development of AE, as seen in post-HSV anti-NMDA receptor encephalitis (20).

## DIAGNOSIS

In 2016, diagnostic criteria were published incorporating clinical and paraclinical (magnetic resonance imaging [MRI], electroencephalography (EEG), and cerebrospinal fluid) findings to divide patients into possible, probable, or definite AE categories (21). AE should be considered in ICU patients with subacute onset (rapid progression in less than 12 weeks) of working memory deficits, altered mentation, refractory seizures, or psychiatric symptoms. The presence of new-onset focal neurological findings, new onset seizures, CSF pleocytosis (WBCs  $\geq 5/\text{mm}^3$ ), or findings on magnetic resonance imaging (MRI) suggestive of encephalitis are required for the diagnosis of possible AE and higher levels of certainty can be achieved when more specific findings (Table 1) or plausible autoantibodies are detected with reasonable exclusion of other diagnoses. Care during interpreting antibody results is needed in the absence of specific findings, as both false positives and negatives can occur (22,23).

Features of AE can be seen in several other etiologies, and it is necessary to rule out alternative diagnoses. Infectious etiologies require close attention as immunotherapies employed in treating AE may result in worsening the patient's condition. In addition, misdiagnosis of patients with other primary neurological and psychiatric conditions with AE can expose them to adverse effects of immunotherapies and delay appropriate care. Strict adherence to diagnostic criteria reduces this risk (24).

## MANAGEMENT

Ultimately, treatment of AE requires immunomodulatory and immunosuppressive therapy, as well as management of any associated neoplastic process or trigger if present (25). Symptomatic treatments and supportive care are employed while these treatments take effect.

Earlier treatment with immunotherapy is associated with better outcomes (21,26). Once infectious etiologies have been excluded, immunotherapies can be initiated before the results of antibody testing (21).

Treatments are separated into first-line (corticosteroids, intravenous immunoglobulin [IVIg], and plasma exchange [PLEX]) and second-line (rituximab, cyclophosphamide, mycophenolate mofetil, azathioprine) therapies. Other agents may be used for refractory cases. However, only anecdotal evidence is available, and their discussion is beyond the scope of this review.

### FIRST LINE

**CORTICOSTEROIDS** - Methylprednisolone given intravenously at a dose of 1 gram per day for 3–5 days is commonly used as initial therapy. Active infection must be treated before initiation if present. Monitoring for hyperglycemia in diabetic patients is needed, and worsening hypertension is common. There is an increased risk for infection with corticosteroid use, so strict adherence to infection prevention guidelines is needed. Other potential side effects should be taken into consideration (e.g., infection, avascular necrosis of the hip, peptic ulcer, insomnia, psychosis, depression, hypertension, edema) (27).

**INTRAVENOUS IMMUNOGLOBULIN (IVIg)** - Fast immunomodulation with IVIg given at a 2 g/kg dose over 2–5 days is a convenient option when corticosteroids are contraindicated. It can also be used concurrently or following steroid use if there is inadequate response to treatment (26). IgA levels should be measured before use since IgA deficiency is associated with a higher risk of anaphylaxis (or use non-IgA formulation).

Potential side effects include headache, aseptic meningitis, renal failure, myocardial infarction, and venous thromboembolism.

**PLASMA EXCHANGE (PLEX)** - Another option for acute immunomodulation when corticosteroids are contraindicated is PLEX, with 5 to 10 sessions every other day. In a small retrospective study, PLEX demonstrated better improvement in the modified Rankin score (mRS) compared to those treated with corticosteroids alone in patients diagnosed with NMDAR-antibody encephalitis (28). Use is limited by availability, the need for close monitoring, and central access. The fluid shifts with this therapy need to be taken into consideration in patients with heart failure or severe dysautonomia.

## SECOND LINE

Second-line immunosuppressant therapy may be administered during the induction phase in acute inpatient situations and is generally guided by patient condition, comorbidities, and antibody subtype if known(29,30).

**RITUXIMAB** - Administered as continuous infusion of 1000 mg for 2 doses 2 weeks apart, or 375 mg/m<sup>2</sup> weekly for 4 weeks. This can be re-administered every 6 months if continued immunosuppression is desired because the CD20-expressing lymphocytes targeted by the medication begin to recover after that timeframe. Potential side effects include infusion reactions, hypogammaglobulinemia resulting in chronic sino-pulmonary infections (which can be treated with IVIg), and other infections, including a rare risk of progressive multifocal leukoencephalopathy (31).

**CYCLOPHOSPHAMIDE** - It can be used as an alternative to rituximab either orally at 1-2 mg/kg/day or by infusion of 500 mg/m<sup>2</sup> to 1000 mg/m<sup>2</sup> monthly. Considerable side effects make it less favorable and include infertility, hemorrhagic cystitis, teratogenicity, infection, and heightened malignancy risk. Typically reserved for cases refractory to rituximab given the side effect profile.

**MAINTENANCE** - A neurologist with experience in treating AE and immune-mediated neurological conditions is crucial during this phase of the treatment. Experience in monitoring for side effects and complications of treatment and assessing response to therapy helps inform decision-making.

Corticosteroids are typically continued after the induction phase. This may continue to be administered as a 1-g IV methylprednisolone infusion every 7 to 14 days with gradually increasing

intervals or daily oral prednisone 1 mg/kg/d (adult, 60 mg daily maximum). Treatment is typically continued for 6 to 12 months, and oral dosages are reduced gradually every few weeks (27). Alternatively, IVIg 0.4 g/kg once weekly after induction with gradually increasing inter-dose intervals while the response is monitored, most commonly monthly over the following 6 to 12 months (26). Steroid-sparing therapies are often needed and in addition to rituximab include MMF and AZA.

## COMPLICATIONS AND THEIR MANAGEMENT

**SEIZURES** - they are a common cause of ICU admission in AE, and greater than 20% of ICU patients due to AE are found to have seizures (32). Refractory status epilepticus is commonly seen with AE due to antibodies targeting the NMDA receptor, GABA type A receptor, and GABA type B (13,33,34). Although faciobrachial dystonic seizures are pathognomic of LGI1 antibody encephalitis, other seizure types such as focal, focal with impaired awareness, focal to bilateral tonic-clonic, and bilateral tonic-clonic seizures can be seen in almost all subtypes (35).

EEG (ideally continuous) can be helpful in the diagnosis (Table 1) and monitoring of subclinical seizures that require treatment with antiseizure medications (ASMs). Findings on EEG are generally non-specific and can be seen in other populations of critically ill patients. A characteristic EEG pattern, 'extreme delta brush', is found in patients with NMDAR encephalitis and is associated with more severe disease, increased length of stay, need for additional therapies, lower mRS scores, and higher risk of death (36). Video EEG is recommended to discriminate between movement disorders and seizures, and continuous EEG is needed to look for subclinical seizures that are common(25).

Although antiseizure medications (ASMs) are used, they are insufficient, and treatment with immunotherapy is needed to improve seizure control (32). No strong evidence is available to support the use of one ASM over the other, and choice should be influenced by the patient's comorbidities, side effects, and drug-drug interactions. SE should be treated according to the institution's protocols or international guidelines (37).

Patients with status epilepticus can be treated with standard status-epilepticus protocol. (Figure 1) Treatment should start with fast-acting benzodiazepines or phenobarbital, after which a loading dose of intravenous antiseizure medication such as fosphenytoin, valproic acid, and levetiracetam can be given (37). In the case of new-on-

set refractory status-epilepticus (NORSE), coma can be induced with midazolam, pentobarbital, propofol, or thiopental in the intensive care unit (ICU)(37).

For super-refractory status epilepticus in patients with anti-NMDA receptor encephalitis, Santoro et al. suggested that a ketamine protocol of administering a loading dose followed by maintenance infusion (0.05 mg/kg/min) could result in clinical and/or electrographic seizure cessation in less than 48 h. Moreover, outcomes were favorable regarding seizure freedom, and better epilepsy outcomes were observed with earlier treatment(38). In super refractory status epilepticus (SRSE), seizure may not be controlled until sufficient immunosuppression takes place(39).

**MOVEMENT DISORDERS** - they are common in AE, occurring in up to 87% of patients in the ICU (40,41). A diverse array of hyperkinetic disorders (dyskinesia, dystonia, chorea, tremor, myoclonus) and hypokinetic disorders like parkinsonism have been described (42)(43).

Severe symptoms are associated with complications that increase hospital stay, such as respiratory failure, fever, and bulbar dysfunction (44). Dystonia or dyskinesia affecting the trunk, neck, or chest wall muscles may require intubation if they affect respiration (45).

Early immunotherapy can result in complete resolution of the symptoms in a majority of patients, and aggressive supportive care during acute illness can prevent morbidity and mortality (45).

While immunotherapies take effect (days to weeks), symptomatic treatment is needed. Dystonia, chorea, and dyskinesia can be treated with anti-cholinergic drugs (e.g., trihexypenidyl, benztropine), alpha-receptor blockers such as clonidine, dopamine receptor blockers or depletes (e.g., haloperidol, tetrabenazine respectively ) and benzodiazepines such as midazolam (45). Tremors can be treated by beta blockers like propranolol and nadolol, as well as primidone (46). Myoclonus is typically treated with long-acting benzodiazepines such as clonazepam or certain antiseizure medications (sodium valproate, levetiracetam, zonisamide) (47). Severe dyskinesias may require deep sedation and anesthesia (22,45). Parkinsonism, which is less common, can be the predominant feature in some older patients. This can be dopamine receptor agonists such as levodopa, pramipexole, or bromocriptine (40,45,48). Clinicians should be alert that severe cases of movement disorder might be only suppressed by deep sedation and anesthesia (22,45,47).

**AUTONOMIC DYSFUNCTION (DYSAUTONOMIA)** - Dysautonomia has been reported in up to 45% of patients with AE and can occur at higher rates with certain subtypes, such as anti-NMDAR encephalitis, affecting up to 60% (12,13).

Common manifestations of autonomic dysfunction include cardiac rhythm abnormalities (tachycardia, bradycardia, asystole), respiratory abnormalities (hyper- or hypoventilation), labile blood pressures, temperature dysregulation (hyperthermia or hypothermia), gastrointestinal dysmotility and urinary retention(39,49–51). Dysautonomia results in significant morbidity and is an indicator of poor outcomes (51).

Most cases of autonomic dysfunction can be treated conservatively with supportive therapy and continuous monitoring in an ICU setting, along with immunotherapy (39). However, some patients might require symptomatic treatment for sympathetic overactivity using non-selective beta-blockers (e.g., propranolol), alpha-2 agonists (e.g., clonidine), or gabapentin (12,22). Midodrine and fludrocortisone may be used in patients with symptomatic hypotension (39) (52). A temporary pacemaker may be needed in cases of asystole or symptomatic not responsive to atropine (50). Physicians should be cautious when treating cardiac and blood pressure abnormalities as these can fluctuate rapidly, making management difficult.

Given the increased risk of infections, it is important to rule them out in patients with temperature dysregulation before attributing this to central dysautonomia. Therapeutic measures to manage hyperthermia include external and internal cooling and administration of IV dantrolene (51).

**RESPIRATORY FAILURE** - Respiratory failure in AE is usually a consequence of central dysautonomia or severe movement disorders, both of which are discussed in other parts of this review. Although patients with AE may develop prolonged hypercapnic respiratory failure, recovery with early and appropriate immunotherapy often results in recovery(32). It can be caused by central hypoventilation or movement disorders.

Patients with AE often require heavy sedation for delirium, agitation, and movement disorders caused by their condition. Intubation and mechanical ventilation are often needed, and when prolonged, the placement of tracheostomy and gastrostomy tubes in the third week (or per institutional policies) is needed to improve patient safety and the benefit of less sedation and earlier rehabilitation. In addition, clinicians



should pay particular attention to managing tracheostomy complications due to salivary contamination of tracheostomy wounds in case of hypersalivation (53).

#### **ALTERED MENTAL STATUS AND PSYCHOSIS**

- Subacute mental status changes are a hallmark of AE. Patients can present with difficulties with memory (anterograde amnesia or retrograde amnesia, confabulation) (54,55), cognitive impairment (disorientation, confusion, and delirium) (54), or decreased level of consciousness (32). A severely depressed level of consciousness is common for mechanical ventilation and ICU admission and can be a direct result of CNS inflammation, seizures, or increased ICP (45).

Psychiatric symptoms are common and include agitation, hallucinations, delusions, and mood lability (13,54). Behavioral changes, such as irritability, temper tantrums, and reduced verbal output, can also be present. Catatonia is common in anti-NMDAR encephalitis and may even be the presenting symptom (13).

Management of psychiatric disorders in AE involves the use of neuroleptics, benzodiazepines, or electroconvulsive therapy in refractory cases. However, some patients may not tolerate antipsychotics (32). Safety measures (e.g., padding, soft restraints, continuous observation, etc.) are important to prevent injury to the patient and others (39).

Patients often require high doses of benzodiazepines for appropriate sedation and antipsychotics to control agitation and psychosis (56). In cases of extreme agitation, anesthetic-induced coma may be required (53).

Manic symptoms should be treated with mood stabilizers such as lithium or valproic acid (preferred if seizures present) (57). It should be noted that elimination or dose reduction of certain medications may help to improve behavioral symptoms in some patients (e.g., steroids, benzodiazepines) (39).

In patients with seizures, agents that lower the seizure threshold (e.g., clozapine and olanzapine) should be avoided. Moreover, agents that cause prolongation of QT interval (e.g., ziprasidone and IV haloperidol) should be cautiously used or avoided in dysautonomic patients who have symptomatic bradycardia or heart block (39,58).

In certain cases, worsening of agitation or involuntary movements can develop after initiation of antipsychotics; in such cases, it should be stopped and substituted with another agent (59).

Patients with NMDAR-antibody encephalitis can be particularly sensitive to the extrapyramidal side effects of antipsychotics, in addition to worsening of catatonia and other involuntary movement and even development of neuroleptic malignant syndrome and worsening of autonomic instability. Consequently, second-generation antipsychotics with the lowest risk for seizures and extrapyramidal side effects (e.g., quetiapine) and benzodiazepines may be preferred in such patients (58).

#### **ELEVATED INTRACRANIAL PRESSURE**

- There is a wide variability in the prevalence of intracranial hypertension reported among patients with AE in the literature, with reports ranging from 20 to 40% (60–62). The clinical implications of this complication are not well-researched in literature and have conflicting results. The initial steps in managing intracranial hypertension include elevation of the head bed, hyperventilation with normal oxygenation, and adequate sedation. This should be followed by hyperosmolar or hypertonic saline therapy, IV corticosteroid, or invasive neurosurgical interventions, depending on the patient's status and the underlying etiology of their elevated ICP (50,63).

**PROGNOSIS** - Appropriate, timely management improvement is noted in 53% and 80% of patients at 4 and 24 months, respectively. If left untreated, AE can result in coma, permanent brain injury, and even death. Previous studies reported mortality rates ranging between (2-18%) (64–66).

Predictors of poor outcomes are older age, presence of comorbidities, and compromised immunity (67–69). Better outcomes are seen in AE involving cell surface antigens as opposed to those with antibodies targeting intracellular antigens. Although antibody subtype can help prognosticate, no relationship between antibody titers and disease severity or prognosis has been established (50,51,68). On EEG, the lack of normal background activity and the presence of  $\geq 50\%$  slow waves on EEG have been associated with severe neurological dysfunction and a poor prognosis (67,70). In addition, AE complications like autonomic dysfunction, disturbance of consciousness, severe sepsis/septic shock, central hypoventilation, cerebral edema, and the need for mechanical ventilation or tracheostomy were all associated with a poor neurologic outcome at hospital discharge (51,67,68,70). Earlier treatment and the use of second-line treatments when first-line options fail were associated with improved outcomes and reduced relapse rates (68)(71)(72).

---

## AUTHORS' CONTRIBUTION

AA and OY contributed equally to this manuscript, and accordingly both are first authors. All authors helped conceive the study, contributed to its design, data collection, and helped draft and review the manuscript.

All authors read and approved the final manuscript.

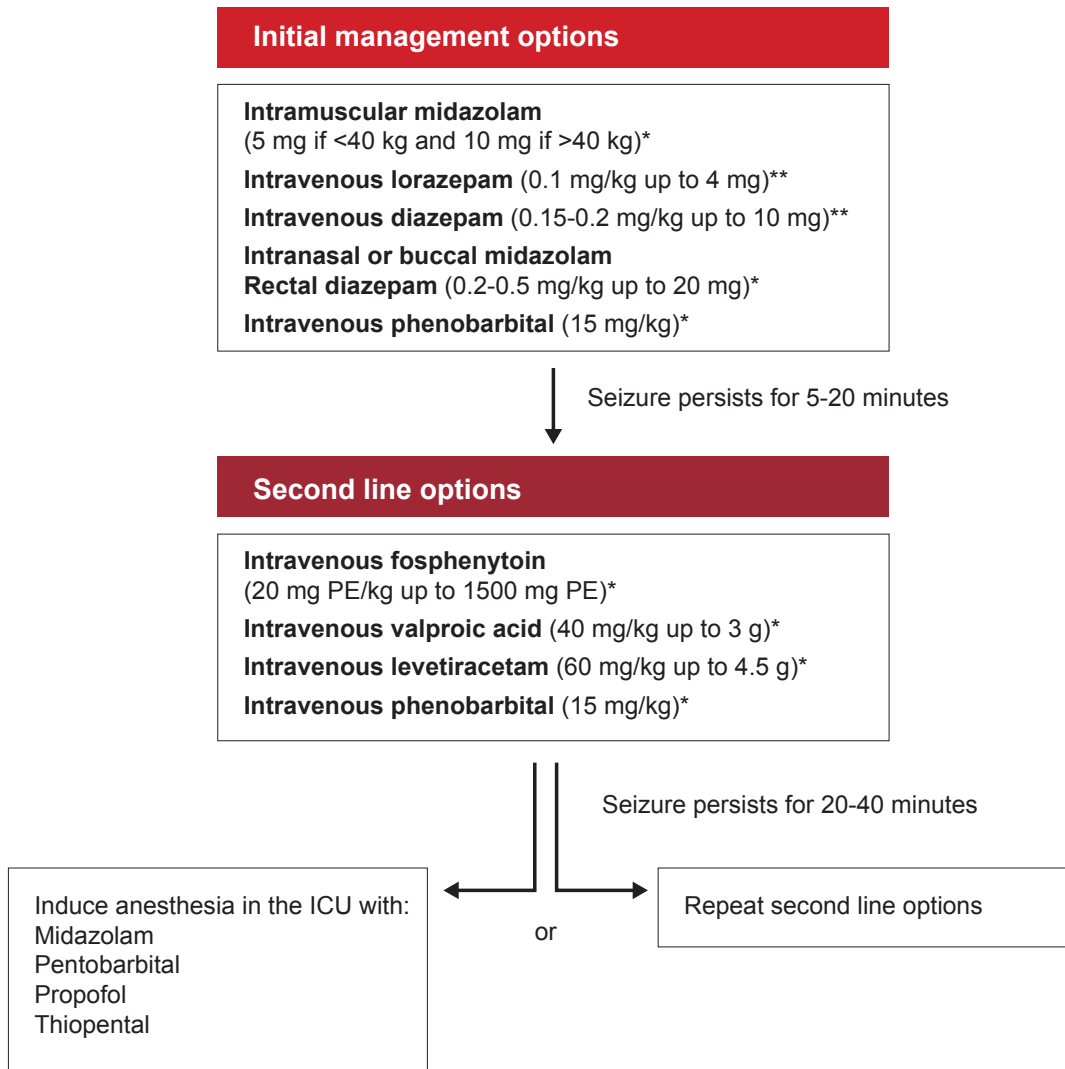
## DISCLAIMER

This article was made possible by the support of the American people through the United States Agency for International Development (USAID). The contents are the sole responsibility of the authors and do not necessarily reflect the views of USAID or the United States Government. The authors declare that they have no competing interests

---

## SUPPLEMENTAL MATERIALS

**Figure 1.** Management of status epilepticus (29)



**Table 1.** Diagnostic criteria for AE as proposed by Graus et al (12)

Certainty	Criteria		
<b>Possible</b>	<ol style="list-style-type: none"> <li>Onset of altered mentation, psychiatric symptoms, or memory deficits within three months</li> <li>At least one of the following: <ul style="list-style-type: none"> <li>New onset of seizures</li> <li>New focal CNS findings</li> <li>Pleocytosis seen in the CSF (white blood cell count &gt; 5 cells/mm<sup>3</sup>)</li> <li>Features of encephalitis seen on MRI</li> </ul> </li> </ol>		
<b>Probable</b>	<table border="0"> <tr> <td style="vertical-align: top;"> <p>Anti-NMDAR encephalitis:</p> <ol style="list-style-type: none"> <li>Four of the following major groups of symptoms appearing within three months: <ul style="list-style-type: none"> <li>Abnormal behavior or cognition</li> <li>Seizures</li> <li>Speech abnormalities</li> <li>Abnormal movement, dyskinesia, or rigidity/abnormal postures</li> <li>Decreased level of consciousness</li> <li>Central hypoventilation or dysautonomia</li> </ul> </li> <li>Any of the following test results: <ul style="list-style-type: none"> <li>EEG Abnormalities (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush)</li> <li>Pleocytosis or oligoclonal bands seen in the CSF</li> </ul> </li> </ol> </td> <td style="vertical-align: top;"> <p>Seronegative AE:</p> <ol style="list-style-type: none"> <li>Onset of altered mentation, psychiatric symptoms, or memory deficits within three months</li> <li>Exclusion of other well-defined autoimmune encephalitides</li> <li>Lack of characteristic autoantibodies in blood and CSF, with at least two of these criteria: <ul style="list-style-type: none"> <li><b>MRI findings indicating potential autoimmune encephalitis</b></li> <li><b>Pleocytosis in the CSF, oligoclonal bands, or elevated CSF-IgG index</b></li> <li><b>Brain biopsy revealing inflammatory infiltrates with the absence of other pathologies (e.g., tumor)</b></li> </ul> </li> </ol> </td> </tr> </table>	<p>Anti-NMDAR encephalitis:</p> <ol style="list-style-type: none"> <li>Four of the following major groups of symptoms appearing within three months: <ul style="list-style-type: none"> <li>Abnormal behavior or cognition</li> <li>Seizures</li> <li>Speech abnormalities</li> <li>Abnormal movement, dyskinesia, or rigidity/abnormal postures</li> <li>Decreased level of consciousness</li> <li>Central hypoventilation or dysautonomia</li> </ul> </li> <li>Any of the following test results: <ul style="list-style-type: none"> <li>EEG Abnormalities (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush)</li> <li>Pleocytosis or oligoclonal bands seen in the CSF</li> </ul> </li> </ol>	<p>Seronegative AE:</p> <ol style="list-style-type: none"> <li>Onset of altered mentation, psychiatric symptoms, or memory deficits within three months</li> <li>Exclusion of other well-defined autoimmune encephalitides</li> <li>Lack of characteristic autoantibodies in blood and CSF, with at least two of these criteria: <ul style="list-style-type: none"> <li><b>MRI findings indicating potential autoimmune encephalitis</b></li> <li><b>Pleocytosis in the CSF, oligoclonal bands, or elevated CSF-IgG index</b></li> <li><b>Brain biopsy revealing inflammatory infiltrates with the absence of other pathologies (e.g., tumor)</b></li> </ul> </li> </ol>
<p>Anti-NMDAR encephalitis:</p> <ol style="list-style-type: none"> <li>Four of the following major groups of symptoms appearing within three months: <ul style="list-style-type: none"> <li>Abnormal behavior or cognition</li> <li>Seizures</li> <li>Speech abnormalities</li> <li>Abnormal movement, dyskinesia, or rigidity/abnormal postures</li> <li>Decreased level of consciousness</li> <li>Central hypoventilation or dysautonomia</li> </ul> </li> <li>Any of the following test results: <ul style="list-style-type: none"> <li>EEG Abnormalities (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush)</li> <li>Pleocytosis or oligoclonal bands seen in the CSF</li> </ul> </li> </ol>	<p>Seronegative AE:</p> <ol style="list-style-type: none"> <li>Onset of altered mentation, psychiatric symptoms, or memory deficits within three months</li> <li>Exclusion of other well-defined autoimmune encephalitides</li> <li>Lack of characteristic autoantibodies in blood and CSF, with at least two of these criteria: <ul style="list-style-type: none"> <li><b>MRI findings indicating potential autoimmune encephalitis</b></li> <li><b>Pleocytosis in the CSF, oligoclonal bands, or elevated CSF-IgG index</b></li> <li><b>Brain biopsy revealing inflammatory infiltrates with the absence of other pathologies (e.g., tumor)</b></li> </ul> </li> </ol>		
<b>Definite</b>	<table border="0"> <tr> <td style="vertical-align: top;"> <p>Anti-NMDAR encephalitis:</p> <ol style="list-style-type: none"> <li>Existence of any of the six major groups of Anti-NMDAR encephalitis symptoms</li> <li>Identification of IgG anti-GluN1 antibodies</li> </ol> </td> <td style="vertical-align: top;"> <p>Limbic encephalitis:</p> <ol style="list-style-type: none"> <li>Onset of seizures, psychiatric symptoms, or memory deficits within three months suggesting involvement of the limbic system</li> <li>T2-weighted FLAIR MRI demonstrating bilateral brain abnormalities restricted to the medial temporal lobes</li> <li>At least one of the following: <ol style="list-style-type: none"> <li>CSF pleocytosis</li> <li>Specific EEG findings involving the temporal lobes (epileptic or slow-wave activity)</li> </ol> </li> </ol> </td> </tr> </table>	<p>Anti-NMDAR encephalitis:</p> <ol style="list-style-type: none"> <li>Existence of any of the six major groups of Anti-NMDAR encephalitis symptoms</li> <li>Identification of IgG anti-GluN1 antibodies</li> </ol>	<p>Limbic encephalitis:</p> <ol style="list-style-type: none"> <li>Onset of seizures, psychiatric symptoms, or memory deficits within three months suggesting involvement of the limbic system</li> <li>T2-weighted FLAIR MRI demonstrating bilateral brain abnormalities restricted to the medial temporal lobes</li> <li>At least one of the following: <ol style="list-style-type: none"> <li>CSF pleocytosis</li> <li>Specific EEG findings involving the temporal lobes (epileptic or slow-wave activity)</li> </ol> </li> </ol>
<p>Anti-NMDAR encephalitis:</p> <ol style="list-style-type: none"> <li>Existence of any of the six major groups of Anti-NMDAR encephalitis symptoms</li> <li>Identification of IgG anti-GluN1 antibodies</li> </ol>	<p>Limbic encephalitis:</p> <ol style="list-style-type: none"> <li>Onset of seizures, psychiatric symptoms, or memory deficits within three months suggesting involvement of the limbic system</li> <li>T2-weighted FLAIR MRI demonstrating bilateral brain abnormalities restricted to the medial temporal lobes</li> <li>At least one of the following: <ol style="list-style-type: none"> <li>CSF pleocytosis</li> <li>Specific EEG findings involving the temporal lobes (epileptic or slow-wave activity)</li> </ol> </li> </ol>		



## REFERENCES

- 1 Hiesgen J, Schutte CM. Autoimmune encephalitis: Epidemiology, pathophysiology and clinical spectrum (part 1). *South African Med J*. 2023;
- 2 Greenfield JG. Subacute spino-cerebellar degeneration occurring in elderly patients. *Brain*. 1934;
- 3 Leyboldt F, Wandinger KP, Bien CG, Dalmau J. Autoimmune encephalitis. *Eur Neurol Rev*. 2013;
- 4 Bloch KC, Glaser CA. Encephalitis surveillance through the emerging infections program, 1997–2010. *Emerg Infect Dis*. 2015;
- 5 Dubey D, Pittock SJ, Kelly CR, McKeon A, Lopez-Chiriboga AS, Lennon VA, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann Neurol*. 2018;
- 6 Yeshokumar AK, Gordon-Lipkin E, Arenivas A, Cohen J, Venkatesan A, Saylor D, et al. Neurobehavioral outcomes in autoimmune encephalitis. *J Neuroimmunol*. 2017;
- 7 Harutyunyan G, Hauer L, Dünser MW, Karamyan A, Moser T, Pikija S, et al. Autoimmune Encephalitis at the Neurological Intensive Care Unit: Etiologies, Reasons for Admission and Survival. *Neurocrit Care*. 2017;
- 8 Varvat J, Lafond P, Page Y, Coudrot M, Reynaud-Salard M, Tardy B. Acute psychiatric syndrome leading young patients to ICU: Consider anti-NMDA-receptor antibodies. *Anaesth Intensive Care*. 2010;
- 9 De Montmollin E, Demeret S, Brulé N, Conrad M, Dailier F, Lerolle N, et al. Anti-N-methyl-D-aspartate receptor encephalitis in adult patients requiring intensive care. *Am J Respir Crit Care Med*. 2017;
- 10 Chen X, Li JM, Liu F, Wang Q, Zhou D, Lai X. Anti-N-methyl-d-aspartate receptor encephalitis: a common cause of encephalitis in the intensive care unit. *Neurol Sci*. 2016;
- 11 Harutyunyan G, Hauer L, Dünser MW, Moser T, Pikija S, Leitinger M, et al. Risk factors for intensive care unit admission in patients with autoimmune encephalitis. *Front Immunol*. 2017;
- 12 Rubin DB, Batra A, Vodopivec I, Vaitkevicius H. Autoimmune Encephalitis in Critical Care: Optimizing Immunosuppression. *Semin Respir Crit Care Med*. 2017;
- 13 Dalmau J, Graus F. Antibody-Mediated Encephalitis. *N Engl J Med*. 2018;
- 14 van Sonderen A, Roelen DL, Stoop JA, Verdijk RM, Haasnoot GW, Thijs RD, et al. Anti-LGI1 encephalitis is strongly associated with HLA-DR7 and HLA-DRB4. *Ann Neurol*. 2017;
- 15 Kim TJ, Lee ST, Moon J, Sunwoo JS, Byun JI, Lim JA, et al. Anti-LGI1 encephalitis is associated with unique HLA subtypes. *Ann Neurol*. 2017;
- 16 Graus F, Saiz A, Dalmau J. Antibodies and neuronal autoimmune disorders of the CNS. *Journal of Neurology*. 2010.
- 17 Ramanathan S, Mohammad SS, Brilot F, Dale RC. Auto-immune encephalitis: Recent updates and emerging challenges. *Journal of Clinical Neuroscience*. 2014.
- 18 de Beukelaar JW, Smitt PAS. Managing Paraneoplastic Neurological Disorders. *Oncologist*. 2006;
- 19 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.
- 20 Armangue T, Spatola M, Vlasea A, Mattozzi S, Cárcel-Cordon M, Martínez-Heras E, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol*. 2018;
- 21 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.
- 22 M.K. M, A.A. R, S.E. H, S.J. P, E.F. MW, A. M. Autoimmune Encephalitis in the ICU: Analysis of Phenotypes, Serologic Findings, and Outcomes. *Neurocrit Care*. 2016;
- 23 Prüss H, Finke C, Höltje M, Hofmann J, Klingbeil C, Probst C, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol*. 2012;
- 24 Flanagan EP, Geschwind MD, Lopez-Chiriboga AS, Blackburn KM, Turaga S, Binks S, et al. Autoimmune Encephalitis Misdiagnosis in Adults. *JAMA neurology*. 2023.
- 25 Lancaster E. The diagnosis and treatment of autoimmune encephalitis. *Journal of Clinical Neurology (Korea)*. 2016.
- 26 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. *Lancet Neurol*. 2013;
- 27 Shin YW, Lee ST, Park K II, Jung KH, Jung KY, Lee SK, et al. Treatment strategies for autoimmune encephalitis. *Therapeutic Advances in Neurological Disorders*. 2018.
- 28 Desena AD, Noland DK, Matevosyan K, King K, Phillips L, Qureshi SS, et al. Intravenous methylprednisolone versus therapeutic plasma exchange for treatment of anti-n-methyl-d-aspartate receptor antibody encephalitis: A retrospective review. *Journal of Clinical Apheresis*. 2015.
- 29 Viacoz A, Desestret V, Ducray F, Picard G, Cavillon G, Rogemond V, et al. Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. *Neurology*. 2014;
- 30 Toledano M, Britton JW, McKeon A, Shin C, Lennon VA, Quek AML, et al. Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy. *Neurology*. 2014;
- 31 Lee WJ, Lee ST, Byun JI, Sunwoo JS, Kim TJ, Lim JA, et al. Rituximab treatment for autoimmune limbic encephalitis in an institutional cohort. *Neurology*. 2016;

- 32 Sonnevile R, Venkatesan A, Honnorat J. Understanding auto-immune encephalitis in the ICU. *Intensive Care Medicine*. 2019.
- 33 Kwan C, Sia A, O’Gorman C. Status epilepticus from GABA-ABR antibody positive encephalitis due to de novo mixed small cell and adenocarcinoma of the prostate. *BMJ Case Rep*. 2020;
- 34 Alemdar M. Anti-NMDA receptor encephalitis presenting with the new-onset refractory status epilepticus. *North Clin Istanbul*. 2021;10(3):385–9.
- 35 Wang Y, Yu Y, Hu Y, Li Y, Song F, Wang Y. Clinical and Electroencephalographic Features of the Seizures in Neuronal Surface Antibody-Associated Autoimmune Encephalitis. *Front Neurol*. 2020;
- 36 Moise AM, Karakis I, Herlopian A, Dhakar M, Hirsch LJ, Cotsonis G, et al. Continuous EEG Findings in Autoimmune Encephalitis. In: *Journal of Clinical Neurophysiology*. 2021.
- 37 Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: Treatment of convulsive status epilepticus in children and adults: Report of the guideline committee of the American epilepsy society. *Epilepsy Curr*. 2016;
- 38 Santoro JD, Filippakis A, Chitnis T. Ketamine use in refractory status epilepticus associated with anti-NMDA receptor antibody encephalitis. *Epilepsy Behav Reports*. 2019;
- 39 Abboud H, Probasco JC, Irani S, Ances B, Benavides DR, Bradshaw M, et al. Autoimmune encephalitis: Proposed recommendations for symptomatic and long-term management. *Journal of Neurology, Neurosurgery and Psychiatry*. 2021.
- 40 Dash D, Ihtisham K, Tripathi M, Tripathi M. Proportion and spectrum of movement disorders in adolescent and adult patients of autoimmune encephalitis of non-neoplastic aetiology. *J Clin Neurosci*. 2019;
- 41 Zhang Y, Liu G, Jiang M, Chen W, He Y, Su Y. Clinical Characteristics and Prognosis of Severe Anti-N-methyl-d-aspartate Receptor Encephalitis Patients. *Neurocrit Care*. 2018;
- 42 Kempster P, Monif M. Movement disorders in cell surface antibody mediated autoimmune encephalitis : a meta-analysis. (1).
- 43 Honnorat J, Joubert B. Movement disorders in autoimmune encephalitis and paraneoplastic neurological syndromes. *Revue Neurologique*. 2018.
- 44 Termsarasab P, Frucht SJ. Dystonic storm: a practical clinical and video review. *J Clin Mov Disord*. 2017;
- 45 Ali F, Wijdicks EF. Treatment of Movement Disorder Emergencies in Autoimmune Encephalitis in the Neurosciences ICU. *Neurocritical Care*. 2020.
- 46 Puschmann A, Wszolek ZK. Diagnosis and treatment of common forms of tremor. *Semin Neurol*. 2011;
- 47 Caviness JN. Treatment of Myoclonus. *Neurotherapeutics*. 2014.
- 48 Mohammad SS, Dale RC. Principles and approaches to the treatment of immune-mediated movement disorders. *European Journal of Paediatric Neurology*. 2018.
- 49 Yan L, Zhang S, Huang X, Tang Y, Wu J. Clinical Study of Autonomic Dysfunction in Patients With Anti-NMDA Receptor Encephalitis. *Front Neurol*. 2021;
- 50 Diaz-Arias LA, Pardo CA, Probasco JC. Autoimmune Encephalitis in the Intensive Care Unit. *Curr Clin Neurol*. 2020;249–63.
- 51 Schubert J, Brämer D, Huttner HB, Gerner ST, Fuhrer H, Melzer N, et al. Management and prognostic markers in patients with autoimmune encephalitis requiring ICU treatment. *Neurol Neuroimmunol NeuroInflammation*. 2019;
- 52 Rafanelli M, Walsh K, Hamdan MH, Buyan-Dent L. Autonomic dysfunction: Diagnosis and management. In: *Handbook of Clinical Neurology*. 2019.
- 53 Lin KL, Lin JJ. Neurocritical care for Anti-NMDA receptor encephalitis. *Biomedical Journal*. 2020.
- 54 Voronova M, Sharko A. Severe Central Hypoventilation Syndrome in a Patient With Anti-N-Methyl-D-Aspartate Receptor Encephalitis: Case Report and Review of the Literature. *Cureus*. 2022;
- 55 Uy CE, Binks S, Irani SR. Autoimmune encephalitis: Clinical spectrum and management. *Practical Neurology*. 2021.
- 56 Bost C, Pascual O, Honnorat J. Autoimmune encephalitis in psychiatric institutions: Current perspectives. *Neuropsychiatric Disease and Treatment*. 2016.
- 57 Chapman MR, Vause HE. Anti-NMDA receptor encephalitis: Diagnosis, psychiatric presentation, and treatment. In: *American Journal of Psychiatry*. 2011.
- 58 Sarkis RA, Justin Coffey M, Cooper JJ, Hassan I, Lennox B. Anti-N-Methyl-D-aspartate receptor encephalitis: A review of psychiatric phenotypes and management considerations: A report of the american neuropsychiatric association committee on research. *J Neuropsychiatry Clin Neurosci*. 2019;
- 59 Warren N, O’Gorman C, McKeon G, Swayne A, Blum S, Siskind D. Psychiatric management of anti-NMDAR encephalitis: A cohort analysis. *Psychol Med*. 2021;
- 60 Wang R, Guan HZ, Ren HT, Wang W, Hong Z, Zhou D. CSF findings in patients with anti-N-methyl-d-aspartate receptor-encephalitis. *Seizure*. 2015;
- 61 Wang Y, Zhang W, Yin J, Lu Q, Yin F, He F, et al. Anti-N-methyl-D-aspartate receptor encephalitis in children of Central South China: Clinical features, treatment, influencing factors, and outcomes. *J Neuroimmunol*. 2017;
- 62 Chi X, Wang W, Huang C, Wu M, Zhang L, Li J, et al. Risk factors for mortality in patients with anti-NMDA receptor encephalitis. *Acta Neurol Scand*. 2017;
- 63 Ragland J, Lee K. Critical Care Management and Monitoring of Intracranial Pressure. *J Neurocritical Care*. 2016;

- 64 Dechambenoit G. AUTOIMMUNE ENCEPHALITIS: A MISSED DIAGNOSTIC AND THERAPEUTIC OPPORTUNITY. *African J Neurol Sci.* 2018;20(1):66–79.
  - 65 Thakur KT, Motta M, Asemota AO, Kirsch HL, Benavides DR, Schneider EB, et al. Predictors of outcome in acute encephalitis. *Neurology.* 2013;
  - 67 Gu Y, Zhong M, He L, Li W, Huang Y, Liu J, et al. Epidemiology of Antibody-Positive Autoimmune Encephalitis in Southwest China: A Multicenter Study. *Front Immunol.* 2019;
  - 68 Mo Y, Wang L, Zhu L, Li F, Yu G, Luo Y, et al. Analysis of risk factors for a poor prognosis in patients with anti-n-methyl-d-aspartate receptor encephalitis and construction of a prognostic composite score. *J Clin Neurol.* 2020;
  - 69 Qiao S, Wu HK, Liu LL, Zhang RR, Wang ML, Han T, et al. Characteristics and Prognosis of Autoimmune Encephalitis in the East of China: A Multi-Center Study. *Front Neurol.* 2021;
  - 70 Schwarz L, Akbari N, Prüss H, Meisel A, Scheibe F. Clinical characteristics, treatments, outcome, and prognostic factors of severe autoimmune encephalitis in the intensive care unit: Standard treatment and the value of additional plasma cell-depleting escalation therapies for treatment-refractory patients. *Eur J Neurol.* 2023;
  - 71 Gitiaux C, Simonnet H, Eisermann M, Leunen D, Dulac O, Nabbout R, et al. Early electro-clinical features may contribute to diagnosis of the anti-NMDA receptor encephalitis in children. *Clin Neurophysiol.* 2013;
  - 72 Ellul MA, Wood G, van Den Tooren H, Easton A, Babu A, Michael BD. Update on the diagnosis and management of autoimmune encephalitis. *Clin Med J R Coll Physicians London.* 2020;
  - 73 Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: A systematic review. *Expert Review of Neurotherapeutics.* 2015.
-